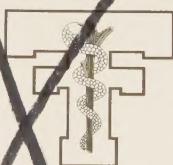


THROMBOHEMORRHAGIC PHENOMENA

HANS SELYE

Texas Tech University
School of Medicine
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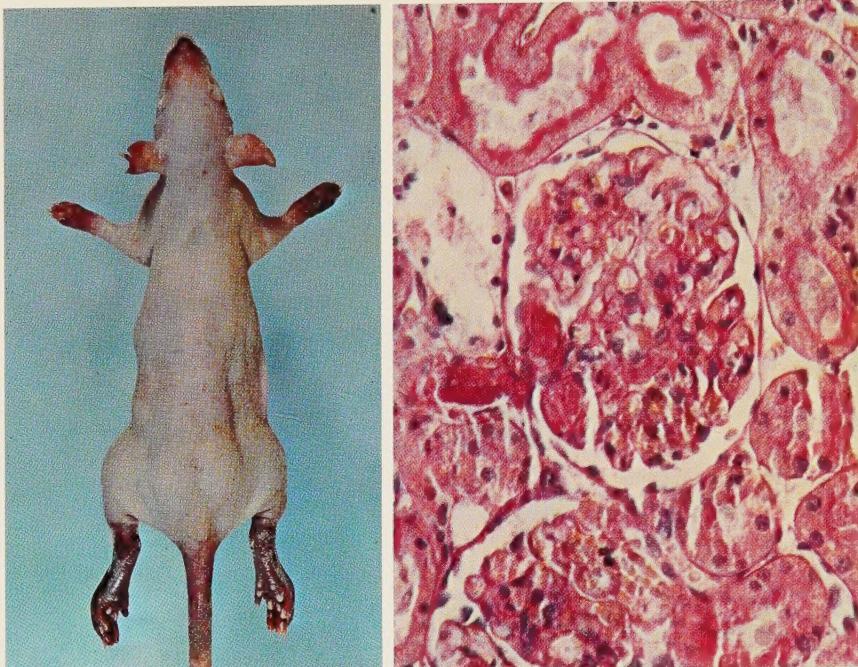


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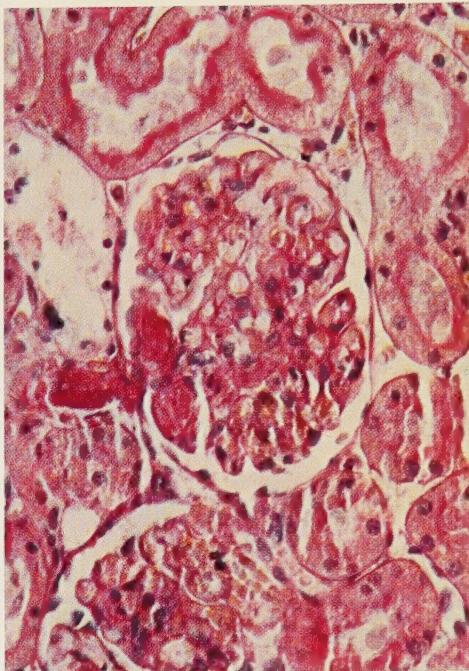


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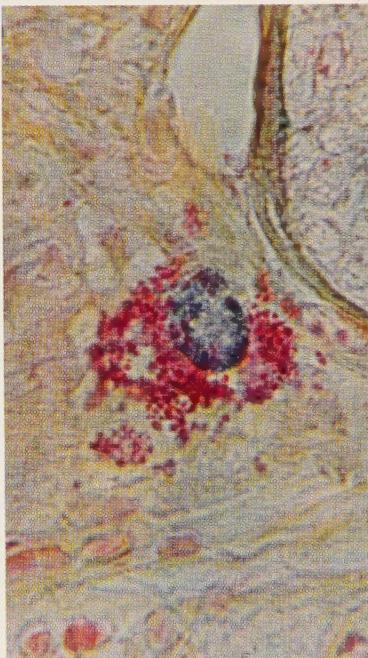
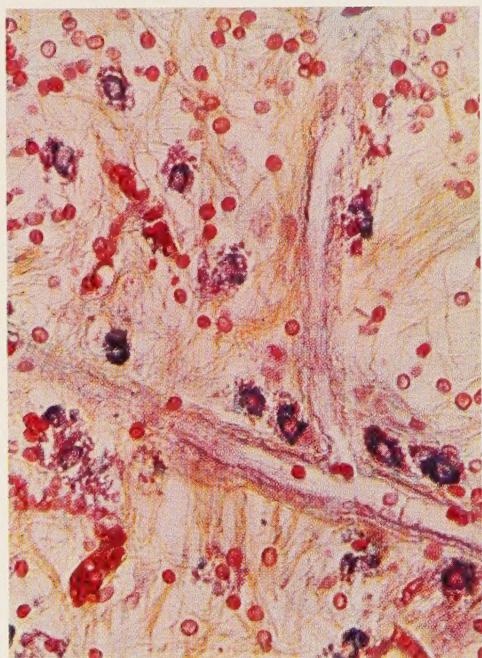
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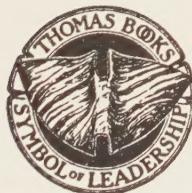
FRONTISPIECE. *Anaphylactoid purpura produced by agar + dextrin.* A: Hemorrhagic lesions in the anaphylactoid shock organs (snout, ears, paws, root of tail). B: Glomerulus with thrombus in afferent arteriole and adjacent glomerular capillaries (PAS, $\times 460$). C: Erythrocytes and partially discharged mast cells in connective tissue of paw (multipurpose polychrome, $\times 460$). D: A single mast cell from preceding preparation, clearly indicating purplish-blue intracytoplasmic and red discharged mast-cell granules (multipurpose polychrome, $\times 1000$). (After Selye & Tuchweber, G19,430/65.)

THROMBOHEMORRHAGIC PHENOMENA

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Springfield · Illinois · U.S.A.

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CHARLES C THOMAS • PUBLISHER

BANNERSTONE HOUSE

301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

NATCHEZ PLANTATION HOUSE

735 North Atlantic Boulevard, Fort Lauderdale, Florida, U.S.A.

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Library of Congress Catalog Card Number: 66-16821

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PREFATORY REMARKS ON THE STYLE OF THIS BOOK

IN my previous monograph, *The Mast Cells* (Butterworth, Washington 1965), I first tested the practicality of what might be called the "analytico-synthetic style" in the compilation of scientific monographs. In essence, it attempts to facilitate fact-finding by strictly separating: 1. the *analysis* of previous publications in search of facts, which must be objective, and 2. the author's evaluation and *synthesis* which, being guided by his personal experience, is largely subjective.

The lessons learned in compiling *The Mast Cells* are incorporated in the present volume and, since no major changes have been made, the rationale of the analytico-synthetic style may be described here in essentially the same terms.

Conventionally, the preparation of a monograph progresses in two stages:

1. The author surveys the literature and makes brief abstracts of each publication pertinent to his subject.
2. In writing the successive chapters of his book, the author transforms these abstracts into a current narrative.

In theory, this seems to be a perfectly logical procedure, and undoubtedly it can be successfully applied in some cases. However, the second phase of the work usually meets with virtually insurmountable difficulties. Whenever numerous data are accumulated by many investigators who used different techniques, the interpretations may be consonant, contradictory or unrelated, so that a unified, concise report of all relevant facts and views is hardly possible without confusing distortions or oversimplifications.

Take a sentence such as: "Allegedly, it is possible to produce thrombohemorrhagic phenomena by a single intravenous injection of substance X in the rabbit (Smith and Johnson, 1943; Jones, 1944; Jackson, 1952) but not in the mouse (Simpson, 1961; Walker, 1964); however, these claims have been challenged by several investigators (McKay, 1963; Dow, 1963; Fisher, 1964), who claim to have obtained positive results in both these species." Did all these investigators use exactly the same technique? Did all of them use the same criteria for a "positive result"? Were the animals used of the same age and weight? Were the animals invariably killed after the same length of time following the injection, so as to give them an equal chance to develop the lesions? Only in the rarest instances would the answers to all these questions be affirmative. In other words, the sentence designed to combine the three reports has made them quite meaningless.

But why stoop to the customary practice of verbal acrobatics to give the un-unifiable the appearance of unity? To make sense, the incongruous monster sentences painfully synthesized by the author must later be mentally broken down into their constituent parts by the reader. What the author has coded, the reader must decode. Statements must be very diplomatically worded to fit several papers because different authors bracketed after one remark have rarely, if

ever, said exactly the same thing. Hence, such texts are difficult to read and, in the final analysis, they accomplish little more than to act as indices to the literature, which still has to be procured and read in the original before it can serve as a reliable guide to further work. The essential weakness of this conventional style is that the author must formulate his remarks very vaguely whenever he wants to cite several related, but of course never identical, papers in support of a statement. This procedure is necessary for unification, but the result is uninformative or misleading, usually both.

I have learned these facts by bitter experience while writing my sixteen earlier medical texts in the conventional style. Could the usual drawbacks of monographs be avoided by a totally different approach? In compiling a scientific treatise it is undoubtedly necessary first to peruse all pertinent publications and to prepare concise abstracts of them. (Incidentally, I never minded this part of the work, which was instructive and pleasant; it gave me a broad panoramic view of the observations and reflections of others, the very basis for any correlative scientific study.) But then came the deadly and uninstructive task of modifying and paraphrasing portions of my summaries so that they could be squeezed into more or less cohesive, current prose. Why bother? All that was accomplished in this second stage was to conform with the style sanctified by common usage, but in the process the practical value of my abstract collection was largely lost. I must admit that even after the book appeared in print, I usually still preferred to look up my original résumés. After all, the book contained only portions of these, and even they were not expressed as clearly as in the abstracts mainly for three reasons:

1. Whenever several references are cited to document a statement, certain details have to be eliminated or put vaguely to make the text fit all the publications quoted in support of it.

2. Transitional sentences are needed to connect one idea with another and these are only confusing ballast which does no real work.

3. Many circumlocutions are necessary to distinguish tactfully between data which are fully, partly, or not at all, acceptable.

In other words, the first part of the work, the reading and abstracting, is pleasant, instructive and comparatively easy, while the second part, the paraphrasing into current narrative, is tedious and largely spoils the accomplishments of the first phase.

Of course, a collection of abstracts is not a monograph; it does not possess any overall structure or continuity and, even with the aid of an extensive index, it cannot act as a handy guide to a new field. Such a compendium is also necessarily uncritical and devoid of originality. It gives none of the interpretations and personal findings of the reviewer.

How could we devise a style which would combine concise, objective reporting with original interpretations without creating any confusion between the two? This is what I have tried to accomplish here and it may be worthwhile to describe the technique in detail for those interested in the compilation of extensive monographs. We proceeded as follows:

1. **Collection of Literature.** A list comprising most of the literature on the thrombohemorrhagic phenomena was compiled from abstract journals, the Index

Medicus and the bibliographies given by previous authors who wrote on this subject. The corresponding original articles were then obtained in the form of reprints or as photoreproductions. These came mostly from the journals in our two local university libraries (Université de Montréal and McGill University) and from the National Medical Library in Washington, D. C. More than 5,000 articles thus became available for study in original form and, of these, 1,300 were finally selected as being sufficiently relevant to warrant inclusion in the bibliography of this volume. There (pp. 267-319) they are listed in alphabetic order, with the accession number they carry in our library. These same numbers, followed by a stroke and the year of publication, are also used in the text for identification (e.g., *Sanarelli, D89,454/16*).

2. Abstracting. Every abstract was dictated on magnetic tape with the original source material before me. I had to quote at second hand only a few quite unavailable Doctors' theses, remarks made at congresses which published no proceedings, and "personal communications" cited by others. To avoid constant spelling out and to facilitate the task of transcription, key words, names, numbers, and complex technical terms were underlined in the original texts for the guidance of our typists.

In preparing the abstracts, we tried to incorporate all the essentials, including the species on which an observation was made, the route of administration of drugs, the techniques of determination, etc., wherever these facts may have significantly influenced the findings. However, equal care was taken to eliminate all irrelevant data in order to make the abstracts concise and readable.

Whenever an author summarized a salient point concisely or expressed a particularly unexpected view, his own wording was quoted. Each abstract was preceded by a brief title identifying its subject matter. Articles which contained data pertaining to several chapters of this monograph were separately abstracted for each section. However, the same summary could often be used for this purpose, changing only the title. For example, in analyzing an article concerned with the production by a certain diet of the thrombohemorrhagic phenomenon in the pregnant rat, I first dictated my abstract with the title "Pregnancy" (for the section "Effect of Pregnancy on Thrombohemorrhagic Phenomena") and then merely added "repeat the same abstract with the title 'Diet'" (for the section on the "Effect of Diet").

Finally, the pages containing these abstracts were cut up into slips and taped into proper position—according to the "rail paper technique" (*Selye, E24,140/64 p. 350*)—on a master copy provided with index tabs.

Throughout this phase of the work, my main concern was to reflect the authors' statements objectively whether I agreed with them or not. Only in a few instances (e.g., when the statements were contradictory or the technique faulty) was it necessary to point out possible sources of confusion, but this was done after the reference in separate, initialed comments.

The resulting classified abstract collection corresponds to the small print in this volume.

3. Critique and Personal Observations. We now had a classified collection of concise abstracts which served as a convenient guide to the literature on the

thrombohemorrhagic phenomena. However, precisely because of its strict objectivity and the absence of any connecting sentences between the abstracts, this text completely lacked both originality and continuity. It was useful for the experienced specialist who only wants to look up the literature on a certain point, but it gave no guidance to the beginner and contributed no unpublished new thoughts or observations.

While this bibliographic work was in progress, my associates and I were also engaged in experimental research on the thrombohemorrhagic phenomena. It was felt that the results of these investigations and the personal views formulated during the systematic study of the world literature should also be incorporated in this volume.

The published data of our group were handled in the usual manner, by preparing objective abstracts of them for the small print sections. However, my own interpretation of the literature and our hitherto unpublished observations were reported in an entirely different, current narrative form; this text is clearly separated from the rest by being printed in large type. Here, there are no references, it being tacitly understood that the conclusions are my own, based on a critical interpretation of the literature and my personal experience. In addition, numerous photographs and diagrams were prepared to make the report informative.

Thus, we end up having a book within a book: the *small-print* sections represent concise and impersonal abstracts of published data, formulated in telegraphic style, to be looked up but not to be read through from cover to cover; the *large-print* text, on the other hand, is a critical evaluation of the literature and an illustrated description of unpublished observations. The reader who only wishes to get an overall view of the present status of knowledge on the thrombohemorrhagic phenomena can do so without getting lost in detail and confusing contradictory statements by reading only the large-type sections. The investigator who wants to verify a special point quickly will find it without having to wade through much text by merely consulting the classified abstracts in the corresponding section.

This "analytico-synthetic style" would not lend itself to the writing of textbooks for students, nor would it be suitable for monographs on entirely new subjects on which there is virtually no earlier literature; however, I think it could be profitably employed in the compilation of any review, monograph or handbook which is to combine an extensive literature survey with personal observations and critical interpretations.

In our era, in which interest and material support for research has reached unprecedented proportions, one of the greatest handicaps to the further development of science is the growing difficulty of keeping track of the ever expanding mass of literature. Hence, a generally acceptable, simplified style of reporting could be of immeasurable value. Of course, many laboratory men will say that they lack the time, money, library facilities, or the knowledge of foreign languages necessary for a thorough personal search of the original literature in an extensive field. Yet, any competent scientist must master his own subject. The breadth of his investigations may be very limited by lack of documentation, but in his

restricted field he will eventually gather valuable, expert knowledge which should be made available to others as well. It is hoped that the extreme simplicity of reporting in the style recommended here will encourage the writing of surveys by authors who would not have ventured to do so in the more time-consuming conventional form. Should this be the case, correlative investigations would certainly receive a welcome stimulus at a time when mass production threatens to discourage the integration of knowledge.

ACKNOWLEDGMENTS

I WOULD like to take this opportunity to express my heartfelt gratitude to Doctors Giulio Gabbiani, Beatriz Tuchweber, Dusan Baić, Lorand Bertók, Alfred Gregory, Raghbir and Shakuntla Mahajan, Pavel Rohan, Béla Solymoss and Gérard Winandy, who assisted me in many of the original experiments that formed the subject matter of this volume.

My very special thanks are due to Mrs. N. Vailles and also to Mrs. Y. Côté, Miss T. Gauvin and Miss M. A. Leduc (for the extraordinary care and devotion with which they prepared the typescript and read the proofs), to Mr. J. Krzyzanowski (Chief Librarian, who ingeniously collected even the most inaccessible publications), Miss B. Koretz (who compiled the bibliography), Mr. K. Nielsen (who prepared the histologic slides and photographic illustrations), and above all to Mrs. E. Staub (who supervised and coordinated the entire work on the manuscript and prepared the index).

I would also like to thank Charles C Thomas, Publisher for the care and attention given to all details of manufacture and design.

The original experimental work done at our Institute, which inspired this volume, was subsidized by the: Medical Research Council of Canada; Canadian Heart Foundation, National Cancer Institute of Canada, John A. Hartford Foundation, U. S. Army, Medical Research and Development Command (Contract No. DA-49-193-MD-2039), U.S.P.H.S. National Heart Institute (Grant No. H-6182), and Ministry of Health of the Province of Quebec (Grants Nos. 604-9-277, 604-7-426).

Université de Montréal

H.S.

INTRODUCTION

THE principal purpose of this book is to collate and interpret the literature on what might be called the "thrombohemorrhagic phenomena." Many clinical and experimental diseases are characterized by a singular combination of thrombosis and hemorrhage, often leading to necrosis. This lesion is well exemplified by the "red infarct" commonly encountered in the lung and intestine. Here, in an area damaged by thrombotic occlusion of a major nutrient vessel, massive hemorrhage results from an associated venous stasis or a sudden inflow of blood through collaterals.

There are other thrombohemorrhagic phenomena which develop as a result of still poorly understood changes in the microcirculation. This group includes a great variety of clinical and experimental diseases whose only salient common feature is hemorrhagic thrombosis, usually accompanied with a coagulation defect. For example, in man, such changes dominate the picture in eclampsia, abruptio placentae, amniotic fluid embolism, the crush syndrome, the Waterhouse-Friedrichsen syndrome, various allergic and infectious purpuras, certain snake bites and bilateral renal cortical necrosis. Similar lesions develop in animals during the "eclampsia-like syndrome" elicited by dietary means, the Reilly phenomenon, the Sanarelli-Shwartzman phenomenon, combined treatment with heparinoids and catecholamines, hog cholera, swine erysipelas, and the "hemorrhagic tumor necrosis" induced by bacterial endotoxins. In most of these conditions, erythrocyte aggregation and lysis in small vessels are followed by the local accumulation of platelets and fibrin. The latter tends to be transformed gradually into fibrinoid material similar to that seen in rheumatic fever, lupus erythematosus, malignant hypertension or periarteritis nodosa; hence, some common derangement in fibrin metabolism may represent a link between the thrombohemorrhagic phenomena and the large group of collagen diseases.

The understanding of this vast field in pathology has been greatly handicapped because the voluminous and polyglot pertinent literature, which goes back to the middle of the nineteenth century, has never been collated for critical evaluation. Thus, while additional observations were constantly being made on thrombohemorrhagic phenomena, no matter how great their inherent interest as isolated facts, they could be put into no meaningful frame of reference. Indeed, as far as the structuralization of the subject is concerned, each new finding tended to complicate and confuse rather than clarify the picture.

This difficulty became particularly acute in 1928 when Shwartzman described his "phenomenon of tissue sensitivity to bacterial filtrates," one of the most fascinating and puzzling observations in this domain. If a rabbit first receives an intracutaneous "preparatory" and next day an intravenous "provocative" injection of *S. typhosa* filtrate, the prepared skin site soon becomes bloodshot and often

necrotic as a consequence of thromboses and hemorrhages in its microcirculation. It was soon discovered that the phenomenon can also be elicited by endotoxins of numerous other gram-negative bacteria and that it is closely related to the generalized thrombohemorrhagic lesions which Sanarelli had induced many years earlier by an intravenous injection of *V. cholerae* followed next day by the intravenous administration of *E. coli* or *proteus* filtrates. It has become customary to refer to this type of response as the Sanarelli-Shwartzman phenomenon. Sanarelli is credited with the discovery of the general, Shwartzman, with that of the local variant of a thrombohemorrhagic response to two properly spaced injections with certain microbial products.

These discoveries were of enormous heuristic value. Of course, innumerable thrombohemorrhagic lesions (the red infarct, various infectious and allergic purpuras, eclampsia, etc.) had been known long before. Even the formation of hyaline thrombi in the glomerular capillaries of the kidney and renal cortical necrosis (considered characteristic of the generalized Sanarelli-Shwartzman phenomenon) were well known to earlier investigators, but the intriguing novelty of the Sanarelli-Shwartzman phenomenon was its strict dependence upon two properly spaced treatments with microbial products. The reason for this dependence is still improperly understood, despite the volume of work performed in efforts to elucidate it. However—as so often happens with fashionable subjects in medicine—it became customary to interpret virtually any kind of thrombohemorrhagic lesion as a Shwartzman phenomenon, no matter how it was produced. This laxity in terminology reflected a certain lack of precision in thinking and greatly interfered with the understanding and classification of the hemorrhagic thromboses. The very identity of the Sanarelli-Shwartzman phenomenon would be lost if we regarded (as many investigators still do) the hemorrhagic thromboses produced by certain diets or single injections of heparinoids, snake venoms and thrombin as mere variants of the “phenomenon of local tissue sensitivity to bacterial filtrates.”

My associates and I became especially interested in this field when, in the course of our work on calciphylaxis and calcergy, we accidentally noted that treatment with certain combinations of simple, chemically well-characterized compounds (e.g., ferric chloride, cerium chloride, lanthanum chloride, tannic acid, serotonin, epinephrine or norepinephrine) can produce both general and local hemorrhagic thromboses structurally similar to those of the Sanarelli-Shwartzman phenomenon. To elicit these lesions, it was not necessary (indeed not permissible) to allow a time interval between treatments; also the evocative agents were not microbial products. Thus, our procedure differed from that required to produce the Sanarelli-Shwartzman phenomenon in both of the latter's essential characteristics. On the other hand, it was striking that, given alone, none of the simple, chemical compounds we employed produced thrombohemorrhagic lesions even at fatal dose levels.

We met with a somewhat similar situation a few years ago when we found that various types of cardiac lesions could be produced in animals only by combined treatment with diverse pathogens. Apparently, these morbid changes are due not to one damaging agent but to a “pathogenic constellation”; hence, we called

them "pluricausal cardiopathies." Presumably, "the heart possesses a multitude of safety mechanisms through which it can maintain homeostasis when any one of its chemical systems is overtaxed; it breaks down only when all the alternative pathways that subserve the same function are blocked." (Selye: *The Pluricausal Cardiopathies*, Thomas, Springfield, Ill., 1961.) More recently, we encountered a similar phenomenon in calciphylaxis, which is also an essentially pluricausal morbid lesion, since it depends upon an appropriately spaced treatment, first with a sensitizer, then with a challenger. (Selye: *Calciphylaxis*, The University of Chicago Press, 1962.)

In the same sense, it seems proper to speak of "pluricausal thrombohemorrhagic phenomena" in referring to those vascular accidents that can only be elicited by concurrent treatment with several pathogens. Here—as in the pluricausal cardiopathies and in calciphylaxis—the possibility of "synthesizing" pathogenic situations by treatment with appropriate combinations of chemically and pharmacologically well-characterized drugs may help us to identify the individual mechanisms involved. In any event (as we shall see in Chapter III), by concurrent treatment with several drugs, it has already become feasible to induce selective thrombohemorrhagic lesions at will in one or the other organ. We have also succeeded in preventing the development of such changes under conditions which would normally induce them. Furthermore, it has become evident that a drug (e.g., an adrenergic blocking agent) which prevents one form of pluricausal thrombohemorrhagic phenomenon does not necessarily protect against another. Indeed, an agent which suppresses such lesions in one part of the body (e.g., the skin of the extremities) may actually aggravate their intensity elsewhere (e.g., the kidney). Thus, we have learned to manipulate thrombohemorrhagic phenomena by increasing or decreasing their intensity either throughout the body or only in certain predetermined regions.

Originally, it was only to assist our group in the evaluation and further planning of such experiments that we embarked on the rather forbidding task of coordinating the entire world literature on thrombohemorrhagic phenomena in the form of typewritten notes. However, as our survey progressed it became increasingly more evident that the newly devised experimental models of disease could be used as convenient test objects for the study of many thrombohemorrhagic and collagen diseases of man. We felt, therefore, that this would be an opportune time to publish a systematic treatise on the subject. Perhaps the coordination of the numerous observations on thrombohemorrhagic phenomena—from Botkin's first publication in 1858 to some of our most recent reports—scattered in the journals of so many specialties and printed in so many languages, could help progress elsewhere as well. As I mentioned at the beginning of this Introduction, the thrombohemorrhagic syndromes concern not only experimental pathologists but also internists, dermatologists, allergists, hematologists, bacteriologists, obstetricians and pharmacologists who may not have the time or library facilities necessary to acquire a thorough general orientation in this complex field. If this volume can assist them to some extent in the task of evaluating their findings, it will fulfill its purpose.

GLOSSARY

IN order to avoid unnecessary neologisms, abbreviations and acronyms, we have used only very few technical terms not immediately familiar to any physician. However, it would have been cumbersome to use throughout the text such lengthy expressions as "Sanarelli-Shwartzman phenomenon" or "pluricausal thrombohemorrhagic phenomenon," especially since in both these instances it is also necessary to distinguish between the local and the general forms. Before going any further, the reader is strongly advised, therefore, to peruse this glossary carefully.

Critical period—The time interval that must elapse between the preparatory and provocative injection in order to produce an SSP.

EACA—Epsilon aminocaproic acid.

Fe-OS—Ferric oxysaccharate.

i.c.—intracutaneous or intradermal.

i.m.—intramuscular.

i.p.—intraperitoneal.

i.v.—intravenous.

Liquid—Sodium polyanetholsulfonate.

Preparatory treatment—Shwartzman's term for the initial application of bacterial endotoxins which sensitizes an animal for subsequent provocation.

Provocative or reacting treatment—Shwartzman's term for the application of bacterial endotoxins to elicit an SSP after an appropriate preparatory treatment.

RES—Reticuloendothelial system.

s.c.—subcutaneous.

SSP—Sanarelli-Shwartzman phenomenon. *SSP-L* its local, *SSP-G* its general form.

"SSP"—A thrombohemorrhagic phenomenon which resembles the SSP but is not produced in the classical manner by two appropriately spaced injections of microbial products. "*SSP-L*" its local, "*SSP-G*" its general form.

SSP-active materials—Endotoxins used in the production of an SSP.

THP—Any thrombohemorrhagic phenomenon, irrespective of the causative agent. (The term includes the SSP and pluricausal THP as well as other forms of structurally similar lesions.) *THP-L* its local, *THP-G* its general form.

(For more detailed explanations of these and other less commonly used terms, see Definitions pp. 3-17.)

REVIEWS

ON SSP

- Shwartzman D3,592/30*
Gross D51,461/31
Gonzalez G24,145/32
Shwartzman D7,928/32
Apitz D10,355/33
Cassuto G26,876/33
Carlinfanti G29,348/35
Gerber G24,336/35
Kielanowski G24,146/35
Toscano G25,691/35
Bordet D1,280/36
Shwartzman B19,913/37
Alechinsky D88,312/39
Basile G23,055/41
Plichet G22,423/41
Boquet E51,824/42
Semmola G27,498/44-45
Hernandez B80,084/45
Valbranca G27,043/45
Masson B98,278/48
Shwartzman & Gerber B19,259/48
Lewi G22,702/49
Bennett & Beeson E51,260/50
Shwartzman B63,812/52
Shwartzman G23,251/52
Thomas B92,009/54
Thomas D1,020/57
Stetson E74,348/59
Thiers et al. G28,165/59
Thomas E57,805/59
Thomas D6,152/61
Bernard G27,049/63
Gans D85,447/63
Hardaway & McKay G33,254/63
McKay & Hardaway G33,263/63
Bernard E61,957/64
Illig F37,811/64
Krecke E4,840/64
Hjort & Rapaport G32,971/65
McKay E4,788/65

ON BACTERIAL TOXINS

- Bennett & Cluff G27,224/57*
Thomas D1,020/57
Rosen D15,415/61
McKay E4,788/65

METHODS FOR INDUCING EXPERIMENTAL THROMBOSIS

- Henry G33,285/62*

CONTENTS

| | <i>Page</i> |
|---|-------------|
| <i>Prefatory Remarks on the Style of This Book</i> | v |
| <i>Acknowledgments</i> | xi |
| <i>Introduction</i> | xiii |
| <i>Glossary</i> | xvii |
| <i>Reviews</i> | xix |
| <i>Chapter</i> | |
| I. HISTORY, DEFINITIONS AND TERMINOLOGY | 3 |
| General Overview | 3 |
| First Observations on Microthrombi | 4 |
| Induction of Thrombohemorrhagic Lesions by Bacterial Products | 5 |
| Hemorrhagic Tumor Necrosis | 6 |
| The Sanarelli Phenomenon | 7 |
| The Shwartzman Phenomenon | 9 |
| Terminology of the microbial products that can produce an SSP | 11 |
| Terminology of the SSP and its variants | 11 |
| Definition of the SSP | 12 |
| The Bordet Phenomenon | 13 |
| The Thomas Reactions | 14 |
| The Catecholamine Induced Thrombohemorrhagic Phenomena | 14 |
| Other Experimental Thrombohemorrhagic Phenomena | 15 |
| The antiplatelet serum-induced hemorrhagic syndrome | 15 |
| The Apitz phenomenon | 15 |
| The Arthus phenomenon | 15 |
| The Auer phenomenon | 15 |
| The Masson phenomenon | 15 |
| The McKay phenomenon | 15 |
| The Symeonidis phenomenon | 16 |
| The plasma-transfusion reaction (PTR) | 16 |
| The Reilly phenomenon | 16 |
| The Renaud syndrome | 16 |
| The "Shwartzman-like reaction" | 16 |
| Thrombohemorrhagic Phenomena in Man | 16 |
| Pluricausal Thrombohemorrhagic Phenomena | 17 |

| <i>Chapter</i> | <i>Page</i> |
|---|-------------|
| II. THE THP ELICITED BY MICROBIAL AGENTS ALONE | 18 |
| Single or Variably Spaced Injections | 18 |
| Two Injections Spaced About 24 Hours Apart (The SSP-L and SSP-G) | 20 |
| Methods of Production | 20 |
| Methods of Assessment | 29 |
| The Critical Period | 29 |
| Route of Preparation and Provocation | 32 |
| Dosage | 34 |
| Passive Transfer | 34 |
| III. NONMICROBIAL AGENTS AS ELICITORS OR MODIFIERS OF THE THP | 37 |
| Adjuvants | 37 |
| Species and Genetic Predisposition | 37 |
| Age | 42 |
| Pregnancy | 43 |
| Immune Reactions | 47 |
| Production of THP | 47 |
| Prevention of THP | 53 |
| The RES | 58 |
| Microbial Agents | 58 |
| Nonmicrobial Agents | 61 |
| Factors Influencing Blood Coagulation | 62 |
| Thrombin, Thromboplastin | 63 |
| Heparin | 64 |
| Liquoid (Sodium Polyanetholesulfonate) | 68 |
| Other Heparinoids | 69 |
| Dicoumarol and Related Substances | 69 |
| EACA (Epsilon-aminocaproic Acid) | 70 |
| Antiplatelet Serum | 71 |
| Hormones and Hormone-like Substances | 71 |
| Catecholamines | 72 |
| ACTH, Adrenalectomy and Corticoids | 75 |
| Other Pituitary Hormones and Hypophysectomy | 80 |
| Gonadal Hormones (Female) | 81 |
| Other Hormones | 82 |
| Histamine, Antihistaminics, Histamine Dischargers, Histaminase | 83 |
| Serotonin (5-HT), Antiserotoninins | 85 |
| Bradykinin, Antib Bradykinins, Kallikrein | 85 |
| Other Biologic Materials | 86 |
| Blood | 86 |
| Exudates | 89 |

| <i>Chapter</i> | | <i>Page</i> |
|--|--|-------------|
| Placental extracts | | 90 |
| Amnionic fluid | | 91 |
| Tumor extracts | | 91 |
| Leukocyte extracts, "leukotaxin" | | 92 |
| Extracts of other animal tissues and biologic fluids | | 92 |
| Snake venoms | | 93 |
| Ascaris and liver fluke extract | | 95 |
| Yeast extracts | | 95 |
| Plant pollens | | 95 |
| Nervous Stimuli | | 96 |
| Drugs | | 98 |
| Stress, Physical Agents, Surgical Interventions | | 119 |
| Trauma and Nonspecific Chemical Irritation | | 119 |
| Temperature Variations | | 121 |
| Electricity | | 122 |
| Ionizing Rays | | 123 |
| Ultraviolet rays | | 123 |
| Hemorrhage | | 123 |
| Extracorporeal Circulation | | 124 |
| Nervous Stimulation | | 124 |
| Nephrectomy and Other Renal Operations | | 124 |
| Splenectomy | | 125 |
| Hepatic lesions | | 125 |
| Hysterectomy | | 125 |
| The Hemorrhagic Stress Syndrome of Jaques | | 125 |
| The Pluricausal THPs | | 125 |
| History | | 125 |
| Comparison of Pluricausal THPs and Calciphylaxis | | 130 |
| Comparison of Monocausal and Pluricausal THPs | | 131 |
| The Pluricausal THP-factors | | 132 |
| The Pluricausal THP-L | | 134 |
| The Pluricausal THP-G | | 137 |
| Nonspecific distribution | | 137 |
| Organ specific distribution | | 138 |
| Factors Influencing Pluricausal THPs | | 140 |
| Summary and Classification | | 142 |
| IV. MORPHOLOGIC CHANGES | | 154 |
| Skin | | 154 |
| Blood Count | | 155 |
| Hemopoietic and Lymphatic Organs | | 156 |
| Kidney | | 157 |
| Microbial products alone | | 158 |

| <i>Chapter</i> | | <i>Page</i> |
|---|---|-------------|
| | Nonmicrobial agents alone or in combination with microbial products | 161 |
| | Urinary passages | 163 |
| Lung | | 163 |
| Cardiovascular System | | 164 |
| Single or variably spaced injections of microbial products alone | | 165 |
| Two injections of microbial products spaced about 24 hours apart | | 166 |
| Nonmicrobial agents alone or in combination with microbial products | | 167 |
| Digestive Tract | | 168 |
| Oral cavity | | 168 |
| Stomach and esophagus | | 168 |
| Duodenum, jejunum and ileum | | 169 |
| Appendix | | 169 |
| Colon and rectum | | 169 |
| Liver and Biliary Passages | | 170 |
| Pancreas | | 171 |
| Adrenals | | 171 |
| Nervous System | | 172 |
| Eye | | 173 |
| Ear | | 174 |
| Nose, Tonsil | | 175 |
| Male Sex Organs | | 175 |
| Female Sex Organs | | 176 |
| Joints | | 176 |
| Serosae | | 177 |
| Tumors | | 177 |
| Microbial agents alone | | 178 |
| Yeast and yeast extracts | | 181 |
| Tissue extracts | | 182 |
| Other nonmicrobial agents | | 182 |
| V. CHEMICAL CHANGES | | 184 |
| Body Temperature and BMR | | 184 |
| Carbohydrate Metabolism | | 184 |
| Lipid Metabolism | | 185 |
| Protein Metabolism | | 186 |
| Various Other Metabolites | | 187 |
| SSP-active Substances | | 187 |
| Immune bodies | | 188 |
| VI. FUNCTIONAL CHANGES | | 189 |
| Blood Coagulation | | 189 |
| Single or Variably Spaced Injections of Microbial Products | | 189 |

*Chapter**Page*

| | |
|--|-----|
| Two Injections of Microbial Products Spaced About 24 Hours Apart (the SSP) | 190 |
| Nonmicrobial Agents Given Alone or in Combination with Microbial Products | 193 |
| Thrombin, thromboplastin | 194 |
| Hemorrhage | 194 |
| Liquoid | 194 |
| Various | 195 |
| Vasomotion, Blood Pressure and Capillary Permeability | 195 |
| VII. CLINICAL IMPLICATIONS | 197 |
| Reviews on the General Clinical Implications of the SSP | 197 |
| Infectious Diseases | 197 |
| Various Spontaneous Infections | 199 |
| Focal Infections | 199 |
| The Secondary Syndrome of Chemotherapy | 199 |
| The Malignant Syndrome | 200 |
| The Waterhouse-Friderichsen Syndrome | 200 |
| Typhoid Fever | 202 |
| Scarlet Fever | 202 |
| Rocky Mountain Spotted Fever | 203 |
| Epidemic Hemorrhagic Fever | 203 |
| Leishmaniosis | 203 |
| Cholera | 203 |
| Malaria | 203 |
| Subacute Bacterial Endocarditis | 203 |
| Varicella | 204 |
| Vaccinia | 204 |
| Purpuric Smallpox | 204 |
| Pseudomonas Septicemia | 204 |
| Tuberculosis | 204 |
| Ascaridosis | 204 |
| Hog Cholera | 205 |
| Swine Erysipelas | 205 |
| Mouse-pox | 205 |
| Renal Diseases | 205 |
| Renal Cortical Necrosis | 205 |
| Lower Nephron Nephrosis, Crush Syndrome | 206 |
| Diseases of the Urinary Passages | 207 |
| Nephritis | 207 |
| Diseases of Pregnancy | 207 |
| Obstetrical Hemorrhagic Syndrome in General | 207 |

*Chapter**Page*

| | |
|--|-----|
| Abruptio Placentae | 208 |
| Septic Abortion, Chorioamnionitis, Placentitis | 209 |
| Amniotic-fluid Embolism | 210 |
| Hydatidiform Mole | 211 |
| Eclampsia | 211 |
| The Purpuras | 212 |
| Moschcowitz's Disease | 213 |
| Anaphylactoid Purpura | 215 |
| Symptomatic Afibrinogenemia | 216 |
| Hemorrhagic Thrombocythemia | 216 |
| Purpura Necrotica | 217 |
| Dysproteinemic Purpura | 217 |
| Visceral Thrombophlebitis Migrans | 217 |
| Blood Dyscrasias | 217 |
| Polycythemia Vera | 218 |
| Leukemia | 218 |
| Sickle Cell Disease | 218 |
| Acquired Hemolytic Anemia | 218 |
| Dermatoses (Other than Purpuras) | 218 |
| Pemphigus | 218 |
| Herpes | 219 |
| Dermatitis Nodularis Necrotica | 219 |
| Eczema | 219 |
| Pyoderma | 219 |
| Acrodynia | 219 |
| Various Other Dermatoses | 219 |
| Diseases of the Digestive Tract | 220 |
| Oral Cavity | 221 |
| Peptic Ulcer, Hemorrhagic Duodenitis | 221 |
| Gastroenteritis and Infantile Diarrhea | 221 |
| Intestinal Gangrene | 221 |
| Ulcerative Colitis | 222 |
| Pseudomembranous Enterocolitis | 222 |
| Appendicitis | 223 |
| Immunological Diseases | 223 |
| Blood Transfusion | 224 |
| Vaccination | 224 |
| Paroxysmal Hemoglobinuria | 224 |
| Collagen Diseases | 224 |
| Rheumatic Fever | 225 |
| Lupus Erythematosus | 226 |

Chapter

| | <i>Page</i> |
|--|-------------|
| Periarteritis Nodosa | 226 |
| Raynaud's Disease | 227 |
| Buerger's Disease | 227 |
| Collagenoses in General, "Systemic Fibrinoid Disease" (Including Malignant Hypertension) | 227 |
| Hyperparathyroidism | 229 |
| Pancreatitis | 229 |
| Tumors | 230 |
| Various Other Diseases | 231 |
| Thrombosis of Large Vessels | 232 |
| Shock | 232 |
| Intussusception | 232 |
| Menstrual Bleeding, Metrorrhagia | 233 |
| Diabetes Mellitus | 233 |
| Lipid Embolism | 233 |
| Liver Cirrhosis | 233 |
| Favism | 233 |
| Diseases of the Eye | 233 |
| Diseases of the Ear | 233 |
| Hemorrhagic Leukoencephalitis | 233 |
| Agammaglobulinemia | 233 |
| VIII. THEORIES | 234 |
| Allergic-immunologic Reactions | 234 |
| Allergic-immunologic Phenomena in General with Special Reference to Anaphylaxis | 234 |
| The Arthus Phenomenon | 236 |
| The Auer Phenomenon | 238 |
| Forssman Antigen and Antibody, Anaphylatoxin | 239 |
| Blood Coagulation | 239 |
| The Vascular Factor | 245 |
| The Nervous Factor | 248 |
| The Reilly Phenomenon | 250 |
| The RES | 251 |
| Leukocytes | 255 |
| The Kidney | 258 |
| Stress | 258 |
| Lipids | 260 |
| Enzymes | 261 |
| Catecholamines | 261 |
| Histamine, Serotonin, Antiserotonin, Bradykinin, Antibradykinin, Kallikrein | 262 |

| <i>Chapter</i> | | <i>Page</i> |
|---|--|-------------|
| The Mast Cells and Anaphylactoid Inflammation | | 262 |
| The Possible Defensive Value of the THP | | 263 |
| Nonspecific Mesenchymal Reaction | | 264 |
| Localization of Bacterial Endotoxin | | 264 |
| Various Other Theories | | 265 |
| Smooth Muscle Products | | 265 |
| Erythrocytes | | 265 |
| Histamine | | 266 |
| Mast Cells | | 266 |
| Collagen | | 266 |
| Glucose Metabolism | | 266 |
| Physicochemical Changes | | 266 |
| <i>References</i> | | 267 |
| <i>Index</i> | | 321 |

THROMBOHEMORRHAGIC PHENOMENA

CHAPTER I

HISTORY, DEFINITIONS AND TERMINOLOGY

General Overview. The first observations that helped to develop our present-day concept of the thrombohemorrhagic phenomenon (THP) go back to about the middle of the nineteenth century. Most of these early findings were made accidentally in connection with investigations on very diverse subjects. This circumstance has considerably delayed the development of relevant knowledge because it is difficult to trace and collect such scattered data for orderly arrangement into a system that would reflect the correlations that may exist between them.

The concept that a great many, apparently quite unrelated, agents can produce thromboses and hemorrhages located predominantly in and around small blood vessels has drawn material mainly from the following findings:

1. Accidental observation of *microthrombi* in certain spontaneous or experimentally induced morbid lesions.
2. Certain *microorganisms* and even extracts prepared from them are especially prone to produce thromboses and hemorrhages in the microcirculation, particularly in the renal glomeruli.
3. *Hemorrhagic tumor necrosis* sometimes conducive to complete involution of the neoplasms can occur under the influence of microbial products.
4. The *Sanarelli phenomenon*, induced by two properly spaced i.v. injections of microbes or their products.
5. The *Shwartzman phenomenon*, induced by a "preparatory" i.c. injection of bacterial filtrates, followed after a proper time interval by i.v. "provocation" with the same or some similar material.
6. The *Bordet phenomenon*, the production of hemorrhages and necroses by killed *E. coli* cultures in tuberculous but not in normal guinea pigs.
7. The two *Thomas reactions*: 1. Production of bilateral cortical necrosis by a single i.v. injection of bacterial endotoxin after pretreatment with a glucocorticoid; 2. Development after ACTH pretreatment of petechial hemorrhages at endotoxin-pretreated skin sites (without i.v. provocation).
8. Production of *hemorrhagic necrosis at epinephrine-treated skin sites* after infections or upon concurrent i.v. administration of a bacterial endotoxin.
9. The appearance of thrombohemorrhagic lesions in the course of various *classic immune reactions*, such as, the Arthus phenomenon, the Auer phenomenon, the i.v. administration of antiplatelet serum and plasma transfusion reactions.
10. The *experimental induction of thrombohemorrhagic lesions by various other agents* such as:

Desoxycorticosterone + renin NaCl (Masson phenomenon);
Progesterone administration during pregnancy (Symeonidis phenomenon);

- Feeding, during pregnancy, of a vitamin-E deficient diet supplemented by oxidized lipids (McKay phenomenon);*
High-fat diets supplemented by cholic acid (Renaud phenomenon);
Plasma transfusion reactions (PTR);
Stimulation of the sympathetic nervous system (Reilly phenomenon).

11. The *nonspecific pluricausal thrombohemorrhagic phenomena* (pluricausal THPs), produced by concurrent treatment with certain simple chemical compounds (e.g., metals, RES-blocking agents, tannic acid, mast-cell dischargers) i.v., and catecholamines or serotonin s.c. Using appropriate combinations of such agents, it became possible to localize the thrombohemorrhagic lesions, often with great selectivity, in certain organs (e.g., the adrenals, the anaphylactoid shock organs or the duodenum).

12. The realization that in several *spontaneous diseases of man* (Moschkowitz's disease, typhoid fever, eclampsia, missed abortion, septic abortion, hemoglobinuric nephrosis, etc.) lesions similar to, if not identical with, those of the Sanarelli and Shwartzman phenomena play a decisive role.

13. The discovery that certain pharmacologic substances (heparin, dibenamine, cyproheptadine), dietary measures, pregnancy, specific surgical interventions (transection of nerves, adrenalectomy) and exposure to stress can *increase, decrease, or alter the distribution of THPs at will*. (For the extensive literature concerning the latter point, cf. Chapter III.)

First Observations on Microthrombi. More than a century ago the Russian investigator Botkin (1858) discovered that, following application of irritating fluids to the frog mesentery, the capillaries become maximally dilated and packed with agglutinated erythrocytes so that the circulation stops. These observations were confirmed and greatly extended by Hueter (1874), who claimed that erythrocyte agglutination is caused by toxic substances many of which make the surface of the red blood corpuscles irregular and adhesive. The resulting large erythrocyte aggregates may allegedly even cause embolisms in distant organs.

Multiple hyaline thrombi in the smallest blood vessels were apparently first observed by Klebs (1876) in patients with extensive burns. Then Flexner (1902) noted that both bacterial and nonbacterial pathogens can produce so-called "agglutinative thrombi" which appear to consist almost exclusively of conglutinated erythrocytes; they greatly dilate the small blood vessels and may eventually become hyalinized. Subsequently, microthromboses were seen after i.v. administration of foreign blood, snake venom, placental extracts and many other substances.

Finally, Siegmund (1925) observed the development of minute fibrin nodules attached to the walls of the small veins or the endocardium in guinea pigs repeatedly infected with various microorganisms. These nodules become covered with endothelium and are then organized by invading connective tissue.

Botkin G20,883/1858: First description of what later became known as "erythrocyte agglutination thrombi." By applying 15% NaCl to the frog mesentery, the capillaries become dilated and packed with agglutinated erythrocytes so that the circulation stops. Sim-

ilar results are obtained with other inorganic salts and concentrated sugar or urea solutions. The phenomenon is ascribed to deformation and consequent adhesiveness of the erythrocytes.

Hueter G24,671/1874: Upon topical treatment with ammonia, glycerin, chloroform or phenol, the capillaries of the frog mesentery and skin become engorged with closely packed and partially deformed erythrocytes. This erythrocyte stasis ("globulöse Stase") may be followed by the loosening of entire erythrocyte cylinders which can then cause microembolisms ("globulöse Embolie") in other organs (e.g., the lung). The process is ascribed to primary erythrocyte damage which makes the surface of the red blood corpuscles irregular and sticky. A few observations on rabbits and man suggest that erythrocyte embolism may also occur in mammals and have clinical significance.

Landois D18,258/1875: First description of the fact that injection of foreign blood causes multiple capillary thromboses.

Klebs A71,439/1876: This is apparently the first observation of multiple hyaline thrombi in the small vessels. They were observed in patients who suffered extensive burns.

Flexner E76,861/02: Agglutination of erythrocytes *in vivo* can occur in various infectious diseases of man and animals, in eclampsia, and after i.v. injection of ricin, ether, or dog's serum into rabbits. Such "agglutinative thrombi" were first observed in a vessel of the ileum in a patient who died of typhoid fever. "The vessel was quite occluded by a conglutinated mass made up of globules of different sizes showing different degrees of refraction and varying staining properties. Careful study readily supplied the conviction that the mass was composed of red corpuscles, altered in form, adhesiveness, and staining properties. . . . When such thrombi are old, or when the agglutination is compact, they may present appearances to which the name of 'hyaline thrombi' has been applied." The "hyaline glomerular thrombi occurring in the kidney in infectious diseases" as well as microthrombi in glaucoma and pulmonary infarction may have a similar origin.

Induction of Thrombohemorrhagic Lesions by Bacterial Products. In the course of their classic studies on diphtheria, Roux and Yersin (1888) found that single i.v. injections of diphtheria toxin can produce multiple hemorrhages, particularly in the lung, kidney, adrenal and heart of various experimental animals. Shortly afterwards, Welch and Flexner (1891) noted that this syndrome is associated with the formation of hyaline thrombi in the renal glomerular capillaries. These observations were repeatedly confirmed during the first part of the twentieth century. It became evident, furthermore, that even killed microbes or microbial filtrates are active in this respect and that the predominant localization of the thrombohemorrhagic lesions varies, depending upon the type of pathogenic material used. The kidney, lung, heart and adrenals are most commonly affected but, under certain circumstances, typical lesions may also be found in the gastrointestinal tract or on the hairless parts of the animal body.

Pearce & Winne D82,989/04: Erythrocyte-aggregation thrombi, due to "clumping of red blood corpuscles causing permanent or transient occlusion of capillaries and small vessels," occur in man during certain infections. Similar changes have been reproduced experimentally in dogs and rabbits by the injection of typhoid, hog-cholera and dysentery bacillus filtrates. The thrombi are localized predominantly in the liver, but have also been seen in the kidney, spleen, lymph nodes and other organs. They are presumably initiated by bacterial hemagglutinins but gradually transform themselves into hyaline masses and may be associated with local necrosis.

Pearce D82,984/09: After a survey of the earliest publications on the production of hemorrhages by snake venoms, the author describes hemorrhagic lesions with fibrin deposition in the glomeruli of rabbits given the venom of *Crotalus adamanteus* i.v.

Obata 32,524/19: A thrombohemorrhagic syndrome can be produced in rabbits and Japanese dancing mice by the i.v. injection of an extract of human placenta. The changes are similar to those of eclampsia which are attributed to intoxication with placental products.

Siegmund E53,775/25: First description of the experimental production of fibrin nodules ("Fibrinknötchen") in the small veins of the liver, spleen and lung, as well as in the endocardium of rabbits and guinea pigs repeatedly infected with *B. coli*, *B. typhosus*, *staphylococci*, *pneumococci* and other germs. Similar venous nodules were previously observed in patients suffering from typhoid fever. Morphologically, they consist of fibrin and connective tissue protruding mushroom-like into the lumen and covered by an endothelium. (They are presumably closely related to the capillary fibrin thrombi previously described by Kusama C70,497/13.)

Roux & Yersin G23,900/1888: Live diphtheria bacilli injected i.v. into rabbits produce general dilatation of the blood vessels with hemorrhages into the peritoneum. "The kidneys are intensely congested and almost black in color. The blood does not coagulate normally." Hemorrhages are occasionally also seen in other organs.

Roux & Yersin 7,004/1889: Single injections of diphtheria toxin i.v. produce multiple hemorrhages, particularly in the lung, kidney, adrenal and heart of the guinea pig, dog and rabbit.

Welch & Flexner C41,966/1891: In guinea pigs, rabbits and kittens infected with live diphtheria bacilli, multiple hemorrhages occurred in the adrenals and lungs. In the renal glomeruli, "hyaline substance was found completely filling the lumen of some capillaries."

Heyrovsky G23,661/07: In mice treated with single or multiple i.p. or s.c. injections of filtrates of *Streptococcus mucosus* (designated as "Stojan's strain"), there develops "especially in the naked parts of the body (ears, paws, tail, snout, genitals), a localized hemorrhagic exanthema in the form of livid flat or slightly elevated round or irregularly circumscribed, often confluent efflorescences." The hairy parts of the skin are not affected, except where the filtrate was injected and where the skin was mechanically traumatized. There is also bloody diarrhea with hemorrhages in the palate, lungs, intestine and urinary bladder, enlargement of the spleen and hyperemia of the kidney. Histologically, the hemorrhagic regions show signs of inflammation. The condition is considered to be an experimental equivalent of the purpuric types of septicemia seen in man.

Kraus & von Stenitzer G22,369/09: Single i.v. injections of typhoid endotoxin can produce multiple internal hemorrhages in the rabbit. This syndrome is nonspecific since it is also noted in cholera and dysentery.

Arima G22,331/12: Multiple hemorrhagic necroses, especially in the intestine, and glomerulonephritis with "homogenization" of the glomerular capillaries can be obtained not only by live typhoid bacilli, but also by single or

repeated injections of typhoid endotoxin in the rabbit and goat.

Kusama C70,497/13: In rabbits given two i.v. injections of heat-killed typhoid bacilli with a 24-hr. interval, hemorrhages and fibrin thrombi appeared in various organs including the duodenum, thymus, heart, mesenteric lymph nodes, liver and lungs but, curiously, no thrombi were noted in the kidneys. [SSP-G? (H.S.).]

Frothingham 86,100/14: Single injections of diphtheria toxin i.v. or s.c. produce adrenal hemorrhages, centrolobular necroses in the liver and fibrin deposition in the renal glomerular capillaries of the rabbit. The renal arterioles show necrosis with fibrin formation and diapedesis of erythrocytes. The tubular epithelia, likewise, exhibit necrosis. Essentially similar changes are seen in guinea pigs given large doses of diphtheria toxin.

Olitsky & Kligler D81,601/20: A single i.v. injection of *B. Shiga* endotoxin causes edema, hemorrhages, necroses and ulcerations in the large intestine of rabbits.

Belonovsky E98,228/25: In guinea pigs and mice inoculated i.p. with various bacterial cultures which cause a low grade chronic inflammation, the subsequent s.c. injection of a vaccine of the same or related microbes elicits an often hemorrhagic exudative peritoneal response at the original inoculation site. [Shwartzman reaction? (H.S.).]

Duval & Hibbard G22,333/26: In rabbits, *S. scarlatinae* endotoxin i.v.—"induced nephritic lesions analogous in kind and variety to those of acute scarlatinal nephritis in man, including the 'epithelial crescent' formation, hyaline thrombi of glomerular capillaries, hemorrhage into capsular space and necrosis of capillary tufts."

Julianelle & Reimann D88,216/26; Reimann & Julianelle D93,175/26: Following s.c., i.p., or i.v. injection of pneumococcus extracts, hemorrhages (apparently unaccompanied by anaphylactoid inflammation) were observed in the feet, ears, snout and tail of the mouse. Somewhat similar lesions with a slightly different distribution were noted in guinea pigs and rabbits.

Hemorrhagic Tumor Necrosis. William B. Coley (1891) observed that a patient with an inoperable sarcoma of the neck recovered after two attacks of erysipelas. On searching the literature, he could trace several still earlier case reports recording the regression of inoperable malignant tumors under the influence of infections. With singular dedication he devoted his entire life to the study of this phenomenon and eventually developed a mixture of *S. marcescens* and erysipelas toxin (which became known as "Coley's fluid") for the treatment of malignancies in man. Allegedly, a number of successes were achieved with this and similar

preparations. However, in order to obtain an occasional cure, highly toxic and often fatal amounts of the microbial products had to be injected repeatedly and, as a rule, directly throughout the neoplastic tissue. This was rarely feasible; hence, "Coley therapy" was eventually abandoned. In any event, these early observations furnished no clear-cut evidence of thrombohemorrhagic lesions.

Some forty years later, several investigators stimulated by Coley's work administered *S. marcescens* filtrates and many other endotoxins to rodents bearing tumor transplants. They found that hemorrhagic necrosis of the neoplasms could be induced by single injections of such materials even if administered i.v. or i.p. at a distance from the tumors. Since, meanwhile, Shwartzman had described his phenomenon, it was thought that the tumor tissue is permanently in a state of "preparation" so that it reacts with the typical hemorrhagic response to "provocation" by bacterial products.

Coley G21,530/1891: Review of the early history of the treatment of sarcomas by infection with erysipelas. Report on several additional successfully treated patients. Inoculations were usually made into the tumor itself. There is no clear-cut evidence of hemorrhagic necrosis although many neoplasms involuted completely.

Coley G21,838/1894: The curative action of erysipelas upon malignant tumors is confirmed. The author prepared "soluble toxins of the erysipelas streptococcus" and found that these (especially upon addition of toxins from *Bacillus prodigiosus*) were as effective as infection with live erysipelas streptococci. [This is the first formal description of what later became known as "Coley's fluid" (H.S.).]

Shear G20,191/35: Review of the early history concerning the induction of hemorrhagic

necrosis in tumors by infections and bacterial products. The first observations go back to 1882 and many additional reports appeared during the nineteenth century.

Nauts et al. E46,085/53: Detailed description of the studies of William B. Coley.

Perrault & Shear C4,405/55: The hemorrhagic necrosis induced in various transplantable tumors by a single i.p. injection of polysaccharides, extracted from various tumors or normal tissues as well as by bacterial endoxins, is considered to be a manifestation of the SSP. [Unlike the classical SSP, here the material need not be given in two injections nor be derived from microorganisms. Hence, "Shear's phenomenon" does not correspond to Shwartzman's own definition of the Shwartzman phenomenon (H.S.).]

The Sanarelli Phenomenon. In 1894, Sanarelli noticed that, in the monkey, a first injection of typhoid toxin causes only transient manifestations of disease, but if, two days later, a second injection of the same product is administered, the animal dies with a generalized purpuric eruption. This observation remained virtually unnoticed until 1916, when the same investigator, in the course of studies on the mechanism of the algid stage of cholera, discovered the phenomenon which now bears his name. He found that, if live *E. coli* cultures are injected into the appendix of the rabbit a few hours after the oral administration of cholera vibrios, hemorrhagic lesions appear in the intestines. The same result was obtained by filtrates of *E. coli* given i.v. after such pretreatment, but neither *E. coli* nor cholera vibrios alone were effective.

Subsequently, Sanarelli (1923-24) observed in rabbits that the i.v. injection of a nonlethal dose of *V. cholerae*, followed 24 hrs. later by the administration of a small amount of *E. coli* toxin, causes severe shock associated with hemorrhages in the internal organs. These were accompanied by desquamation of the epithelia of the urinary bladder, gallbladder, and intestinal mucosa; hence, he named this phenomenon "epithalaxis" (desquamation of epithelia).

Zdrodowski and Brenn (1925) repeated and extended Sanarelli's observations,

showing that the phenomenon can also be elicited by two i.v. injections of *E. coli* endotoxin, as well as by the toxins of other organisms, as long as they are given i.v. with a 24-hr. interval.

In his later publications, Sanarelli emphatically insisted that the phenomenon subsequently described by Shwartzman was virtually identical with his "epithalaxis."

Sanarelli D95,751/1894: First observation of what is now considered to be the SSP-G. In the monkey, a first injection of typhoid toxin causes only transient toxic manifestations, but if, two days later, a second injection of the same product is administered, the animal dies with a generalized purpuric eruption.

Kusama C70,497/13: In rabbits given two i.v. injections of heat-killed typhoid bacilli with a 24-hr. interval, hemorrhages and fibrin thrombi appeared in various organs, including the duodenum, thymus, heart, mesenteric lymph nodes, liver and lungs but, curiously, no thrombi were noted in the kidneys. [SSP-G? (H.S.)]

Sanarelli G26,194/16: Oral administration of cholera vibrios produces no cholera in normal rabbits because the germs are digested during their passage through the stomach. However, if the rabbits were given an i.v. injection of *E. coli* endotoxin before being fed cholera vibrios, the latter become pathogenic. [Here, no mention is made of thrombohemorrhagic lesions (H.S.).]

Sanarelli D89,454/16: If live *E. coli* cultures are injected into the appendix of the rabbit a few hours after the administration of cholera vibrios p.o., the manifestations of cholera are elicited in the intestines. The same result is obtained by *E. coli* filtrates i.v. after such pre-treatment. Yet, neither *E. coli* nor cholera vibrios alone reproduces this phenomenon.

Sanarelli E63,717/23: In rabbits given live cholera vibrios i.v., the subsequent injection of proteus or *E. coli* endotoxin i.v. elicits severe shock with desquamation of the intestinal, urinary-bladder and gallbladder epithelia, and associated hemorrhages. The phenomenon is called "epithalaxis" (desquamation of epithelia).

Sanarelli B78,422/24: "If in adult rabbits, about 24 hrs. after the intravenous injection of a non-lethal dose of cholera vibrios, a small quantity of colitoxin or proteotoxin is given intravenously, there often develops a violent crisis which is probably anaphylactic and causes death either suddenly or after a few hours." This crisis is associated with nephritis and desquamative enteritis. There is also desquamation of the epithelium in the urinary bladder and gallbladder.

Zdrodowski & Brenn G23,064/25: Since it is possible to elicit the Sanarelli phenomenon without the use of cholera vibrios by two, in themselves ineffective i.v. doses of *E. coli* endotoxin (given with a 24-hr. interval), the syndrome is designated as a "paracholera phenomenon."

Sanarelli G26,880/26: If an i.v. injection of *V. cholerae* is followed by *E. coli* or *Proteus vulgaris* filtrates i.v., the phenomenon of epithalaxis is elicited.

Zdrodowski & Brenn D70,620/26: Confirmation and extension of Sanarelli's experiments. I.v. injection of *E. coli* followed 24 hrs. later by *E. coli* toxin i.v. produces a typical Sanarelli phenomenon. Even oral administration of *E. coli* can act as a sensitizer if large enough doses are administered. The phenomenon is evidently nonspecific since it can be produced by *E. coli* followed by *coli* toxin, *B. proteus* followed by *proteus* toxin or *V. cholerae* followed by either *coli* or *proteus* toxin. Excellent and detailed description of the morphologic changes associated with the Sanarelli syndrome.

Gratia & Linz G23,076/33; G23,092/33: The SSP is considered to be a manifestation of anaphylaxis because: 1) as in anaphylaxis, it is accompanied by capillary stasis, hypotension, thrombopenia and incoagulability of the blood; 2) rabbits and guinea pigs, which are highly sensitive to anaphylaxis, are also most susceptible to the SSP; 3) the SSP desensitizes against serum shock in proportion to the intensity of its manifestations. Hence, it is suggested that the SSP be designated "hemorrhagic allergy" and, when elicited by nonspecific means, "hemorrhagic heteroallergy." In this sense, the SSP "could be only a variant of the Arthus phenomenon and indeed identical with the latter as regards its manifestations."

Sanarelli G23,516/37: The author reviews the historic development of our knowledge of the SSP and concludes that "concerning the question of my absolute priority, there can be no discussion that this reaction should be described as the 'Sanarelli phenomenon.' At best, the cutaneous form could be designated as the 'Sanarelli-Shwartzman phenomenon.'"

Sanarelli G22,253/38: Attention is called to the first description of "hemorrhagic allergy"

by the author in 1916. "To produce and study the phenomenon in question, all authors have invariably employed the method which we have proposed from the beginning of our experiments, a method to which sometimes, evidently in good faith, a false paternity was attributed. For example, certain authors have ascribed it erroneously to Shwartzman, who applied and studied it a dozen years after our first publications. Yet, it is a fact that the authors who experimented after us have only varied the preparatory or provocative antigens

according to the circumstances. Usually, they employed the antigens which we have recommended, namely filtrates of cultures of *E. coli* or *B. proteus*."

Vanni G22,353/38: The reaction should be called "Epithalaxis" or the "Sanarelli phenomenon."

Alechinsky D88,312/39: Survey of the history of the SSP.

Sanarelli G28,164/39: Vigorous defense of Sanarelli's priority in the discovery of the SSP.

The Shwartzman Phenomenon. In 1928, Shwartzman discovered that, if a rabbit is given a *B. typhosus* filtrate i.c., followed by the i.v. injection of the same material 24 hrs. later, a hemorrhagic necrosis results at the prepared skin site. This report, published in the April number of the *Proceedings of the Society for Experimental Biology and Medicine*, was followed two months later, in the same journal, by a paper in which Hanger reported on the development of the same phenomenon in rabbits treated in exactly the same manner with a filtrate of *B. lepisepticum*. In addition, Hanger noticed the relative nonspecificity of this lesion; i.c. injection of *B. lepisepticum* or *E. coli* prepared the skin so that it also reacted with hemorrhagic necrosis upon the i.v. injection of various other bacterial filtrates, as long as these were given 24 hrs. later.

It may be assumed that both Shwartzman and Hanger were unaware of Sanarelli's earlier publications, since neither cited the Italian investigator's work. It is evident, furthermore, that Hanger could not have known of Shwartzman's paper since it was in press at the time Hanger submitted his manuscript. It must be admitted that the phenomenon observed by Shwartzman and Hanger is essentially a local variant of the Sanarelli phenomenon. This fact appears to have been subsequently recognized by Shwartzman, since in his later papers he referred to the topical lesions (elicited by i.c. preparation) as the local, and the systemic lesions (induced by i.v. preparation) as the general variant of the same phenomenon. However, despite the close relationship implied by this terminology, Shwartzman continued to regard the Sanarelli phenomenon as essentially distinct because the Italian investigator used live organisms for preparation. On the other hand, Zdrodowski and Brenn (1926), who were the first to produce a general phenomenon by two i.v. injections of *E. coli* endotoxin, looked upon their experiment as a mere modification of the procedure for the elicitation of the Sanarelli phenomenon.

The development of our knowledge concerning the induction of thrombohemorrhagic lesions by bacterial products has been reviewed in the preceding pages at some length because of its historic interest. From this survey, it appears that the production of a THP by bacteria, their toxins and even by nonbacterial materials goes back to the nineteenth century. The chief merit of Sanarelli, Zdrodowski, Brenn, Shwartzman and Hanger was to establish that such lesions are most readily produced if there is an interval of 24 hrs. between what have come to be known as the "preparatory" and the "provocative" injections.

This being said, it should be emphasized, however, that the work of Sanarelli

and Shwartzman has given the greatest impetus to the development of this whole field. In recognition of this fact and in conformity with common usage, we shall, therefore, refer to the THP elicited by two properly spaced injections of bacterial products as the Sanarelli-Shwartzman phenomenon (SSP), distinguishing between the general variant (SSP-G) or Sanarelli phenomenon and the local variant (SSP-L) or Shwartzman phenomenon.

Both Sanarelli and Shwartzman insisted that their phenomena are produced by the correctly spaced administration of two injections of microbial products; yet, recent investigators have referred to thrombohemorrhagic lesions produced by any means (even to those elicited by single injections of nonbacterial products!) as the Sanarelli-Shwartzman phenomenon. This lax terminology has created considerable confusion, and has interfered with the proper etiological classification of lesions with similar structural characteristics but induced by wholly distinct mechanisms. Such an identification of morbid changes merely because of their morphologic similarity is unwarranted; it would handicap the progress of research on the THP just as much as the identification of all hemorrhages with hemophilia or of all renal calculi with hyperparathyroidism would block progress in these fields. Consequently, we shall refer to thrombohemorrhagic phenomena (THP) in general as such, without identifying them with any one variant of the group, reserving the terms SSP-L and SSP-G for the two hitherto most carefully studied variants within this large class.

A great many indices have been proposed for the *diagnosis* of the SSP and its variants. In general, microthrombi and hemorrhages are considered to be most characteristic both of the SSP-L and of the SSP-G. Among the organ lesions typical of the latter variant, hyaline thrombi in the renal glomerular capillaries should be mentioned first because of their almost constant presence following two properly spaced i.v. injections of active bacterial filtrates. On the other hand, in view of what we have just said and contrary to the opinion of many investigators, these hyaline thrombi cannot be regarded as pathognomonic: they also occur after single treatments with nonbacterial products, and conversely it is possible to obtain thrombohemorrhagic lesions in other organs without renal participation. Essentially the same criticism applies to the suggestion that renal cortical necrosis be regarded as the pathognomonic feature of the SSP-G.

Numerous *synonyms* have been suggested for the SSPs, their variants and the microbial product responsible for eliciting them. This practice has caused considerable confusion, and the subject will be dealt with separately on pp. 11ff.

Hanger B78,181/27-28: A typical SSP-L is produced by i.c. injection of *B. lepisepticum* filtrate followed 24 hrs. later by i.v. injection of the same material. The reaction is non-specific since i.c. injection of *B. lepisepticum* or *colon bacillus* reacts similarly when a variety of filtrates are given subsequently i.v.

Shwartzman D71,756/27-28: *B. typhosus* culture filtrate i.c. followed by the i.v. injection of the same material 24 hrs. later resulted in a local hemorrhagic necrosis of the prepared

skin site in about 78% of the rabbits. Repeated injections of the filtrate into the same skin area with an interval of 24 hrs. did not result in a comparable hemorrhagic necrosis. Topical irritation by turpentine i.c. failed to prepare the skin for the subsequent i.v. injection of *B. typhosus* filtrate. [This is the first description of what has come to be known as the Shwartzman phenomenon (H.S.).]

Shwartzman E41,370/28: First detailed de-

scription of the "phenomenon of local skin reactivity to *B. typhosus* culture filtrate."

Shwartzman D3,592/30: The SSP-L is described as "a new immunological phenomenon."

Apitz D10,355/33: Topical hemorrhagic necroses induced in rabbits by *B. lepisepticum* filtrate i.c. results in hemorrhagic necrosis of the prepared skin site after i.v. injection of the same material. This response, which is essentially the same as the SSP-L but was described independently by Hanger, is designated "Hanger's phenomenon." Allegedly "there is but one fundamental difference between Hanger's and Shwartzman's reaction and that is the frequent occurrence of a primary allergy [a strong inflammatory edematous reaction at the site of preparation (H.S.)] against the filtrates of *B. lepisepticum*."

Apitz E60,538/35: "Shwartzman injected a local skin area, which developed hemorrhage and necrosis after the intravenous administration of filtrate. Sanarelli infected rabbits intravenously with *V. cholerae*; when, 24 hrs. later coli-filtrate was given by the same route, the animals died in a hypothermic, protracted shock. Intense hemorrhages were found in the same regions where the injected organism had accumulated. Finally, Gratia and Linz modified this experiment by using coli-filtrate for the first intravenous injection as well." The visceral form resembles the cutaneous type in its structural manifestations; hence, it is proposed to call it "the generalized Shwartzman phenomenon."

Shwartzman B19,913/37: "The phenomenon described here is termed as the 'phenomenon of local skin reactivity to bacterial filtrates,'

when the preparatory injection is made into the skin; or as the 'phenomenon of local tissue reactivity to bacterial filtrates,' when the preparatory injection is made into other tissues or organs. Elicitation of the state of reactivity by means of a local injection into the skin or other tissues and organs of a potent bacterial filtrate is termed as 'preparation' and the factors capable of eliciting this state are respectively called 'preparatory' factors." It is considered characteristic of the reaction that an interval (optimally of 24 hrs.) must elapse between the preparatory and the provocative injections.

Thomas & Good B79,249/52: "The first injection will be referred to as the 'preparing' dose of toxin. . . . The second injection of toxin will be designated the 'provoking' or 'challenging' dose. The term 'generalized Shwartzman reaction' will be used to apply to animals which developed bilateral cortical necrosis of the kidneys."

Terminology of the microbial products that can produce an SSP

Thomas B92,009/54; D1,020/57: "The endotoxins of various microorganisms, although consisting of basically similar material, are variously known as 'toxic antigens,' 'somatic antigens,' 'polysaccharide toxins,' 'tumor-necrotizing toxins,' 'Boivin antigens' or 'Boivin glucolipid toxins,' 'shock-producing toxins,' or 'Shwartzman-active toxins.'" In the physiological literature they are commonly referred to as "bacterial pyrogens." Yet, "although different preparations may differ in potency, the effects of different endotoxins are qualitatively indistinguishable."

Terminology of the SSP and its variants. (The common terms "*Sanarelli phenomenon*," "*Shwartzman phenomenon*" and "*Sanarelli-Shwartzman phenomenon*" require no further comment. Here, we shall merely list a few less currently employed designations.)

Sanarelli E63,717/23; B78,422/24; Amantea 43,781/33: "*Epithalaxis*" is the term recommended for the SSP-G because of the associated desquamation of surface epithelia in various organs.

Zdrodowski & Brenn G23,064/25: Sanarelli's observations on the lethal effect of *E. coli* endotoxin in rabbits infected with cholera vibrios are confirmed. However, since two i.v. injections of *E. coli* endotoxin (given with a 24 hr. interval) can elicit the same changes without the use of cholera vibrios, the phenomenon is designated as a "*paracholera phenomenon*."

Zdrodowski & Brenn D70,620/26: Because of its similarity, but non-identity, with anaphylaxis, the phenomenon now known as SSP-G is designated as "*Sanarelli's anaphylactoid phenomenon*."

Gratia & Linz D6,544/32; Sanarelli G22,253/38; Vanni G22,353/38: The term "*hemorrhagic allergy*" ("allergie hémorragique") is recommended as a generic designation for the Sanarelli and Shwartzman phenomena.

Rössle G20,889/33: The term "*pathergy*" is proposed as a class name "for all the morbid manifestations which are due to an altered

reactivity." The term is meant to cover various forms of allergy as well as the SSP, the hemorrhagic necrosis elicited by epinephrine following infections, etc.

Kielanowski & Selzer D71,895/35: Since the SSP is not a true allergy, it is designated as "hemorrhagic heteroallergy."

Bordet B78,032/36: The term "nonspecific allergy" is recommended for all SSP-like phenomena elicited nonspecifically by a variety of bacterial toxins in animals pretreated with a given infectious agent or vaccine.

Renaux & Alechinsky G18,585/36: The term "angiorrhesis" is proposed for the SSP-G and -L in order to emphasize that a rupture in the continuity of the vascular walls is a common manifestation of both the general and the local variety.

Horster G22,366/38: For historic reasons, the author recommends the term "Sanarelli-Shwartzman-Hanger phenomenon (SSH)."

Rössle G17,852/46: The term "nonspecific hemorrhagic pathergy" is proposed for both variants of the SSP because they represent pathologic reaction forms, characterized by hemorrhage.

Definition of the SSP. The SSP is generally defined as a thrombohemorrhagic lesion elicited by two properly spaced injections of certain bacterial endotoxins. The local variant is obtained by introducing the first (preparatory) injection directly into the tissue in which the reaction is to be obtained, usually the skin, while the generalized variant is induced by i.v. preparation. In both instances, the second (provocative) injection is given i.v.

The morphologic characteristics of the SSP-lesions are not very specific: in the SSP-L they consist of thromboses and hemorrhages at the site of preparation, while in the SSP-G these lesions are disseminated, affecting the kidneys, lung, gastrointestinal tract, spleen and other organs. Most investigators consider renal capillary fibrin or fibrinoid thromboses, with or without renal cortical necrosis, to be pathognomonic for the SSP-G, but this view is not unanimously accepted since, in rare instances, the extrarenal manifestations of the SSP-G may be quite characteristic although renal glomerular capillary thromboses are absent.

Smith et al. B82,232/53: Bilateral cortical necrosis "is the identifying lesion of the generalized Shwartzman reaction."

Piel et al. D21,797/55: Fibrin thrombi occur not only in the SSP-G, but also in nephrotoxic nephritis and other conditions; hence, this lesion is considered to be nonspecific.

Black-Schaffer & Garcia-Caceres G28,650/57: Despite earlier observations to the contrary, no SSP-L could be produced in the rabbit kidney by local preparation followed by i.v. provoca-

tion. (The authors used various techniques of preparation, injecting meningococcal or *S. marcescens* polysaccharides into the renal artery or the renal parenchyma.) "Since the local phenomenon could not be produced in the kidney, the wisdom of interpreting renal cortical necrosis as a manifestation of the Shwartzman phenomenon is questioned."

Fehr & Brunson G21,900/57: Renal glomerular capillary occlusion by massive deposits of fibrinoid material "comprise the reaction

known as the generalized Schwartzman phenomenon."

McKay D14,183/62: The SSP-G is defined as a disseminated renal glomerular capillary thrombosis.

McKay E34,050/63: The SSP-G is defined as "renal glomerular capillary thrombosis leading to renal cortical necrosis. This is the one element of the reaction which at present distinguishes it clearly from all others and gives it identity."

Nakai & Margaretten E45,655/63: The bilateral renal cortical necrosis produced by a single i.v. injection of staphylococcal toxin is not preceded by renal glomerular capillary thromboses and is not prevented by heparin or

nitrogen mustard. Hence, "bilateral renal cortical necrosis can no longer be regarded as the hallmark of the generalized Schwartzman reaction."

McKay E4,788/65: After a detailed analysis of the various lesions that may be considered characteristic of the SSP-G, the phenomenon is defined as follows: "It is renal glomerular capillary thrombosis leading to renal cortical necrosis: This is the one element of the reaction which at present distinguishes it clearly from all others and gives it identity. Our problem then is to describe the events that transpire between administration of endotoxin and the lodgement and persistence of fibrin thrombi in the glomerular capillaries."

The Bordet Phenomenon. Roemer (1891) was the first to point out that tuberculous guinea pigs are hypersensitive to various microbial products to which they react as they do to tuberculin. However, it was the merit of Paul Bordet (1931) to have observed that a suspension of killed *E. coli* microorganisms, which is normally well tolerated by guinea pigs, kills them, with hemorrhages in the peritoneal lymph nodes, if they have received BCG vaccine i.p. 2-3 weeks earlier. *E. coli* injected s.c. into guinea pigs thus prepared produced topical hemorrhages with necroses. The phenomenon was thought to be related to the SSP in that it depends upon a properly timed treatment with microbial products, but the timing differs in this case and the long critical period suggests an allergic factor in the pathogenesis of the lesions. In tuberculous animals, two properly spaced endotoxin injections are also especially active in producing a THP, and several variants of this reaction have likewise been designated as the "Bordet Phenomenon."

Selter & Tancré E85,030/25: Review of the literature and personal observations showing that, in tuberculous patients, not only tuberculin but various bacterial products and non-specific proteins can elicit pronounced necrotizing and sometimes hemorrhagic reactions at cutaneous injection sites. Apparently, the hypersensitivity induced by tuberculosis is largely nonspecific.

Bordet G27,221/31; G27,222/31; G23,543/31; G23,083/33: In guinea pigs infected with pseudotuberculosis, as in tuberculous guinea pigs, topical injection with *E. coli* or *B. proteus* endotoxin causes local hemorrhagic necrosis not unlike a tuberculin reaction. Intravenous injection of the same endotoxins results in a generalized tuberculin reaction with the characteristic hemorrhagic halo around preexistent tuberculous foci. The response is considered to be similar to the Sanarelli reaction. The author points out that Roemer, in 1891, was the first to show that tuberculous guinea pigs are hypersensitive to various microbial products, in

that they react to them with lesions similar to those elicited by tuberculin.

Bordet G23,542/35: In tuberculous rabbits, a dermal tuberculin reaction becomes hemorrhagic and similar in appearance to the SSP-L if, 24 hrs. after the administration of tuberculin i.c., *E. coli* endotoxin is given i.v. [This reaction has subsequently become known as the "Bordet phenomenon" (H.S.).]

Bordet B78,032/36: Review of the early history of reactions resembling the SSP. The author injected BCG vaccine i.p. in guinea pigs and found that, if these are infected i.p. with *B. coli* 10-20 days later, they die exhibiting hemorrhagic lesions in the peritoneum. BCG-pretreated guinea pigs are also more sensitive than unpretreated controls to the i.p. injection of sterile *B. coli* cultures or filtrates of *B. coli* or *B. proteus*. Response is considered to be closely related to the SSP.

Gougerot G23,005/36: The production of a THP by *E. coli* or its toxins in tuberculous animals is designated as the Sanarelli-Schwartz-

man-Bordet phenomenon. It probably plays a role in certain hemorrhagic manifestations seen in patients with tuberculosis.

Gougerot & Hamburger G22,527/37: In a syphilitic patient, tuberculin i.c. produced a topical necrosis of the tuberculin-reaction type and, at the same time, a purpuric response in an old syphilitic scar at a distance from the injection site. This is now interpreted as a "Shwartzman-Sanarelli-Bordet" type of response.

Gougerot & Degos G22,251/41: The SSP-like

reaction which is elicited in tuberculous rabbits by the i.v. injection of *E. coli* endotoxin at the site of preparation on the previous day by the i.c. injection of tuberculin is referred to as the Sanarelli-Shwartzman-Paul Bordet phenomenon. When given i.v., tuberculin can also act as a provocative factor, e.g., in tuberculous guinea pigs, in which it elicits hemorrhagic responses at sites where talcum produced a sterile peritonitis. Several apparently quite comparable reactions have been observed in tuberculous patients.

The Thomas Reactions. Lewis Thomas, one of the most fertile contemporary students of thrombohemorrhagic phenomena, has described two reactions which are sometimes designated by his name: 1. the production of bilateral cortical necrosis (which he regarded as pathognomonic of the SSP-G) by a single i.v. injection of bacterial endotoxins following pretreatment with a glucocorticoid; 2. the production in rabbits pretreated with ACTH (but receiving no provocative injection) of petechial hemorrhages at skin sites prepared by meningococcal endotoxin. Lewis Thomas has also greatly contributed to our knowledge of the altered reactivity to catecholamines induced by bacterial products (cf. below).

Thomas & Mogabgab B50,101/50: Although ACTH inhibits the gross hemorrhages of an SSP-L produced by two injections of meningococcal toxin, both ACTH and cortisone can actually elicit small petechial hemorrhages at skin sites prepared by meningococcal toxin in rabbits receiving no provocative injection. The structure of these skin sites differs from those of the typical SSP-L. [Since this so-called "Thomas reaction" is produced by an inhibitor of the SSP-L and differs structurally from the latter, the two responses can hardly be

equated (H.S.).] The authors believe that "conceivably, the abatement of the usual inflammatory reaction to locally injected toxin may have increased the vulnerability of skin tissue to a primary damaging property of the toxin."

Thomas & Good E56,605/52: A single i.v. injection of *S. marcescens* or meningococcal toxin is followed by bilateral cortical necrosis and hyaline thrombosis of the glomerular capillaries in the cortisone-pretreated rabbit. There are also hemorrhages in the lung, spleen, liver and gastrointestinal tract.

The Catecholamine Induced Thrombohemorrhagic Phenomena. The fact that microbial products can remarkably sensitize tissues to the topical actions of epinephrine was first observed by Marcus (1921) who found that rabbits infected with staphylococci develop hemorrhagic necroses at sites where epinephrine is injected s.c. into the ear. These findings were confirmed by Schmidt-Weyland (1932), who observed, in addition that even killed cultures of *E. coli* can thus raise sensitivity to epinephrine. On the basis of their observations, these authors assumed that Raynaud's disease and thromboangiitis obliterans (Buerger's disease) could be due to the activation of adrenergic mechanisms in the presence of infections. However, these early findings aroused little interest until Thomas and his coworkers had thoroughly analyzed this response, which is now often designated as another "Thomas reaction."

Marcus G23,205/21: First demonstration of the fact that following infection with streptococci, s.c. injection of epinephrine into the

rabbit ear produces local hemorrhagic necrosis. In control rabbits, epinephrine had no such effect, except in one animal which proved to

have a spontaneous infection. Since gangrene frequently develops in patients with latent Raynaud's disease under the influence of infection, it is assumed that here adrenergic mechanisms may also play a role.

Schmidt-Weyland G24,461/32: Following infection with live streptococci or tubercle bacilli, as well as after inoculation with killed *E. coli*, rabbits become hypersensitive to epinephrine injected s.c. into the ear. Unlike control rabbits, they develop hemorrhagic necrosis with leukocytic and hyaline thrombi in the capillaries and veins (less frequently in the arteries). These changes are compared to those of thromboangiitis obliterans and it is suspected that some adrenergic mechanism may play a role not only in this disease, but also in the thromboembolic phenomena frequently observed in the course of severe infections (e.g., cholera, dysentery).

Stetson G22,085/55: In BCG-vaccinated rabbits, following i.c. preparation with either

meningococcal endotoxin or tuberculin, the topical application of epinephrine to the prepared skin site resulted in hemorrhagic necrosis.

Thomas & Zweifach C13,964/56: Epinephrine i.c. produces extensive skin hemorrhages in rabbits when given one hour after *E. coli*, *E. typhosa*, or *S. marcescens* endotoxin i.v., presumably because the hormone causes an unusually prolonged local ischemia. When epinephrine is mixed with various bacterial endotoxins and injected i.c., "hemorrhagic lesions resembling local Shwartzman reactions occur within a few hours."

Antopol & Chryssanthou D56,730/63: The SSP-L-like changes produced in rabbits by the i.c. injection of epinephrine and concurrent i.v. administration of bacterial endotoxin is designated as the "Thomas reaction."

Kováts et al. D9,550/64: The "Thomas reaction" is induced by giving epinephrine i.c. and typhoid endotoxin i.v. in rabbits.

Other Experimental Thrombohemorrhagic Phenomena. A number of other phenomena will be only briefly mentioned here for the sake of completeness. The reader is referred to the section "*Nonmicrobial Agents as Elicitors or Modifiers of the THP*" for a more complete listing of relevant original articles.

The antiplatelet serum-induced hemorrhagic syndrome. *Ledingham G24,703/14:* An antiplatelet serum, obtained by immunizing rabbits with guinea-pig platelets, elicits a purpura when given i.v., i.p., or s.c. to guinea pigs. The multiple hemorrhages in the skin, lung, epicardium, intestinal serosa and lymph nodes are associated with erythrocyte agglutination thrombi and a decrease in the red cell count.

Bedson G21,641/22: In guinea pigs given antiplatelet serum i.v., the resulting drop in blood platelets is associated with multiple hemorrhages in the skin, muscles, mesentery, intestine, epididymis, lung, and peritoneal cavity. [No mention is made of thromboses (H.S.).]

The Apitz phenomenon. *Veratti G23,476/36; G26,189/36:* Apitz's (B30,444/34) phenomenon is elicited by repeated i.v. injections of *E. coli* endotoxin given at intervals of about 5-6 hrs. three times a day in gradually increasing doses. It is characterized by fibrin deposition in the glomerular capillaries with hemorrhages into Bowman's capsule in the kidney, followed in a second stage by capillary hemorrhages, unaccompanied by fibrin deposition, in the lungs. Death ensues usually on the second day.

The Arthus phenomenon. *Arthus G22,081/03:* First description of the Arthus phenomenon, a sometimes hemorrhagic anaphylactic inflamma-

tory response to repeated s.c. injection of horse serum in rabbits.

The Auer phenomenon. *Auer G22,074/20:* Xylool applied to the ears of rabbits sensitized with horse serum i.m. or i.p. and then challenged with the same antigen i.m. or i.p., elicits hemorrhagic blister formations at the sites where xylool is gently rubbed in. "The ear lesions of the sensitized reinjected rabbits which develop after the application of xylool are interpreted as a primary anaphylactic reaction. This primary anaphylactic reaction is considered the result of a local autoinoculation of the ear tissues with circulating antigen."

Kirsner & Elchlepp D72,475/57: According to Auer, a sensitized animal can localize the sensitizing antigen in inflamed tissues and thereby produce the state necessary for a local hypersensitivity or anaphylactic response. A survey of the literature on this phenomenon suggests some relationship to the SSP-L.

The Masson phenomenon. *Masson et al. B70,138/52:* An "eclampsia-like syndrome" associated with widespread thrombohemorrhagic lesions in various organs is produced in rats pretreated with desoxycorticosterone + unilateral nephrectomy + NaCl.

The McKay phenomenon. *McKay D15,443/62:* An "eclampsia-like syndrome" is produced

in pregnant rats by feeding a vitamin-E deficient diet supplemented by oxidized lipids.

The Symeonidis phenomenon. Symeonidis B32,969/49: An eclampsia-like syndrome is induced in rats by large doses of progesterone given during the last third of pregnancy. There is abortion or resorption of the embryos, albuminuria, azotemia, edema, and hypertension. "The lesions in other organs, especially in the liver and the kidney, were similar to those of human eclampsia. These were peripheral lobular necrosis of the liver, with capillary dilatation, fibrin thrombi, and hemorrhages, fibrin thrombi in glomeruli, thickening of the glomerular basement membrane, and tubular degeneration and necrosis in the kidney."

The plasma-transfusion reaction (PTR). Crosby & Stefanini D9,062/52: The plasma-transfusion reaction (PTR) occurs when susceptible patients are transfused with compatible blood. The reaction is encountered in hemolytic diseases, terminal cancer, and in paroxysmal, nocturnal hemoglobinuria, when the reaction is always followed by hemolytic crisis. "During the preliminary phase of the reaction, the majority of leukocytes and platelets are swept out of the circulation and about half of the fibrinogen disappears. The white cells are probably removed by the lungs. Emboli composed of platelets or fibrin may be responsible for the various clinical symptoms such as diarrhea, headache, and abdominal pain." The PTR is nonspecific since similar changes have been found during anaphylactic and peptone shock, incompatible blood transfusions, i.v. administration of foreign proteins, tuberculin and typhoid bacilli, or ferric oxysaccharate to susceptible people. The reaction also occurs during the hemolytic paroxysms of cold hemoglobinuria, favism and black-water fever. This pattern of response has been described as "colloidoclastic" or "hemoclastic" reaction. [Although the authors do not mention the SSP-G, a relationship between the latter and the PTR is suggested by their description (H.S.).]

The Reilly phenomenon. Reilly *et al.* G21,897/35; G26,816/36: Injection of typhoid, paratyphoid and diphtheria bacilli or their endo-

toxins into the mesenteric lymph nodes or the vicinity of sympathetic nerves (splanchnics, semilunar ganglion, adrenal medulla) of animals, produces changes similar to those of spontaneous typhoid fever in man. There is swelling and hemorrhage in the mesenteric lymph nodes and Peyer's plaques with exulceration of the latter in a great variety of animal species, including those that are quite insensitive to the same microbial products when administered through other routes. Even intracardiac injection of paratyphoid endotoxin causes intense perineuritis around the splanchnic nerves of the guinea pig, owing to the neurotropic effect of this toxin. The response is largely nonspecific since certain metals (cobalt, nickel, lead, arsenic) as well as nicotine, snake venoms, etc., applied directly to the splanchnics of the guinea pig produce similar gastrointestinal hemorrhagic responses. The same is true of mechanical trauma caused by ligatures placed around the splanchnics or prolonged faradic stimulation of these nerves. It is assumed that sympathetic stimulation is largely responsible for the gastrointestinal hemorrhagic syndrome characteristic of typhoid fever, and that the close anatomical connections between the mesenteric lymph nodes and the splanchnic nerves account for the fact that application of the irritants to either of these structures is effective. This form of hemorrhagic necrosis has become known as "Reilly's syndrome of neurovegetative irritation."

Marquézy E65,247/58: The thrombohemorrhagic syndrome, known in the French literature as "syndrome malin," is considered to be identical with Reilly's syndrome as well as with the alarm reaction phase of the G.A.S.

The Renaud syndrome. Renaud G23,270/62: A thrombotic thrombocytopenia is induced in rats kept for several months on a high-fat diet containing supplements of cholic acid.

The "Shwartzman-like reaction." Arndt & Schneider D9,369/58: Thrombohemorrhagic skin lesions can be produced by a single i.c. injection of *E. coli* or *S. marcescens* into certain strains of mice. The lesions are described as the "Shwartzman-like reaction."

Thrombohemorrhagic Phenomena in Man. As previously stated, thrombohemorrhagic phenomena can occur in man, as they do in experimental animals, after treatment with various microbial and nonmicrobial products. In addition, certain well characterized diseases such as thrombotic thrombocytopenic purpura, typhoid fever (especially the thrombohemorrhagic reactions to vaccine therapy), eclampsia, missed abortion, septic abortion, hydatidiform moles, are thought to be closely related to this group of morbid phenomena. A detailed discussion of the

history of every one of these diseases would not be within the scope of this volume, but their relationship to the THP is discussed in the section "Clinical Implications" of the THP.

Pluricausal Thrombohemorrhagic Phenomena. A special section is devoted in this book to the pluricausal THPs which are presently at the forefront of our interest. As their name implies, the pluricausal THPs depend upon the properly coordinated application of two or more pathogens, none of which are efficacious by themselves.

In essence, the pluricausal THPs depend upon systemic treatment with a "sensitizer" (usually a metal or polysaccharide) and topical or systemic treatment with a "challenger" (e.g., catecholamines, 5-HT). In analogy with the SSP-L and the SSP-G induced by bacterial endotoxins, we distinguish local (THP-L) and general (THP-G) variants of the pluricausal THP. In their morphologic structure (though not in the methods of their production), these are virtually indistinguishable from the SSP-L and SSP-G respectively.

The most noteworthy characteristics of the pluricausal THPs are that:

1. They can be elicited by comparatively simple compounds of known chemical structure which are devoid of demonstrable antigenic properties.
2. Pluricausal THP-Gs, though produced by systemic treatment, can affect certain organs (e.g., the salivary glands, uterus, kidney) selectively.
3. Under suitable experimental conditions, pluricausal THPs can elicit not only disseminated intravascular thromboses in the microcirculation but also massive thromboses of large vessels.
4. Using threshold amounts of systemic sensitizers in combination with comparatively large doses of challengers, it is possible to elicit tissue responses intermediate in type between a THP and ordinary serous inflammation. This fact is of special interest in that it implies a fundamental similarity in the mechanism governing these two basic types of reaction to injury. (For pertinent original publications, cf. pp. 125ff.

CHAPTER II

THE THP ELICITED BY MICROBIAL AGENTS ALONE

LIVE microbes and microbial products (filtrates, extracts) occupy a particularly important place among the agents capable of eliciting the THP. In this chapter, we shall discuss first the production of a THP by single, or more or less arbitrarily spaced multiple injections of microbial products; then we shall deal with classical SSPs that can be elicited only by two injections of such materials spaced about 24 hrs. apart. Nonmicrobial agents (adjuvants, hormones, immune reactions, drugs, etc.), which either modify the THP-producing effects of microbial products or elicit a THP by themselves, will be discussed in Chapter III.

SINGLE OR VARIABLY SPACED INJECTIONS

It has long been known that THPs can be produced by spontaneous or experimental infections, as well as by treatment with bacterial filtrates and extracts. The endotoxins of Gram-negative bacteria proved to be especially effective in this respect. Both local thrombohemorrhagic reactions at the injection site, and generalized manifestations of the THP (including thrombi in the renal glomerular capillaries, lung, liver and other organs) can be produced in this manner either by single or by variably spaced, repeated injections of suitable microbial products. Although two injections given approximately 24 hrs. apart (SSP technique) are especially effective, this timing is by no means indispensable. The literature listed below is concerned only with reports published after 1927, since earlier data have been considered in the historic section (pp. 3ff.). The production of a THP by single endotoxin injections in tumor-bearing (pp. 177ff.) and pregnant (pp. 43ff.) animals will be discussed later.

Bordet G23,082/33: Single i.v. injections of *E. coli* endotoxin at high dose levels are capable of producing pulmonary hemorrhages in the rabbit and guinea pig. Hence, the SSP is ascribed to a "direct toxic action" of the endotoxin rather than to an anaphylaxis-like sensitization. [The author does not comment on the difference between the pulmonary response induced by a single injection and the entire syndrome of the SSP-G elicited in the usual manner (H.S.).]

Michelazzi D92,869/33: Even very large single s.c. doses of *E. coli* endotoxin produce only edema and hyperemia but no hemorrhages in the rabbit. To produce an SSP, it is "absolutely indispensable" that two properly spaced injections of bacterial endotoxins be given.

Apitz B30,444/34: Single i.v. injections of

B. coli endotoxin in rabbits may cause hemorrhagic inflammation of both ears, but even in highly sensitive animals, the systemic lesions in the heart, liver, spleen, lung and kidneys are at most degenerative or necrotic without hemorrhage.

Michelazzi G26,191/35: Rabbits infected with live staphylococci develop a particularly severe SSP-L following two injections of *E. coli* endotoxin. No such accentuation of the phenomenon is seen in animals pretreated with killed staphylococci or staphylococcus filtrate. Rabbits infected with bovine tuberculosis are almost completely refractory to the production of an SSP-L by *E. coli* endotoxin, but no such protection is offered by pretreatment with killed human or bovine tubercle bacilli. Pretreatment with washed *E. coli* bacilli offers considerable resistance to the SSP-L.

Reilly et al. G21,897/35: The application of typhoid, paratyphoid and diphtheria bacilli or their endotoxins by direct injection into the mesenteric lymph nodes or in the vicinity of sympathetic nerves (splanchnics, semilunar ganglion, adrenal medulla) in animals produces changes similar to those of spontaneous typhoid fever in man. There is swelling and hemorrhage in the mesenteric lymph nodes and Peyer's plaques with exulceration of the latter in a great variety of animal species, including those that are quite insensitive to the same microbial products when administered through other routes.

Rigdon E68,987/35: A toxin prepared from a hemolytic strain of *Staphylococcus aureus* produced diffuse hemorrhagic and necrotic lesions in various organs, particularly the gastrointestinal tract, with characteristic renal lesions (dilatation of the glomerular capillaries with swelling of their endothelial cells, proteinuria, hyaline droplet formation in the tubular epithelia) following a single i.v. injection in the dog and rabbit.

Stolyhwo G21,662/35-36: A single injection of typhoid or paratyphoid filtrate suffices to produce a generalized hemorrhagic and necrotizing reaction in the rabbit, if a sufficiently large dose is administered.

Bordet B78,032/36; D1,280/36: An *E. coli* toxin concentrated by precipitation with acetic acid is effective not only in producing the classical SSP but also in eliciting hemorrhagic lesions in BCG-pretreated guinea pigs. At much higher dose levels, even a single i.v. injection of this toxin suffices to produce hemorrhagic changes in the lungs, kidneys and adrenals of unpretreated guinea pigs. It is concluded that "the *coli* toxin produces the same kind of change in unpretreated and in sensitized animals; these differ from each other only in the degree of their sensitivity."

di Stefano G21,836/36: Single i.v. injections of *E. coli* endotoxin can produce hemorrhagic lesions in the rabbit intestine, allegedly because the local flora permanently prepares the gut.

Gerber C95,662/36: A single i.v. injection of meningococcal or typhoid toxin suffices to produce venous thrombi and degenerative changes in various internal organs (exclusive of the kidneys) in rabbits. However, renal capillary thrombosis and focal tubular necrosis with necrotizing arteritis of the interlobular vessels were observed only following two i.v. injections of the bacterial filtrates.

Veratti G23,476/36: "Apitz's (B30,444/34) phenomenon" is elicited in the rabbit by repeated i.v. injections of *E. coli* endotoxin given at intervals of about 5-6 hrs. three times a day

in gradually increasing dosages. It is characterized by fibrin deposition in the glomerular capillaries with hemorrhages into Bowman's capsule in the kidney, followed in a second stage by capillary hemorrhages, unaccompanied by fibrin deposition, in the lungs. Death ensues usually on the second day.

Shwartzman et al. G21,283/38: Repeated injection of meningococcus filtrate i.v. at 6-hr. intervals did not aggravate the resulting SSP-G in the rabbit, even if up to 23 injections were administered.

Alechinsky D88,312/39: If an SSP-L is produced in the usual manner by two injections of *E. coli* endotoxin, a second i.v. injection, 24 hrs. after the first, will add an SSP-G to the already existing SSP-L.

Sanarelli G28,164/39: An SSP-G can be produced by the i.v. injection of sterilized human saliva (presumably the result of its bacterial flora) but only if three injections are given at 24 hr.-intervals. Here, in addition to the usual intestinal, renal and pulmonary lesions, hemorrhages occur in the psoas muscles and the uterine horns.

Cameron et al. G22,075/40: Single i.v. injections of extracts prepared from *B. typhi* murium by tryptic digestion produced marked congestion of the portal vessels with hemorrhage and thrombosis, as well as necrosis in the liver and the lymphatic organs of the mouse and rat. The changes are similar to those seen in mice infected with *B. typhi* murium.

Ayo G22,367/41: A single i.v. injection of meningococcus or typhoid toxin in the rabbit produces miosis, photophobia, lacrimation, congestion of the iris and conjunctiva with a marked pericorneal ring of dilated capillaries and, in some instances, gross conjunctival hemorrhages. Repetition of the i.v. injection after 24 hrs. aggravates these manifestations. Curiously, "these effects may be considerably diminished by a previous local preparation of rabbits to the Shwartzman phenomenon."

Ayo G22,709/43: Among a large variety of bacterial toxins, only those capable of eliciting the SSP-L were found to produce a "toxic ocular reaction" following a single i.v. injection. "The reaction consists of intense iridoconjunctival hyperemia and coagulation of the aqueous humor after its aspiration. It appears several minutes after the intravenous injection of toxin, reaches its maximal intensity in a few hours, and is notably reduced or has completely disappeared in about twelve hours." Protection against this response can be offered by previous i.c. or i.v. administration of SSP-active filtrates or by moccasin snake venom.

Honecker G21,298/47: In a patient who received three s.c. injections of typhoid-paratyphoid vaccine pronounced hemorrhagic necrosis developed at the injection site following the last injection. The phenomenon is interpreted as an SSP-L.

Thomas & Good B79,249/52: Even excessive amounts of meningococcal toxin produce no SSP-G when given in the form of a single i.v. injection.

Stetson G22,085/55: Hemorrhagic skin necrosis can be produced in rabbits by single injections of concentrated meningococcal agar washings.

Gronwall & Brunson C50,109/56: An SSP-G is rarely produced by a single i.p. injection of *E. coli* or meningococcal endotoxin in the rat.

Kelly et al. D3,776/57: Ten strains of mice were found to be nonreactive when tested for the production of an SSP-L by endotoxins of *S. marcescens*, *S. typhosa*, *Ps. aeruginosa* and *H. pertussis*. However, three strains and one *F₁* hybrid subline developed hemorrhagic lesions at the site of injection of a single, relatively high i.c. dose of polysaccharide. When the i.c. dose was followed 24 hrs. later by an i.v. injection, the incidence was somewhat higher.

Kliman & McKay E53,773/58: A single i.v. injection of Shear's polysaccharide suffices to produce thrombi in the lungs, liver, spleen and kidneys, although two injections, 24 hrs. apart, are much more effective.

McKay & Shapiro D85,442/58: Occasionally, in the rabbit, hyaline thrombi occur in the renal glomerular capillaries and the small vessels of the lung, liver and spleen after a single injection of Shear's polysaccharide.

Arndt et al. C82,082/59: In BSVS mice, which are highly susceptible to the production of an SSP-L by two doses of *E. coli* lipopolysaccharide, even a single i.c. dose occasionally produces a topical hemorrhagic response.

Arndt & Schneider G21,207/60: In BSVS strain mice, an SSP-L can be elicited by an i.c. followed by an i.p. or i.v. injection of various bacterial endotoxins. Several types of antigen-antibody complexes can also be used for provocation. Some animals reacted in the usual manner to single i.c. injections of endotoxins but, in these, there was infection of

the lungs with gram-negative microflora. Here, the latter apparently acted as the preparatory agent without any specific critical period, since the animals were permanently responsive.

Gans & Kravit D16,680/60: Endotoxin shock produced in the dog by *E. coli* lipopolysaccharide i.v. causes a fall in blood fibrinogen which can be prevented by pretreatment with heparin or Warfarin. The fatal effect of small doses of endotoxin can also be prevented by heparin.

Conti et al. D4,566/61: *E. coli* or *Sh. flexneri* endotoxin given i.c. simultaneously with, or a few hours before, a suspension of living hemolytic staphylococcus aureus cultures causes intense topical hemorrhagic necrosis of the skin in rabbits and increases the infectivity of the microorganisms. Similar changes are obtained when the endotoxin is given i.v. at sites of concurrent i.c. inoculation with staphylococci.

Hardaway et al. E96,214/61: A single intra-aortic infusion of *E. coli* endotoxin produces an SSP-G like syndrome in the dog with a decrease in blood coagulability which was ascribed to a consumption of blood-clotting factors, mainly fibrinogen. Heparin pretreatment largely prevents the morphologic changes.

Hardaway D12,907/62: A single intraaortic injection of *E. coli* endotoxin produces hemorrhagic necrosis with thrombus formation in the gastrointestinal mucosa, kidneys and pancreas.

Antopol & Chryssanthou D56,730/63: In certain strains of mice, a single i.c. injection of *E. coli* lipopolysaccharide suffices to produce a typical SSP-L.

Kováts et al. D85,430/63: The local lesion, following a single injection of typhoid endotoxin in the rabbit, is rich in mononuclears and eosinophils. It is, therefore, considered to be a delayed hypersensitivity response, attributable to the fact that the animal lives "in symbiosis with endotoxin-producing microorganisms."

Bouissou et al. D19,954/64: A single i.v. injection of *E. coli* endotoxin, unlike two i.v. injections 24 hrs. apart, fails to produce an SSP-G in the rabbit.

TWO INJECTIONS SPACED ABOUT 24 HOURS APART (THE SSP-L AND SSP-G)

Methods of Production. In this section we shall attempt to review the rather complex literature on the production of the classical SSP-L and SSP-G. In consonance with Shwartzman's suggestion, the first injection is called the "preparatory,"

the second, the "provocative" or "reactive" treatment. When the preparatory injection is given i.c., or into some other tissue for the evocation of a local response, we speak of an SSP-L; when it is administered i.v. to produce a general syndrome, we speak of an SSP-G. The time elapsing between the two injections is the "critical period."

Innumerable experiments have been published to document the ability of various microbes and microbial products to act as preparatory and provocative agents. Often the same author has tested many germs and diverse extracts of their products in various combinations, while different investigators have used different techniques; hence, it is virtually impossible to present the results obtained with each microbe in a manner that permits of strictly valid intercomparisons. However (contrary to the style adopted in other sections of this book), the names of the microbes and their toxins will be *italicized* in the following pages to facilitate their detection even by cursory scanning through the text. Thus, readers particularly interested in data concerning certain organisms will be able to trace them without much difficulty.

In the interest of conciseness, we shall speak simply of an SSP-L or SSP-G "produced in the usual manner," omitting any remarks concerning the technique employed, when the preparatory injection was administered i.c. or i.v. respectively, about 24 hours prior to the i.v. provocative injection.

In general, it may be said that the literature on the production of the SSP-L and SSP-G has amply confirmed the following facts:

1. The *endotoxin-containing filtrates of Gram-negative bacteria* are the most potent "SSP factors" (agents capable of eliciting the SSP-G or SSP-L, "Shwartzman-active factors"). However, certain vibrios, spirochetes and other microorganisms also contain active principles.

2. In most instances it is possible to use the SSP-active principles of the same microbe, both for preparation and for provocation, in the production of either the SSP-L or the SSP-G. As we shall see in the next chapter, this is not always so when a THP is produced either by one microbial and one nonmicrobial agent in combination, or by two nonmicrobial factors.

3. A microbial factor of proven SSP-activity can be used either as the preparatory or as the provocative agent in combination with another proven SSP-active factor, as long as an appropriate critical period is allowed to elapse between the two injections. Apparently, in this respect there is no noteworthy qualitative difference between the active constituents of different organisms.

4. The optimal critical period between the two injections is approximately 24 hrs. (For more information about this cf. "The Critical Period.")

5. Although both the SSP-L and the SSP-G can be produced in various species, the most suitable animal is the rabbit, which has been used by the great majority of investigators. (For further data on the production of the SSP in species other than the rabbit and in rabbits of different strains cf. "Species and Genetic Pre-disposition.")

Sanarelli E63,717/23: In rabbits given live *cholera* vibrios i.v., the subsequent injection of *proteus* or *E. coli* endotoxin i.v. elicits severe

shock with desquamation of the intestinal, urinary bladder and gallbladder epithelia, associated with hemorrhages. The phenomenon

is called "epithalaxis" (desquamation of epithelia).

Sanarelli B78,422/24; G26,880/26: If, 24 hrs. following an i.v. injection of a sublethal dose of live *cholera* vibrios, *E. coli* or *proteus* toxin is injected i.v. in the rabbit, there develops an acute nephritis with desquamation of the intestinal epithelium, intestinal hemorrhages and diarrhea reminiscent of cholera. The blood pressure drops and there develops a transient decrease, followed by a rise in the polymorphonuclear leukocyte count of the blood.

Hanger B78,181/27-28: A typical SSP-L is produced by i.c. injection of *B. lepisepticum* filtrate followed 24 hrs. later by i.v. injection of the same material. The reaction is non-specific since i.c. injection sites treated with *B. lepisepticum* or *E. coli* react similarly when other filtrates are given subsequently i.v.

Shwartzman E41,370/28: First detailed description of the "phenomenon of local skin reactivity to *B. typhosus*-culture filtrate." After describing the technique of SSP-L production, special emphasis is placed upon the following facts:

1. The local hemorrhagic necrosis is fully developed 4-5 hrs. after the 2nd injection.

2. Only about 80% of rabbits are susceptible.

3. Different skin areas are about equally susceptible.

4. The intensity and size of the local hemorrhagic reaction is not related to the intensity of the erythema produced by the preparatory i.c. injection. A period of incubation must elapse between preparatory and provocative injection. The optimum is about 24 hrs; 2 hrs. are insufficient and reactivity disappears after about 48 hrs.

5. Repeated i.c. injections are ineffective. The provocative injection must be applied i.v.

6. Turpentine, sterile tryptic digest broth, and culture filtrates of various streptococci did not sensitize the skin for the subsequent i.v. administration of *B. typhosus* filtrate.

7. The active endotoxins are heat-resistant.

8. Certain features distinguish the SSP-L from known hypersensitivity phenomena.

Shwartzman E68,670/28-29: An SSP-L can be elicited by the i.c. injection of various bacterial filtrates followed by the i.v. injection of the same agents. Filtrates of the following microorganisms were effective: *B. coli*, *B. paratyphosus A*, *B. paratyphosus B*, *B. enteriditis*, *B. dysenteriae YZ*, *Mt. Desert*, *Shiga* and *Flexner*, *B. avicida*, 5 strains of *Streptococcus non-hemolyticus* (gamma) isolated from blood cultures of acute rheumatic fever, one strain of *Streptococcus viridans* (alpha) isolated from a pelvic abscess, one strain of *Streptococcus hemolyticus* (beta) isolated from a case of mastoid-

itis, with *Pneumococcus* types I, II, and III, and several strains of *meningococcus*.

Shwartzman D19,822/28-29: Description of the technique for the preparation of *B. typhosus* endotoxin for the production of an SSP-L in the rabbit. There exists an inverse relationship between the minimum effective i.c. dose and the amount given i.v.

Shwartzman D19,745/29: Production of an SSP-L by two injections of *B. typhosus* endotoxin in the rabbit. The preparation of the washings is described in detail.

Shwartzman D87,729/29: Production of an SSP-L with two injections of *menigococcus* agar washings.

Ecker & Welch E43,674/30: A variety of bacterial filtrates were tested for their ability to produce an SSP-L when administered in two injections as usual. It is concluded that "the Shwartzman phenomenon appears to be group or species specific. Filtrates from *enterococci* failed to produce the phenomenon."

Shwartzman E53,222/30: "The specificity and the nature of the phenomenon of local skin reactivity to various microorganisms have been studied. It has been shown that the skin preparatory and reacting factors of various biologically and serologically unrelated microorganisms are able to substitute for each other, provided they have the power of eliciting the phenomenon for themselves." It is concluded "that one substance antigenically totally different from another is able to induce a state of reactivity to it."

Shwartzman D56,194/30: Extensive studies concerning the effect of bacterial variation upon the SSP-activity in filtrates of *B. typhosus*, as judged by tests on rabbits, using the usual technique.

Bordet G27,221/31; G27,222/31: In guinea pigs infected with *pseudotuberculosis* as in *tuberculous* guinea pigs, topical injection with *E. coli* or *B. proteus* endotoxin causes local hemorrhagic necrosis not unlike a tuberculin reaction. Intravenous injection of the same endotoxins results in a generalized tuberculin reaction with the characteristic hemorrhagic halo around preexistent tuberculous foci. The response is considered to be similar to the Sanarelli reaction.

Burnet E42,707/31: If endotoxin from *B. typhosus*, *meningococcus* or *B. pertussis* is used i.c., for preparation, toxins of any of these organisms given i.v. will elicit a typical SSP-L.

Cohn G8,750/31: A typical SSP-L can be produced in the rabbit by *gonococcus* filtrates i.c. followed by the same material given i.v.

Cope & Howell G23,093/31: An SSP-L was

produced in rabbits by *pneumococci* dissolved in bile and given first i.c. then i.v. No such response was obtained by pneumococcal filtrates prepared by methods which do not cause disintegration of the cell body.

Gratia & Linz E65,231/31: Preparation of the rabbit ear by rubbing it with *vaccinia* lymph, followed by *E. coli* endotoxin i.v., causes the developing vaccinal pustules to become hemorrhagic and necrotic, and their subsequent development is stopped. Apparently, the course of a virus infection can be modified by the SSP. Simultaneously, hemorrhages appear in the inguinal ganglia, lungs, uterus, and fallopian tubes. Apparently, topical preparation can result in systemic lesions.

Gratia & Linz E91,473/31: An SSP-L in the testicle of the rabbit is produced by an intra-testicular inoculation of *vaccinia* virus followed by the i.v. administration of *E. coli* endotoxin.

Gratia & Linz D7,456/31: Rabbits inoculated intracerebrally with *rabies* neurovaccine and given the same material two days later i.v. die with diffuse hemorrhages in the brain and spinal cord. *V. cholera* or *E. coli* endotoxins may also be used for provocation, but they induce hemorrhages in the heart, lung, and lymph nodes, without any characteristic SSP-L changes in the brain.

Shwartzman G19,461/31: In rabbits prepared by *B. typhosus* endotoxin i.c., the i.v. injection of *S. hemolyticus scarlatinae* produces an SSP-L.

Debonera et al. B78,075/32: In guinea pigs *B. Preisz-Nocard* s.c. produces an abscess in which an SSP-L can be elicited by the i.v. injection of *E. coli* endotoxin three days later. In guinea pigs infected with an avirulent *tuberculosis* culture (strain of Cheval-Vallée), provocation by *E. coli* endotoxin i.v. is possible only 4-5 days later, but after this prolonged critical period, a typical SSP-L results.

Gratia & Linz D6,544/32: Detailed description of the various bacterial toxins and antigens which are active or inactive in eliciting the SSP. In opposition to Shwartzman, endotoxins rather than exotoxins are thought to be most effective. Dissolution of inactive microbes (e.g., *staphylococcus*) by bacteriophage or *Streptothrix* does not liberate active principles, while dissolution of active microbes (e.g., *E. coli*) does not destroy their SSP-producing potency. The active principles are not dialyzable. Various live microbes and viruses i.c. can also prepare the rabbit for subsequent provocation by *E. coli* filtrate i.v.

Gross D8,306/32: A toxin from *Staphylococcus Pyogenes aureus* produces topical necrosis following i.c. injection in the rabbit. However,

if subthreshold doses are administered for preparation, subsequent i.v. injection of the same material causes a typical SSP-L.

Klein G23,053/32: Formalin treatment markedly reduces both the lethal effect of *meningococcus* endotoxin and its ability to produce an SSP-L by the usual two-injection method. "Inasmuch as these changes paralleled those occurring in the conversion of diphtheria toxin into toxoid, it is justifiable to consider such altered meningococcus toxin as meningococcus toxoid."

Nasta G22,575/32: No SSP-L could be produced either in guinea pigs or in rabbits by two injections of *tuberculin* given in the usual manner.

Plaut E41,413/32: An SSP-L can be produced in the rabbit by two injections of *Spirocheta pallida* filtrates.

Riley & Wilson E68,984/32: Comparison of the SSP-L-producing ability of various *meningococcus* preparations in the rabbit.

Shwartzman E74,952/32: *Pneumococcal* filtrates i.c. are ineffective in preparing the rabbit skin for the elicitation of an SSP-L by subsequent i.v. injection of the same material. An SSP-L can be elicited, however, in rabbits prepared by *B. typhosus* endotoxin i.c. if they are then provoked by *pneumococcus* filtrates i.v., or even with a mixture of *pneumococcus* filtrate and antipneumococcus immune serum.

Apitz D10,355/33: Extensive studies on the morphologic characteristics of the SSP-L produced by two injections of *B. typhosus*, *E. coli*, *pneumococcus*, *nonhemolytic streptococcus* and *B. cuniculisepticum* filtrates. All these produced a typical SSP-L in the rabbit, but only *pneumococcus* filtrates were effective in guinea pigs. Rats were resistant to all filtrates. Necroses and inflammatory reactions in the heart and liver occurred in those rabbits which exhibited a very strong primary response to the intracutaneous preparatory dose before i.v. challenge. [This may have been a combination of the SSP-L and the SSP-G (H.S.).]

Cohen G23,099/33: Among various anaerobic gram-negative microorganisms isolated from a pulmonary abscess, only *B. melaninogenicum* and *Leptothrix* proved to be capable of producing an SSP-L by the usual method in the rabbit.

Apitz G25,132/34: Following single or repeated i.v. injections of *E. Coli* endotoxin, thrombi develop on the chordae tendineae of the rabbit heart. This response is unaccompanied by manifestations of inflammation, and similar changes can be obtained during anaphylaxis induced by repeated injections of horse serum. If rabbits are first given *E. coli*

endotoxin i.v. and 24 hrs. later, cultures of live *Staphylococcus aureus* i.v., the course of the resulting septicemia is greatly altered. Depending upon dosage, there may be complete protection against infection, no effect, or a combination of the usual septicemia with endocarditis. Topical protection against infection may also be obtained by pretreatment of the cutaneous inoculation site with endotoxin as shown by the author's earlier experiments.

Apitz B30,444/34: Detailed description of the organ changes characteristic of the SSP-G induced by two doses of *E. coli* endotoxin in the rabbit.

Gentile D70,282/34; G26,193/34: A nucleoprotein extracted from *E. coli* can produce a typical SSP-L in the rabbit when given first i.c., then i.v. The reaction is nonspecific since it also appears when the i.v. injection consists of a *V. cholerae* filtrate.

Kritschewski & Halperin G23,089/34: It was not possible to elicit an SSP-L in the rabbit by two injections of *B. abortus* filtrate.

Uyeda G25,123/34: In rabbits, an SSP-L could be elicited by two injections of *V. cholerae* filtrate. But filtrates of other vibrios (*El-Tor*, *V. metchnikovi*, *V. albensis*, *V. tyrogenum*) were also effective. The phenomenon is quite nonspecific, in that even preparation with the filtrate of one vibrio or bacterium is followed by an SSP-L if an unrelated filtrate is given i.v.

Koplik E37,432/34-35: An SSP-L is produced in rabbits by two injections of *B. pertussis*-culture filtrates administered in the usual manner.

Apitz E60,538/35: Details concerning the production of the SSP-L and the SSP-G by two successive doses of *B. typhosus*, *B. paratyphosus* and *meningococcus* toxins in the rabbit. By proper i.c. and i.v. preparation, an SSP-L and an SSP-G may even be elicited in the same rabbit simultaneously.

Apitz G23,091/35: Chemical studies on the nature of the substances in *B. typhosus* and *B. paratyphosus* that can elicit an SSP-L in the rabbit.

Boquet B18,399/35: A typical SSP-L can be elicited in the rabbit by two injections of filtrates of *B. lepisepticum*. Animals made resistant by pretreatment with repeated i.v. injections of killed *B. lepisepticum* cultures remain sensitive to the production of an SSP-L by *B. lepisepticum* filtrates. The response is nonspecific, since *E. coli* filtrate can be used for preparation or provocation when *B. lepisepticum* is administered as the other injection.

Koplik E50,642/35: "Vaccine virus cultures

are effective in preparing the skin of rabbits for the Shwartzman phenomenon when the intradermal inoculation of such cultures is followed after an interval of 3 to 6 days by an intravenous injection of similar culture virus, of neurovirus or of *B. typhosus* culture filtrate."

Linton et al. G23,261/35: An SSP-L can be produced by various *vibrios* (including *El Tor*).

Michelazzi G28,490/35: Rabbits, infected with *staphylococci* become hypersensitive to the production of an SSP-L by subsequent treatment with two injections of *E. coli* endotoxin. Following infection with *tuberculosis* bacilli, there is an initial decrease, followed by an increase in the sensitivity to the production of an SSP-L by *E. coli* (Bordet phenomenon).

Morimoto D20,130/35: Endotoxin-containing filtrates of *gonococcus* cultures produce an SSP-L in the rabbit.

Olitzki & Leibowitz G23,667/35: An SSP-L is produced by a purified extract of *B. typhosus* endotoxin.

Rigdon E68,987/35: Description of pathologic changes induced by the toxin of a hemolytic strain of *Staphylococcus aureus*. It is incidentally mentioned that, if two injections are given i.v. with an interval of 22 hrs., bilateral renal cortical necrosis develops. [The author does not mention the SSP (H.S.).]

Shwartzman G23,095/35: Certain toxic substances in *tuberculin* or *old tuberculin* provoke an SSP-L, providing heterologous bacterial filtrates of high potency are used either for the preparatory or the provocative injection. "The toxic substances apparently have no relationship to the tuberculin substances proper."

Vassiliadis D73,783/35: Filtrates of *V. cholerae* elicit the SSP-L in rabbits when given in two injections according to the usual procedure. Filtrates of *EL Tor* vibrios are ineffective in rabbits, and neither filtrate elicits an SSP-L in the guinea pig.

Watanabe & Misumi G28,170/35: In *tuberculous* guinea pigs, an SSP-L can be elicited by the i.v. injection of *E. coli* or *S. typhosa* endotoxin.

Aitoff et al. G23,079/36: An SSP-L can be produced by two injections of the newly discovered "dysentery bacillus of the new-born."

Aitoff et al. G23,080/36: An SSP-L can be produced in the rabbit by two injections of *S. marcescens* endotoxin.

Alechinsky G23,081/36: An SSP-L can be produced in the rabbit by two injections of *staphylococcus aureus* in the rabbit.

Anderwont & Shear E59,714/36: A purified fraction of *E. coli* endotoxin produces an SSP-L in the rabbit when given with the usual two-injection technique.

Daddi G28,642/36: An SSP-L can be produced in rabbits by two injections of extracts of a medium in which bovine tubercular mycobacteria Vallée have been grown.

Ivanovics G22,056/36: Purified fractions of paratyphoid B (Typus Breslau) bacilli produce an SSP-L when given first i.c., then i.v., in the rabbit.

Laporte G23,880/36; G23,881/36: In guinea pigs and rabbits given live paratyphoid-B organisms i.c., the simultaneous administration of a typhoid-culture filtrate i.p. or i.v. elicits a hemorrhagic necrosis at the site of cutaneous infection. [Although no reference is made to the SSP-L, it appears that this response may be related to it despite the fact that the "provocative" and "preparatory" injections are administered simultaneously (H.S.).]

Michelazzi G28,852/36: In tuberculous rabbits, various bacterial endotoxins, and particularly *E. coli* filtrates, i.c., produce a topical hemorrhagic response. In rabbits immunized to *E. coli*, this reaction can no longer be produced by *coli* endotoxin.

Semmlola G27,056/36: No SSP-L can be produced in rabbits with diphtheria toxin or anatoxin given either as the preparatory or as the provocative injection in combination with active bacterial filtrates.

Witebsky & Salm E54,103/36: *B. typhosus* filtrates were injected i.v. into rabbits which, 24 hrs. previously, had received i.c. injections of *H. influenzae* or *H. pertussis*; an SSP-L resulted only after preparation with *H. influenzae*. Conversely, living or dead *H. influenzae*, injected i.v., activated areas prepared by *B. typhosus* filtrates i.c.

Witebsky et al. G24,343/36-37: An SSP-L can be produced in rabbits by two injections of live *H. influenzae*. Three groups of microorganisms are differentiated on the basis of their capacity to produce hemorrhagic necrotic lesions.

Zuwerkalow & Woloskova G27,874/36: Chemical studies on the active components of tuberculin and mallein which are capable of eliciting an SSP-L in the rabbit.

Antopol G23,098/37: "Extracts of *B. typhosus*, *B. coli*, pneumococcus type III, meningococcus, *B. dysenteriae* (Flexner and Sonne) and *B. proteus* (vulgaris and X19) were capable of producing the Shwartzman phenomenon. These extracts could be used interchangeably with one another and with filtrates of *B. typhosus*, i.e., extracts from one source

for skin preparatory dose and another source for the provocative dose."

de Blasio G27,517/37: An SSP-L can be produced in the rabbit by two injections of human, bovine or avian tuberculosis filtrates.

Buch G25,470/37: Negative or doubtful results were obtained in attempts to produce an SSP-L by extracts of *E. coli*, *B. typhosus* and *B. Friedlaenderi*, believed to contain the carbohydrate or lipid haptens of these organisms. These extracts exhibited no definite SSP-activity when given as the preparatory or the provocative injection in combination with potent SSP-active endotoxins.

Cerruti G25,138/37: An SSP-L can be produced in the rabbit by two injections of *Brucella* (*Br. melitensis*, *Br. abortus*, *Br. paramelitensis*) endotoxin.

Horster & Müller G25,124/37: If, in rabbits, a mild infection is produced by i.c. injection of live *staphylococci*, the local lesion flares up and often becomes hemorrhagic upon the subsequent i.v. administration of *meningococcal* endotoxin. The fact that bacterial products can thus activate an infected focus, is interpreted as evidence supporting the concept of focal infection.

Moritz E65,873/37: Living *B. aertrycke* can replace aertrycke filtrate as either the preparatory or the provocative injection in the production of an SSP-L when aertrycke filtrate is employed for the other injection. When living *B. aertrycke* were injected s.c., inflammation was more severe and more organisms survived at the inoculation site in rabbits that had received, 24 hrs. later, *B. aertrycke* filtrate i.v. than was the case in similarly infected rabbits not otherwise treated. After *B. aertrycke* filtrate was given s.c., the i.v. injection of living *B. aertrycke* led to the localization of these germs in the developing hemorrhagic cutaneous lesions. The importance of the SSP for the localization of infections in general is emphasized.

Sanarelli G23,516/37: In guinea pigs and rabbits infected with *Spirocheta ictero-hemorrhagiae* and *Spirocheta autumnalis*, hemorrhagic lesions appear only during the final stages when the resistance of the animals is so decreased that secondary infections with other germs occur. However, it was possible to produce such hemorrhagic complications even at early stages of the spirochetal infections by i.p. inoculations of various other microbes.

Shwartzman B19,913/37: Extensive review of the methods used for the production of the SSP (preparation of endotoxins, susceptibility of various species, optimum time lapse be-

tween preparation and provocation, induction of resistance by repeated elicitation of the SSP, topical reactions following preparation of various internal organs, elicitation of the SSP by nonbacterial products, etc.).

Shwartzman et al. G23,253/37: The SSP-active factors in *B. typhosus*, *meningococcus* and *E. coli* filtrates are retained during dialysis by cellophane membranes, whereby a certain degree of purification can be achieved.

Vanni G28,854/37: In rabbits, i.c. preparation with *Sarcocystis* (sporozoa) filtrate, followed by i.v. provocation with the same material, results in generalized visceral hemorrhages (especially in the heart, kidney and lung) and death without signs of a local response in the directly prepared skin region.

Witebsky & Salm G23,252/37: Following i.c. injection of living or heat-killed *H. influenzae*, i.v. injection of the same organism or of *H. pertussis* produces an SSP-L in the rabbit. I.v. injection of *B. typhosus* elicits an SSP-L in skin sites prepared by *H. influenzae* but not in those prepared by *H. pertussis*. In rabbits prepared by *B. typhosus* i.c., both *H. influenzae* and *H. pertussis* i.v. elicit an SSP-L. "The effectiveness of suspensions of *H. influenzae* apparently is confined to the bacteria themselves rather than to the supernatant fluids."

Alechinsky E23,396/38; E54,349/38; G27,356/38: Heat-killed cultures of *E. coli* and *B. Morgan*, injected i.c. in the rabbit for preparation, sensitize the skin to the production of an SSP-L by the administration of one or the other of these bacilli s.c. or i.m. It has been shown previously that living cultures of these microorganisms are similarly effective, while in the case of preparation by filtrates, the s.c. or i.m. route of administration is not suitable for provocation.

Sanarelli G22,253/38: A generalized SSP-G can be produced in rabbits by heat-killed mixed bacteria collected from human saliva. However, in this case, 3 i.v. injections given at 24-hr. intervals are required. An SSP-L can be produced by the same material if the first injection is given i.c., the second i.v. Rabbits pretreated with small amounts of killed salivary microbes become immune to this response.

Shwartzman & Morell G27,949/38; *Morrell & Shwartzman* G27,948/38: Studies on the physicochemical properties of *S. typhosa*, *meningococcus* and *E. coli* filtrates capable of eliciting an SSP-L in the rabbit.

Shwartzman et al. G21,283/38: Following i.v. injection of living or heat-killed *Streptococcus viridans* cultures, *meningococcus* filtrate i.v.

24-72 hrs. later produces an SSP-G in the rabbit.

Tanaka & Terada G22,393/38: Extraction from meningococci of material capable of producing an SSP-L in the rabbit.

Witebsky & Neter E56,476/38: An SSP-L can be produced in the rabbit by *H. influenzae* i.c. followed 24 hrs. later by the i.c. injection of *H. influenzae*, killed *influenzae* bacilli or filtrates of *B. typhosus*, *E. coli* or *meningococcus*. Conversely, these filtrates, given i.c., may be activated by i.v. injection of *H. influenzae*. When a suspension of heat-killed *B. Friedländer* is injected i.c., an SSP-L results upon subsequent i.v. injection of a suspension of living or heat-killed *B. Friedländer*. Rabbit-virulent strains of *pneumococci* produce hemorrhagic necrosis upon i.c. injection without any i.v. provocation, but subsequent i.v. injection of *B. typhosus* filtrate aggravates this response.

Alechinsky D88,312/39: If live *E. coli* or *B. Morgan* cultures are given s.c. or i.m. to rabbits, even s.c. administration of *E. coli* or *B. Morgan* endotoxin will elicit an SSP-L at the site of infection. Apparently, live organisms are especially effective in preparing the tissues even for the smaller amounts of endotoxin that are absorbed from an s.c. injection site. However, even heat-killed cultures of the same microbes are very potent.

Gatto G25,243/39: An SSP-L can be produced in the rabbit by two injections of *Leishmania donovani* filtrate. "The hemorrhagic phenomena observed in visceral leishmaniasis may possess a mechanism similar to that of Sanarelli-Shwartzman's phenomenon."

Germanoff G28,152/39: Although filtrates of gonococci do not produce an SSP-L in the rabbit, positive reactions are obtained with gonococcus suspensions.

Glick & Antopol G22,256/39: The SSP-L produced by two injections in the rabbit was used as a test-object. It was found that "protein-free carbohydrate fractions of *B. proteus* possessed considerable provocative but no preparative power. *Shiga* polysaccharide gave irregular results, but a protein-free *Shiga* preparation of Morgan containing fatty and polypeptide materials in addition to polysaccharide was shown to have both factors."

Mertzling G27,483/39: An SSP-L can be elicited in the rabbit by two injections of typhoid or dysentery bacteriophage.

Walker & Handman G22,717/39: Various fractions of *S. typhimurium* endotoxin produced an SSP-L when given in two injections as usual to rabbits, but only the nucleoprotein and polysaccharide fractions induced hemor-

rhagic necroses in murine sarcoma-180 transplants.

Ogata & Akimoto G26,267/39; G26,280/39; G6,161/40: Rabbits prepared by diphtheria endotoxin i.c. can be provoked by *E. coli* endotoxin and vice versa.

Bronfenbrenner & Kalmanson G22,716/40: Attempts to demonstrate the in vivo interaction of bacteriophage with its antibody by means of the Shwartzman test were not successful in rabbits sensitized to bacteriophage either actively or passively.

Mariotti & Zanchi G28,859/40: An SSP-L cannot be elicited in the rabbit by two injections of various (human, bovine, avian) tuberculosis bacilli. However, following preparation of the skin with human tubercle bacilli, an SSP-L was produced in two rabbits subsequently challenged by *E. coli* endotoxin i.v.

Ayo G22,367/41: A single i.v. injection of meningococcus or typhoid toxin in the rabbit produces miosis, photophobia, lacrimation, congestion of the iris and conjunctiva with a marked pericorneal ring of dilated capillaries and in some instances with gross conjunctival hemorrhages. Repetition of the i.v. injection after 24 hrs. aggravates these manifestations. Curiously, "these effects may be considerably diminished by a previous local preparation of rabbits to the Shwartzman phenomenon."

Morgan G25,738/41: An SSP-L is obtained in the rabbit when *S. typhosa* antigen is used both as the preparatory and the provocative factor.

Sacharow G23,066/41: Using the classical SSP-L procedure in the rabbit, it was possible to show both preparatory and provocative activity in a *Leptothrix lanceolata* *Giz*, and an *Actinomyces* culture obtained from the oral cavity of man. It is possible that anaerobic germs of the oral cavity may play a role in focal infection.

Wise & Kerby G22,711/43: Various strains of *Brucella suis*, *Brucella melitensis* and *Brucella abortus* have been studied for their ability to elicit the SSP-L. Filtrates of two strains of *Brucella suis* were effective for skin preparation when *E. coli* endotoxin was given i.v. None of the *Brucella* endotoxins possessed provocative potency.

Gerber & Gross G22,255/44: An SSP-L is produced in rabbits sensitized to sulfonamide-conjugates at sites prepared by meningococcal toxin i.c., when either the homologous conjugate, the homologous native protein, or a related hapten attached to a different protein is given i.v.

Shwartzman G22,355/44: *S. marcescens* endo-

toxin and extracts prepared from this material can produce an SSP-L in rabbits.

Urbach et al. B19,915/44: In a patient who received three treatments with *typhoid vaccine* at 24 hr. intervals as a treatment for infectious arthritis, a typical SSP-G developed with widespread cutaneous and visceral petechiae as well as renal, hepatic and adrenal necrosis. Although several similar cases could be gathered from the literature, this appears to be the first report in which the SSP-G has been recognized as such in man.

Love & Driscoll B19,916/45: A patient who received two injections of *typhoid vaccine* with a 24 hr. interval for nonspecific therapy died with generalized petechiae throughout the parenchymal organs and with massive necrosis of the liver and kidneys (SSP-G?).

Hansen G21,299/47: In several patients who suffered from typhoid, treatment with *typhoid-vaccine* was followed by a generalized hemorrhagic reaction which is interpreted as an SSP-G.

Reich D92,102/48: In *typhoid* patients treated with Pyrifex, a fatal generalized hemorrhagic diathesis can occasionally result, presumably through the production of an SSP-G.

Takeda et al. G23,065/49: Purification of the SSP-active factors in *E. coli* and *B. typhosus* endotoxins.

Yamashita B84,101/49: By fractionation of *B. coli* toxin, it was found that an SSP-L can be produced by two injections of the polysaccharide, but not of the protein fraction.

Geks G23,262/50: It is not possible to produce an SSP-L either in the guinea pig or in the rabbit by two injections of Pyrifex (a suspension of killed *E. coli*) under conditions in which *E. coli* filtrates are active. Presumably lysis of the organisms is necessary to liberate the active principle. The claim of Reich (D92,102/48) that Pyrifex can produce an SSP when used for therapeutic purposes in patients with typhoid fever, has been contested by Höring (D72,058/48) and is also rejected by the present author.

Geks & Hagemann G23,263/50: It is impossible to produce an SSP-L in man by Pyrifex injected first i.c. and 24 hrs. later i.v. Hence, there is no reason to fear that, when Pyrifex is used as a nonspecific therapeutic agent (e.g., in the treatment of typhoid fever), an SSP-L might be produced in man.

Gonçalves G22,359/50: Following preparation by infiltration of the vagus or splanchnic nerves with live *herpes simplex virus*, the i.v. injection of the same material 24 hrs. later produces gastroduodenal ulcers with local

hemorrhages and necrosis. These are interpreted as an SSP-L. Herpes simplex is allegedly common in patients with gastroduodenal ulcers. Perhaps localization of a virus in the autonomic nerves with a subsequent SSP-L is involved in the pathogenesis of gastroduodenal ulcers in man.

Filipp & Kelenhegyi G23,257/51: An SSP-L can be produced in the rabbit by two injections of a live *E. coli* culture suspension.

Takeda & Kashiba G18,530/52: Using the SSP-L of the rabbit as a test object, a toxic carbohydrate of high SSP-activity was obtained from the endotoxin of *Ohno paradyssentery bacilli*.

Thomas et al. G21,523/52: If an SSP-G is produced in the rabbit by two i.v. injections of meningococcal toxin, acute myofiber necrosis sometimes occurs in the heart. When living group-A streptococci are substituted for the first i.v. injection and the meningococcal toxin is given 48 hrs. later i.v., a new type of cardiac lesion results which conspicuously affects the coronary arteries. The latter show extensive deposits of fibrinoid within their walls and in the perivascular spaces; this is sometimes conducive to necrosis. Such lesions were not seen outside the heart, although almost 50% of the animals exhibited bilateral renal cortical necrosis.

Alechinsky G22,361/53: If simultaneously with the usual i.c. preparatory injection of *E. coli* endotoxin, the same material is injected i.v., provocation with *E. coli* endotoxin i.v. 24 hrs. later causes neither local nor generalized SSP-manifestations.

Thomas et al. G21,293/53: Cutaneous and systemic infections with Group A streptococci prepare the rabbit for the SSP-L and SSP-G respectively by subsequent i.v. injection of meningococcal or *S. marcescens* toxin. Under optimal conditions of dosage and timing, fibrinoid deposits appear in the coronary arteries in approximately 50% of the animals. "These are obvious points of resemblance between the vascular lesions of fibrinoid necrosis produced in rabbits and the changes in blood vessels which occur in certain human disease states, characterized by fibrinoid deposition, such as rheumatic fever, periarthritis nodosa, thrombotic thrombocytopenia, and disseminated lupus erythematosus."

Holzberger & Packalén G22,357/54: In guinea pigs infected with *M. tuberculosis*, old tuberculin i.v. is less effective than *E. coli* filtrate i.v. in producing focal injury at sites of dermal tuberculin inflammation. Direct injection of *E. coli* endotoxin into the sites of moderate tuberculin reactions causes hemorrhagic ne-

crotic lesions in tuberculous guinea pigs, but sterile broth has a similar, though much less pronounced effect. The mechanism of this type of THP "might well be analogous to the Shwartzman-like phenomenon which Black-Schaffer and associates (G22,334/50) produced in sensitized animals through a mixed single injection of homologous antigen and a Shwartzman-preparatory toxin."

Eichenberger et al. C13,546/55: An SSP-L can be elicited in the rabbit by two injections of *S. abortus equi* polysaccharide (Pyrexal). This substance is also effective, both as the preparatory and as the provocative agent, if killed *E. coli* is used as the other agent. Previous immunization with *S. abortus equi* endotoxin prevents the response.

Raška et al. G23,259/56: In rabbits in which an SSP-L is elicited by means of an extract from streptococcal skin lesions and Streptolysin O, intranasal infection with β -hemolytic streptococci, 3-4 weeks later, produced a polyarthritis. "The clinical and histological aspects of these lesions exhibited a close similarity to the findings in acute rheumatic fever and in the postrheumatic myocardium."

Stetson G24,711/56: Both an SSP-L and an SSP-G can be produced by "crude streptococcal lysates, and the data suggest that streptococci possess an endotoxin similar to those of Gram-negative bacterial species."

Meier et al. C57,198/57: Polysaccharides, obtained from various species of *proteus*, could be used for the production of an SSP-L in the rabbit. Alechinsky (G15,976/52) reported that *E. coli* filtrates, injected i.v. simultaneously with the preparatory i.c. dose, largely inhibited the SSP-L. This has now been confirmed with the *proteus* polysaccharide.

Pirsch et al. G27,360/57: In guinea pigs infected with *Coxiella burnetii* i.p., provocation with *Brucella*, *E. coli* or *S. typhosa* endotoxin, intracardially 3 days later, caused death with adrenal hemorrhages interpreted as an SSP-G, although no characteristic changes were found in the kidneys and hemorrhages in other organs were very inconstant.

Bordet G27,044/58: I.c. preparation with influenza virus does not prepare the rabbit for the production of an SSP-L by the subsequent i.v. administration of *E. coli* endotoxin. However, if the virus is given i.v., provocation with *E. coli* endotoxin 24 hrs. later results in a typical SSP-G with predominant hemorrhagic manifestations in the lung and trachea. Influenza virus was not found to be effective when used as the provocative agent following preparation with *E. coli* endotoxin.

Rizzo & Mergenhagen G28,648/60; Mergen-

hagen G33,250/60: An SSP-L has been produced both in the skin and in the oral mucosa of the rabbit by topical preparation followed by i.v. provocation with an extract of *Veillonella* organisms.

Kato et al. G33,253/61: Influenza virus particles possess both skin preparatory and provocative potency in the production of an SSP-L in rabbits. This is true whether the virus is used both for the preparatory and the provocative injection, or when one of these treatments is replaced by *E. coli* endotoxin.

Jablonska & Rzucidlo G27,943/63: *E. coli* endotoxin, partially detoxified by acetylation, can still serve both as the preparatory and the provocative factor in the production of an SSP-L in the rabbit, although its activity is diminished.

Minervin & Yaroshik G27,942/63: When *streptococcus* allergen is added to *E. coli* filtrate, the ability of the latter to produce an SSP-L in the rabbit is greatly increased. The authors assume that, in rheumatic patients, the intestinal microflora intensifies the sensitization caused by the streptococcus.

Sourek G28,488/63: An SSP-L can be pro-

duced in rabbits with various types of *Sh. dysenteriae* endotoxins.

Cheng et al. G27,293/64: *S. typhosa* endotoxin can be partially detoxified by treatment with LiAlH_4 in vitro, whereupon its ability to produce an SSP-L is much more considerably reduced than its antigenicity.

Emmrich et al. F8,082/64: Two i.v. injections of a purified lipopolysaccharide, prepared from *Salmonella abortus equi* (Pyrexal), are particularly effective in eliciting the SSP-G in the rabbit.

Lawson & Dow G27,197/64: An SSP-G can be produced in rabbits by two i.v. injections of *Salmonella cholerae-suis* endotoxin.

Beer et al. G27,945/65: Earlier investigations suggested that particle size is a decisive factor in determining the toxicity of bacterial endotoxins. However, it has now been found that the production of an SSP-L by two injections of *E. coli* endotoxin is unchanged when the endotoxin aggregates are dissociated with sodium dodecyl sulfate. "Particle size is thereby ruled out as a significant determinant of toxicity."

Methods of Assessment. As a rule, the SSP-L is assessed by the intensity of the local reaction (hemorrhage, edema, necrosis) at the site of the preparatory injection, in terms of an arbitrary scale (e.g., "mild," "moderate" and "severe" response, or +, ++, +++). More nearly quantitative data can be obtained by measuring the mean diameter of the local lesions, or by determining the affected surface planimetrically. It is also possible to assess the degree of the response by determining the hemoglobin content of the affected tissue.

The development of the vascular lesions can be observed microscopically *in vivo* (e.g., on the exposed mesentery of the rabbit) or post mortem (e.g., on stained mesenteric spreads).

The intensity of the SSP-G is commonly assessed by the gravity of the thrombohemorrhagic lesions in various tissues. The production of hyaline thrombi in the renal capillary glomeruli is generally (though not unanimously) considered to be most characteristic (Cf. pp. 157ff.).

Hugues et al. C76,931/59: The development of an SSP-L can be easily observed *in vivo* on the mesentery of the rabbit, following topical preparation and subsequent i.v. provocation with *S. typhi murium*. It is initiated by the rupture of small veins with only slight agglutination of platelets and leukocytes along the vessel walls but without platelet emboli. Histologically, the phenomenon can be con-

veniently examined on a mesenteric spread, attached to a plastic ring on which it is fixed for subsequent staining. The earliest lesions are intense perivenous hemorrhagic infiltration without thrombosis.

Ferina & Buccheri E53,256/62: Quantitation of the SSP-L is possible by determining the hemoglobin content of the cutaneous lesions.

The Critical Period. The development of the SSP-G and SSP-L (just as that of the local and systemic forms of calciphylaxis) depends upon the application of

two consecutive treatments with a definite "critical period" between them. It is generally agreed that in the rabbit the most constant and severe changes are obtained if about 24 hrs. elapse between the preparatory (i.v. or i.c.) and the provocative (i.v.) injections of SSP-active materials.

Actually, very little work has been done on the factors that influence the critical period, yet it is generally assumed that the necessity of a 24-hr. time lapse is quite characteristic of the SSP under all circumstances. The need for an interval between treatments has been ascribed either to the time necessary for the development of local changes that make the target organs receptive, or to alterations in the physico-chemical properties of the blood, particularly the coagulation system. However, even the few published pertinent data make it clear that the length of the critical period is subject to wide variations. For example, repeated i.c. preparation or the introduction of the preparatory endotoxin into a temporarily occluded segment of a vein may shorten the critical period, while repeated injections of neosalvarsan (given after the preparatory injection) have been said to prolong it. The length of the critical period also depends upon the species (it appears to be especially variable in guinea pigs), and upon the type of endotoxin preparation employed. Furthermore, as we shall see later, certain tumors and the placenta are constantly in a state of preparation in that they respond with a THP to single provocative injections.

Shwartzman E53,222/30: In rabbits, reactivity to the SSP-L disappears completely within 48 hrs. after a preparatory i.c. injection of bacterial endotoxin.

Gratia & Linz E65,234/31: If two preparatory injections of bacterial endotoxin are given s.c. into the rabbit ear, i.v. provocation becomes possible during the following 4-8 hrs. If one injection is given, an incubation period of about 20 hrs. is necessary. Apparently, "a first preparatory injection can favorably influence the effect of a second preparatory injection." [Although the authors fail to mention it, they presumably used *E. coli* endotoxin, since this was the material usually employed in their other publications (H.S.).]

Debonera et al. B78,075/32: In guinea pigs, the bacillus of Preisz-Nocard s.c. produces an abscess in which an SSP-L can be elicited by the i.v. injection of *E. coli* endotoxin three days later. In guinea pigs infected with an avirulent tuberculosis culture (strain of Cheval-Vallée), provocation by *E. coli* endotoxin i.v. is possible only 4-5 days later, but after this prolonged critical period, a typical SSP-L results.

Gratia & Linz D6,544/32: In rabbits, the optimum critical period between two injections of bacterial filtrate is about 24 hrs., but some response can be obtained after 5-6 hrs.

Alechinsky D70,636/35: A typical SSP-L can be produced in the ear of the rabbit by topical

preparation and simultaneous i.v. provocation with *E. coli*. Even i.m. injection of the provocative dose is effective. The author concludes that "the hemorrhagic phenomenon can be produced just as well when the preparative and the provocative injections are given simultaneously and irrespective of the site at which the provocative injection is administered." [It must be kept in mind, however, that the author used his unique method of preparation (cf. below), injecting the endotoxin into the temporarily clamped vein of the rabbit's ear (H.S.).]

Shwartzman G23,096/35; G28,161/35: In rabbits the duration of the critical period varies. Reactivity "lasts for 96 hrs. with meningococcus 'agar washings' filtrates; for 72 hrs. with *B. typhosus* 'agar washings' filtrates; it disappears within 48 hrs. with *B. typhosus* tryptic digest broth culture filtrate and *B. typhosus* 'agar washings' filtrates previously heated in the Arnold sterilizer for 20 minutes."

Gayta G26,873/36: In guinea pigs, an SSP-L cannot be produced by two injections of diphtheria endotoxin given at 24-hr. intervals, but the response is often positive if the critical period is prolonged to 48 hrs.

Gerber C95,662/36: In rabbits given two i.v. injections of meningococcal or typhoid filtrates, a 24-hr. interval proved to be optimal.

Laporte G23,880/36; G23,881/36: Small amounts of live typhoid bacilli i.c. cause only

transitory swelling of the skin in guinea pigs, while large doses produce hemorrhagic necrosis. If the i.c. administration of small doses of typhoid bacilli is accompanied by a simultaneous i.p. injection of typhoid-culture filtrate, hemorrhagic necrosis develops at the dermal injection site after 8-12 hrs. The response thus differs from the SSP-L in that there is no critical period between the two injections and that, following provocation, the dermal lesion is slower to develop. With this experimental arrangement, s.c. provocation yields inconstant results but if, instead of the filtrate, live typhoid bacilli are used for provocation, hemorrhagic necrosis invariably occurs at the site of preparation even if the provocative injection is given s.c. However, in this event, it may take 48 hrs. for the skin lesions to become evident. Similar results have been obtained with pneumococcus and pasteurella organisms.

Renaux & Alechinsky G18,585/36: If a preparatory i.v. injection of *E. coli* endotoxin is followed by daily i.v. injections of neosalvarsan, a provocative i.v. injection of *E. coli* endotoxin, given on the fourth day, produces cutaneous purpura and internal lesions characteristic of the SSP-G. It is concluded that neosalvarsan prolongs the critical period and alters the response so that both cutaneous and internal hemorrhages occur.

Veratti G26,189/36: In attempting to reproduce the Apitz phenomenon, the most reliable procedure consisted in administering 5-6 i.v. injections of *E. coli* endotoxin at 3-4 hr. intervals in ascending doses, each injection doubling the preceding one. Thrombohemorrhagic lesions occurred primarily in the lung and intestine accompanied by fibrin thromboses of the renal glomerular capillaries. Passive transfer of the phenomenon was not possible by transfusion of large amounts of blood from an animal about to develop the lesions to a new one.

Horster & Müller G25,124/37: In rabbits sensitized to pig serum, it is possible to elicit an SSP-L with two injections of meningococcal endotoxin, even if the critical period is extended to 48 hrs.

Alechinsky D88,312/39: If one ear of the rabbit is compressed at the base so as to stop the circulation, and then *E. coli* endotoxin is injected into a vein distad from the compression, no obvious local change is noted upon re-establishment of the circulation. However, if within 24 hrs. the same filtrate is injected into the marginal vein of the opposite ear, a hemorrhagic response is obtained on the pretreated side. Thus, it is possible to prepare a region by the local intravascular application

of endotoxin. If the ear is prepared in this manner, it will respond with hemorrhage even if the i.v. injection is given into the contralateral ear almost simultaneously with the preparatory injection. Thus, the critical period of incubation can be greatly shortened.

Sanarelli G28,164/39: An SSP-G can be produced by the i.v. injection of sterilized human saliva (presumably the result of its bacterial flora) but only if three injections are given at 24-hr. intervals. Here, in addition to the usual intestinal, renal and pulmonary lesions, hemorrhages occur in the psoas muscles and the uterine horns.

Thomas & Good B79,249/52: Data concerning the optimal timing and dosage of meningococcal toxin for the production of the SSP-G in the rabbit. Excessive amounts of toxin actually inhibit the reaction. The optimum time between the two injections lies between 12 and 72 hrs.

Valeton & Doepfmer C5,901/54: It is possible to produce an SSP-L by two injections of *E. coli* endotoxin in the guinea pig if a concentrated filtrate is administered twice with an interval of only 10-14 hrs. This shortened critical period is held responsible for success in this comparatively resistant species, but no control experiments were made with longer intervals.

Arndt & Schneider G21,207/60: In BSVS strain mice, an SSP-L can be elicited by an i.c. followed by an i.p. or i.v. injection of various bacterial endotoxins. Several types of antigen-antibody complexes can also be used for provocation. Some animals reacted in the usual manner to single i.c. injections of endotoxins but, in these, there was infection of the lungs with gram-negative microflora. Here, the latter apparently acted as the preparatory agent without there being any specific critical period, since the animals were permanently responsive.

Jaeger & Honegger D3,635/60: An SSP-L can be produced in the nictitating membrane of the rabbit by topical preparation with 0.05 µg. of *S. abortus equi* endotoxin and subsequent provocation with various macromolecular substances (e.g., Liquoid, dextran, PVP). Under these conditions, preparation and provocation are best applied simultaneously and the response occurs within a few minutes.

Mezzano & Peluffo D9,326/60: In rabbits given *S. typhosa* filtrate i.c. and 1-2 hrs. later norepinephrine i.v., there develops a central ischemic necrosis surrounded by a halo of hemorrhagic necrosis at the site of the filtrate injection. Intravascular blood clots are never

observed and hence the response differs essentially from the SSP-L.

Conti et al. D4,566/61: E. coli or Sh. flexneri endotoxin given i.c. simultaneously with, or a few hours before, a suspension of living hemolytic staphylococcus aureus cultures causes intense topical hemorrhagic necrosis of the skin in rabbits and increases the infectivity of the microorganisms. Similar changes were obtained when the endotoxin was given

i.v. at sites of concurrent i.c. inoculation with staphylococci.

Fukui et al. G33,120/64: Allegedly, a "reversed Shwartzman phenomenon" can be produced in rabbits at sites of i.c. E. coli endotoxin administration if the animals previously received an i.v. injection of the same endotoxin. An SSP-L in the urinary bladder is obtained under the same circumstances but it is of lesser intensity than in the skin.

Route of Preparation and Provocation. In most of the work on the SSP-L, the preparatory injection was given i.c., not only because the derma is particularly sensitive but also because the resulting surface reactions are easily observed in vivo. However, as we shall see later (cf. Chapter IV), a typical SSP-L can be produced in virtually any vascularized organ following topical administration of the preparatory material.

For successful provocation, rapid flooding of the circulation with SSP-active factors appears to be essential; hence, i.v. injection is most effective; i.p. provocation is also possible, while i.c., s.c., or i.m. administration of the provocative factor is usually ineffectual. Injection of the provocative agent into the bone marrow is almost as effective as i.v. provocation, presumably because the great vascularity of hemopoietic tissue allows much of the material introduced into it to enter blood vessels directly.

Following the injection of endotoxin into a temporarily clamped ear vein of the rabbit, i.v. injection of the same material (after release of the clamp) produces an SSP-L at the site of preparation. Indeed, under these conditions even s.c. provocation can be efficacious.

Reilly succeeded in producing hemorrhagic reactions in the mesenteric lymph nodes and Peyer's plaques by single injections of bacterial endotoxins, metals and other compounds into sympathetic nerves and ganglia. It remains debatable however, whether the Reilly phenomenon represents a modified form of the SSP.

Hanger B78,181/27-28: While B. lepisepticum filtrate, administered first i.c. and 24 hrs. later i.v., produces a typical SSP-L, no local hemorrhagic necrosis can be produced if both injections are given i.c. with a 24-hr. interval.

Frisch E95,434/30: "Rabbits in which the intraperitoneal injection of B. typhosus culture filtrate was able to elicit the Shwartzman phenomenon in previously prepared skin sites were rendered negative to this phenomenon by repeated injections of this culture filtrate intraperitoneally. It was then shown that this skin reaction could still be produced if the reacting factors were introduced intravenously. It must thus be concluded that the immunity produced under these circumstances was of a distinctly local character involving only the peritoneum."

Bock E72,616/32: Following i.c. preparation with E. coli endotoxin, an SSP-L can be elicited

much more readily if the provocative injection of the same material is given into the right rather than into the left ventricle. Presumably, to be fully effective, the endotoxin must first traverse the pulmonary circulation. Preparation of the rabbit ear is possible both by i.c. and percutaneous administration of E. coli endotoxin.

Gratia & Linz D6,544/32: The provocative injection of bacterial filtrate can be given i.p. but not s.c. or i.m. (Details concerning these experiments are not given.) Apparently, the important factor for provocation is that the agent must rapidly flood the circulation. Filtrates of cholera vibrios injected first i.c. and 24 hrs. later i.v. produce not only an SSP-L but also an SSP-G with hemorrhages in the intestine, peritoneal cavity and uterus.

Apitz D10,355/33: Topical re-injection of the i.c. prepared skin site with typhosus, coli or

cuniculisepticum filtrates can produce intense local edema with leukocytic infiltration but no hemorrhage. "Thus, the resulting change in reactivity can also be demonstrated by this technique; only the hemorrhage is apparently dependent upon the intravascular administration of the antigen. Therefore, the morphologic specificity of the Shwartzman reaction depends upon the manner in which the filtrates are administered. The response is changed in the case of local re-injection and then becomes identical with local anaphylaxis."

Reilly et al. G21,897/35: The application of typhoid, paratyphoid and diphtheria bacilli or their endotoxins by direct injection into the mesenteric lymph nodes or the vicinity of sympathetic nerves (splanchnics, semilunar ganglion, adrenal medulla), produces changes similar to those of spontaneous typhoid fever in man. There is swelling and hemorrhage in the mesenteric lymph nodes and Peyer's plaques with exulceration of the latter in a great variety of animal species, including those that are quite insensitive to the same microbial products when administered through other routes. Even intracardiac injection of paratyphoid endotoxin causes intense perineuritis around the splanchnic nerves of the guinea pig owing to the neurotropic effect of this toxin. The response is largely nonspecific since certain metals (cobalt, nickel, lead, arsenic, as well as nicotine, snake venoms, etc.) applied directly to the splanchnic nerves of the guinea pig, produce similar gastrointestinal hemorrhagic responses. The same is true of mechanical trauma by ligatures placed around the splanchnics or prolonged faradic stimulations of these nerves. It is assumed that sympathetic stimulation is largely responsible for the gastrointestinal hemorrhagic syndrome characteristic of typhoid fever and that the close anatomical connections between the mesenteric lymph nodes and the splanchnic nerves accounts for the fact that application of the irritants to either of these structures is effective. This form of hemorrhagic necrosis has become known as "Reilly's syndrome of neurovegetative irritation."

Alechinsky G21,634/35; D70,636/35; G21,635/36: Following injection of *E. coli* endotoxin into a temporarily ligated ear vein of the rabbit, i.v. injection of the same material after release of the compression produces an SSP-L at the site of preparation. When thus prepared, even s.c. injection of *E. coli* endotoxin can produce an SSP-L in the ear in which the same material had previously been injected into the temporarily ligated vein for preparation.

Stolyhwo G21,662/35-36: Typhoid or paratyphoid filtrate given i.c. twice with a 24-hr. interval does not produce an SSP-L in the rabbit.

Vanni G28,854/37: In rabbits, i.c. preparation with *Sarcocystis* (sporozoa) filtrate followed by i.v. provocation with the same material results in generalized visceral hemorrhages (especially in the heart, kidney and lung) and death without signs of a local response in the directly prepared skin region.

Alechinsky E54,349/38; G27,356/38; E23,396/38; D88,312/39: Heat-killed cultures of *E. coli* and *B. Morgan* injected i.c. in the rabbit for preparation, sensitize the skin to the production of an SSP-L by the administration of one or the other of these bacilli s.c. or i.m. It has been shown previously that living cultures of these microorganisms are similarly effective, while in the case of preparation by filtrates, the s.c. or i.m. route of administration is not suitable for provocation.

Fabiani G22,337/39: In rabbits prepared by i.c. injection of *Sh. dysenteriae* endotoxin, a subsequent injection of the same material into the bone marrow produces a cutaneous SSP-L. This is ascribed to the ready absorption of the toxin from the hemopoietic tissue.

Ogata G22,362/41: When *E. coli* endotoxin is repeatedly given i.c. at the same site at a few hours' interval, an SSP-L develops. "These results are a clear evidence that the rabbit may develop skin lesions of the Shwartzman type on repeated intradermal injections of the Shwartzman filtrate. The failure of Shwartzman to induce the phenomenon in this way may be attributed to insufficient repetition of the injection at proper time interval."

Shwartzman et al. D71,760/50: The "assumption receiving most support is that the damage to vascular endothelium necessary for the production of the reaction can be elicited only when the provocative agent is brought in contact with the endothelium intravascularly."

Stetson G22,085/55: In opposition to Shwartzman (B19,913/37) and confirming Ogata (G22,362/41), it was found that hemorrhagic skin necrosis could be obtained in rabbits given two i.c. injections of bacterial endotoxins into the same skin area with a 24-hr. interval. "Skin lesions similar to those described above could also be produced by the reinjection of tuberculin into 24-hr.-old tuberculin reactions in rabbits vaccinated 3 weeks previously with BCG." The degree of hypersensitivity attained was insufficient to permit hemorrhagic necrosis by a single dose of tuberculin.

Rall & Gaskin C13,122/56: In rabbits given *S. marcescens* endotoxin i.c., the subsequent injection of epinephrine or norepinephrine into the prepared skin sites produces a local hemorrhagic necrosis.

Raška et al. G23,259/56: In rabbits in which an SSP-L is elicited by means of an extract from streptococcal skin lesions and Streptolysin O, intranasal infection with β -hemolytic streptococci, 3-4 weeks later, produced a polyarthritidis. "The clinical and histological aspects

Dosage. In general, there exists a reciprocal relationship between the strength of the preparatory and the provocative injection necessary to obtain constant and pronounced reactions.

Antopol G23,098/37: With extracts of various endotoxins, it could be shown that, the larger the i.v. dose, the smaller the minimal i.c. dose necessary to produce an SSP-L in the rabbit.

Shwartzman B19,913/37: Using various bacterial endotoxins, "the paradoxical observation was made that sites prepared with dilutions as high as 1:1000 reacted, providing the same animals were also prepared by injection of lower dilutions. On the other hand, if higher dilutions alone were employed for preparation, no reactions were obtained." . . . "There exists a distinct reciprocal relationship between the amounts of filtrate necessary to be injected intradermally and intravenously in order to elicit the phenomenon. Thus, even the highest

of these lesions exhibited a close similarity to the findings in acute rheumatic fever and in the postrheumatic myocardium."

Rall & Kelly C36,395/57: In rabbits given *S. marcescens* endotoxin i.c. in the right upper quadrant of the abdomen, the ear, costovertebral angle or hind leg, the incidence of positive SSP-L reactions, following subsequent i.v. administration of the same toxin, varied between 58 and 92%.

dilution employed is able to prepare the skin of some rabbits for severe hemorrhagic necrosis, provided large amounts of the filtrate are injected intravenously. As the intravenous dose is decreased, well-pronounced reactions are elicited only in areas prepared with lower dilutions." Furthermore, "a considerably smaller amount of reacting factors is required in order to elicit reactions in one site than when several sites are prepared."

Takeda et al. G23,061/54: Using a purified preparation of the O antigen from cultures of Ohno dysentery bacilli in rabbits, the minimum i.c. preparatory dose is 5 μ g, the minimum i.v. provocative dose 200 μ g, and the minimum pyrogenic dose between 0.025 and 0.05 μ g.

Passive Transfer. Much attention has been given to the possibility that the SSP-L may be passively transferred from one animal to another in analogy to some allergic reactions. To test this concept, a sponge impregnated with endotoxin was implanted s.c. into a rabbit subsequently given a provocative injection. The fluid obtained from such a sponge contains preparative potency; indeed, when it is injected s.c. into another rabbit, the latter responds with an SSP-L even if the provocative injection is given as soon as 4-5 hrs. after preparation. In view of this short critical period it was thought that the exudate could not act by virtue of residual endotoxin. However, later investigations revealed that normal serum or tissue extracts exert an adjuvant effect upon concurrently administered endotoxin, thereby shortening the critical period. It is probable therefore, that the sponge exudate is so efficacious merely because of the combined effect of residual endotoxin and adjuvating action of tissue fluid.

The blood of rabbits, which had developed an SSP-L after two injections of endotoxin, possesses neither preparatory nor provocative potency. It is true that certain types of SSP which depend in part upon immunologic sensitization, can be passively transferred but, here, it is presumably the immunological sensitization and not the SSP that is transferable.

It is possible to elicit an SSP-G in a nonpretreated rabbit if it receives massive

amounts of blood (through carotid-jugular cross transfusion) from another rabbit in which an SSP-G has been elicited. Selective renal lesions characteristic of the SSP-G can be produced in this manner if only the kidneys are thus perfused. The reactions observed in the recipient animals have been ascribed to the transfer of fibrinoid and not to a true passive immunological reaction. In any event, this form of "passive transfer" experiment could be used in support of any humoral theory (e.g., anaphylaxis), or ascribed to the combined effect of residual endotoxin and the adjuvant effect of blood.

Shwartzman E53,222/30: It was not possible to obtain passive transfer to the local skin reactivity in rabbits by the i.c. injection of *B. typhosus* immune sera followed by i.v. injection of *B. typhosus* filtrates.

Gratia & Linz E65,234/31: A sponge, impregnated with bacterial endotoxin is implanted s.c. into a rabbit which receives a provocative i.v. injection 24 hrs. later. This sponge contains substances which can produce an intense SSP-L in another rabbit subsequently treated with endotoxin i.v. Preparation with this exudate produces an SSP-L even if the provocative i.v. dose is given as soon as 4-5 hrs. after preparation; hence the activity of the exudate cannot be ascribed to residual endotoxin. Preparation with endotoxin 5 hrs. prior to provocation is ineffective. [Although the authors fail to mention it, they presumably used *E. coli* endotoxin, since this was the material usually employed in their other publications (H.S.).]

Bock E72,616/32: The serum of rabbits which have developed an SSP-L after two injections of *E. coli* endotoxin is inactive both for preparation and for provocation in a recipient rabbit in which *E. coli* endotoxin is used for the other injection. It is also impossible to elicit the Prausnitz-Küstner phenomenon with the blood of such endotoxin-treated rabbits.

Shwartzman G23,071/32: Rabbits sensitized a week previously to some animal protein, receive a skin-preparatory injection of a potent bacterial filtrate. Twenty-four hrs. later, the i.v. injection of the same animal protein produces an SSP-L at the prepared skin sites. It is also possible to elicit an SSP-L in the prepared skin of nonsensitized rabbits by separate i.v. injections of non-bacterial and bacterial antigens plus homologous antibodies. This is considered a "passive transfer."

Shwartzman G22,681/33: In rabbits, *B. typhosus* or meningococcal endotoxins were given i.c. Twenty-four hrs. later, the prepared skin sites were injected with the antibody-containing sera while the homologous antigens

were given i.v. The resulting SSP-L was considered evidence of "passive transfer."

Michelazzi G26,872/35; G26,871/35: An extract of the skin of a rabbit previously given an i.c. injection of *E. coli* endotoxin, is incubated with the same endotoxin and then injected i.c. into another rabbit. Often, though not always, this mixture produces an "SSP-L" without subsequent provocation. [It remains to be seen whether this phenomenon is related to passive transfer, adjuvination, or—as the author believes—the formation of an antibody in the prepared skin site (H.S.).]

Michelazzi G28,490/35: Rabbits infected with tuberculosis become hypersensitive to the production of an SSP-L by two injections of *E. coli* endotoxin. If their blood is injected i.p. into guinea pigs, the hypersensitivity can be transferred since these animals develop an SSP-G upon a single i.v. injection of *E. coli* endotoxin. If an SSP-L is elicited by *E. coli* endotoxin in rabbits rendered hypersensitive to this response by infection with tuberculosis, their blood, given i.v. to a guinea pig, suffices in itself to produce an SSP-G in the latter.

Michelazzi G26,190/36: Twenty hrs. following i.c. preparation of the skin with *E. coli* endotoxin, the treated region was removed, homogenized and injected i.c. into a new rabbit which received *E. coli* endotoxin i.v. 1-6 hrs. later. No passive transfer of the phenomenon could be obtained in this manner.

Veratti G26,189/36: In attempting to reproduce the Apitz phenomenon, the most reliable procedure consisted in administering 5-6 i.v. injections of *E. coli* endotoxin at 3-4 hr. intervals in ascending doses, each injection doubling the preceding one. Thrombohemorrhagic lesions occurred primarily in the lung and intestine accompanied by fibrin thromboses of the renal glomerular capillaries. Passive transfer of the phenomenon by transfusion of large amounts of blood from an animal about to develop the lesions to a new one, gave negative results. Pretreatment with small amounts of endotoxin offered immunity.

Alechinsky G22,308/37: An extract was made of rabbit skin prepared by topical injection of *E. coli* endotoxin. This extract, injected i.c. into another rabbit, prepares the latter for the production of a particularly rapid development of an SSP-L following subsequent i.v. injection of the same endotoxin. This rapid response is obtained whether or not the donor rabbit was given a provocative injection of endotoxin. Similar extracts from normal skin or from cutaneous areas which underwent inflammation (under the influence of tapioca or turpentine injections) are inactive. Since previous observations had shown that normal serum or tissue extracts exert an adjuvant effect upon concurrently administered *E. coli* endotoxin, it is incorrect to ascribe this phenomenon to a passive transfer of the SSP. The acceleration of the response is merely due to the adjuvant effect of tissue extract upon bacterial endotoxin remaining at the injection site.

Alechinsky G22,554/37; D88,312/39: A sponge soaked with *E. coli* endotoxin is implanted s.c. in a rabbit and removed 24 hrs. later. This fluid given i.c. to another rabbit can so prepare the skin that a provocative injection of *E. coli* endotoxin i.v. causes an SSP-L at the dermal preparation site within 4-5 hrs. Since such a short interval between the preparatory and provocative dose is normally insufficient, passive transfer of the response had been suspected by Gratia & Linz (E68,252/31) who performed similar experi-

ments before. However, if the serum of a prepared rabbit or even that of a normal one is injected i.c. into the same region, before or together with a normally ineffective dose of *E. coli* endotoxin, then provocation by *E. coli* endotoxin i.v. 24 hrs. later induces an SSP-L at the prepared site. Apparently, normal rabbit serum (and indeed even the serum of other species) can act as an adjuvant for endotoxin.

Gamble & Brunson G21,645/55: The blood of donor rabbits in which an SSP-G was elicited by two injections of meningococcal endotoxin or by one injection of meningococcal endotoxin plus sodium polyanethol sulfonate (Liquoid), was perfused 2-4 hrs. after the last injection into unprepared recipients by carotid-jugular cross transfusion. This resulted in the development of a typical SSP-G in the recipients except that the renal lesions were somewhat less pronounced than usual. Renal lesions characteristic of the SSP-G were produced by isolated renal perfusion with the use of donor animals prepared with meningococcal endotoxin and sodium polyanethol-sulfonate. Normally endotoxin is rapidly cleared from the blood, hence it is unlikely that residual endotoxin in the blood of donor animals could be responsible for the observed changes. "The presence of fibrinoid following transfusion in unprepared recipient animals offers considerable evidence for its transfer by way of the blood stream."

CHAPTER III

NONMICROBIAL AGENTS AS ELICITORS OR MODIFIERS OF THE THP

THE preceding chapter has dealt with the production of a THP, and particularly the SSP-L and the SSP-G, by purely microbial means. Now we shall turn our attention to nonmicrobial agents that can produce, prevent or qualitatively modify a THP elicited by any means. Accordingly, even observations on the influence of nonmicrobial agents upon a THP produced by microbial products will be dealt with in the following pages.

ADJUVANTS

Comparatively little work has been done with the specific purpose of investigating the effect of various adjuvants, beyond the observation that serum mixed with bacterial endotoxins enhances the local preparative potency of the latter. However, the definition of the term "adjuvant" is somewhat vague, and any agent that enhances an activity could be thus designated. If we think of adjuvants in this broader sense, we shall find many additional examples of "adjuvation" in later sections of this chapter.

Bordet G23,078/34: Rabbit or guinea pig serum i.c. or peptone i.c. fail to prepare the rabbit for the production of an SSP-L by a subsequent i.v. injection of *E. coli* endotoxin. However, if rabbit or guinea pig serum is injected first, and 24 hrs. later peptone is introduced into the same dermal region, the subsequent i.v. injection of *E. coli* elicits an SSP-L. "The previous local injection of serum undoubtedly possesses the power to augment the sensitivity of the skin to the irritating properties of these substances which cannot manifest themselves when the injections are made in previously unprepared skin."

Michelazzi G26,872/35; G26,871/35: An extract of the skin of a rabbit previously given an i.c. injection of *E. coli* endotoxin is incubated with the same endotoxin and then injected i.c. into another rabbit. Often, though not always, this mixture produces an "SSP-L" without subsequent provocation. [It remains to be seen whether this phenomenon is related to passive transfer, adjuvation, or—as the

author believes—the formation of an antibody in the prepared skin site (H.S.).]

Alechinsky G22,554/37: A sponge soaked in *E. coli* endotoxin is implanted s.c. in a rabbit and removed 24 hrs. later. This fluid given i.c. to another rabbit can so prepare the skin that a provocative injection of *E. coli* endotoxin i.v. causes an SSP-L at the dermal preparation site within 4-5 hrs. Since such a short interval between the preparatory and provocative dose is normally insufficient, passive transfer of the response had been suspected by Gratia & Linz (E68,252/31) who performed similar experiments before. However, if the serum of a prepared or even that of a normal rabbit is injected i.c. into the same region, before or together with a normally ineffective dose of *E. coli* endotoxin, then provocation by *E. coli* endotoxin i.v. 24 hrs. later induces an SSP-L at the prepared site. Apparently, normal rabbit serum (and indeed even the serum of other species) can act as an adjuvant for endotoxin.

SPECIES AND GENETIC PREDISPOSITION

In *amphibia, reptiles and birds*, it has not yet been possible to produce a typical SSP by two appropriately spaced injections of endotoxin. However, hemor-

rhagic necrosis was obtained in Rous chicken-sarcoma transplants and in chick embryos by bacterial endotoxins under certain conditions.

Dogs are apparently very resistant to the production of a typical cutaneous SSP by two endotoxin injections although allegedly an SSP-L has been elicited in this manner in the tonsil and pancreas of the dog. Furthermore, under certain circumstances, a THP-G can be produced in this species by single injections of sufficient magnitude.

The few observations dealing with the goat suggest that this species is resistant to the production of a cutaneous SSP-L, although it is possible to produce one in the pancreas by topical preparation followed by i.v. provocation.

In the guinea pig, several investigators succeeded in producing an SSP-L or SSP-G by two injections of various bacterial endotoxins given in the usual manner. However, it appears that in this species the critical period is very variable and occasionally even simultaneous i.c. and i.v. endotoxin injections can produce an "SSP-L."

In hamsters, a single i.v. injection of endotoxin or colchicine suffices to produce a THP-G with severe renal lesions during pregnancy and after cortisone pretreatment. It has also been possible to elicit a typical SSP-L in hamsters by two injections of *E. coli* endotoxin.

In the monkey, no SSP-L could be induced by two injections of an *S. marcescens* endotoxin which was highly effective in rabbits.

The mouse is sensitive to the production of an SSP-L or SSP-G by the usual techniques, although certain strains are more resistant than others. In this species, it is possible to achieve provocation by i.p. injections of endotoxin, and topical THPs can be produced (at least in certain strains) by a single i.c. dose of such materials.

In the pig, two injections of *S. marcescens* endotoxin given in the usual manner failed to produce an SSP-L but after various infections repeated i.m. injections of BAL elicited thrombohemorrhagic necroses at the BAL injection sites and these have been interpreted as an SSP.

It is generally agreed that the rabbit is the most suitable species for the study of the SSP and we need not discuss its responsiveness at length here, as most of the work reported in this volume deals with experiments on rabbits. Suffice it to point out that even in this species not all individuals respond with an SSP to the usual treatment, and sensitivity varies considerably in different strains.

The rat is singularly resistant to the production of an SSP when the usual techniques are used. But pregnant rats respond with SSP-G-like manifestations to single i.v. injections of endotoxin or even to feeding a vitamin-E-deficient diet containing supplements of oxidized lipids. Curiously, the rat is especially sensitive to the production of the nonspecific pluricausal variant of the THP which will be described separately (pp. 125ff.).

The production of a THP in man will be discussed at length in Chapter VII.

AMPHIBIA, REPTILES, BIRDS

Jacobi D28,674/36: By injecting *B. typhosus* endotoxin first into the tumor and then i.v.,

hemorrhagic necrosis was obtained in Rous chicken-sarcoma transplants.

Sirotinin G24,594/37: Attempts to produce

an SSP-L by two injections of *E. coli* endotoxin in the classical manner in the pigeon, chicken, duck, goose, turkey, frog, axolotl, turtle (*Testudo graeca*, *Emys orbicularis*), lizard (*Lacerta agilis*) and grass-snake (*Python natrix*) have failed. Apparently, the SSP-L cannot be produced in poikilothermic animals.

Smith & Thomas C97,047/56: Inoculation of various bacterial endotoxins into the chorio-allantoic membrane or i.v. produces multiple hemorrhages, blood sludging and death of developing chick embryos. Injection of the same materials into the allantoic sac is ineffective. Susceptibility is greatest on the 10th day of incubation and absent in 6- or 16-day embryos as well as in fowl after hatching.

Ball et al. D32,833/62: Attempts to produce an SSP-G by two i.v. injections of *E. coli* endotoxin in the turkey were unsuccessful.

Higginbotham & Bass F10,987/64: Extracts of *E. coli* and *S. aureus* produce hemorrhage and death in chick embryos but the latter, though highly toxic, elicits comparatively little bleeding. Cortisol exerts a protective action.

DOG

Ridgon E68,987/35: In dogs and rabbits a single i.v. injection of a toxin, prepared from a hemolytic strain of *Staphylococcus aureus*, produced diffuse hemorrhagic and necrotic lesions in various organs, particularly the gastrointestinal tract, with characteristic renal lesions (dilatation of the glomerular capillaries with swelling of their endothelial cells, proteinuria, hyaline droplet formation in the tubular epithelia).

Bezza G28,396/38: An SSP-L can be elicited in the pancreas of the dog by the injection of *E. coli* endotoxin into the pancreatic duct, followed 24 hrs. later by the i.v. administration of the same material.

Barbera G23,051/42: An SSP-L could be elicited in the tonsil of the dog by topical preparation followed by i.v. provocation on the next day with *B. typhosus* endotoxin.

Johnstone et al. G21,295/58: Two injections of *S. marcescens* endotoxin (highly effective in rabbits) produced no skin hemorrhage in the dog.

Gans & Krivit D16,680/60: In dogs given a single i.v. injection of *E. coli* endotoxin, death occurs from extensive hemorrhages in the lungs, gastrointestinal tract and kidneys, associated with a drop in blood fibrinogen. All these changes are prevented by heparin. However, "the dog does not develop the complex

which is so characteristic for the Shwartzman reaction."

GOAT

Thal & Brackney B93,944/54: Fulminating hemorrhagic pancreatitis can be produced both in the rabbit and in the goat if *E. coli* endotoxin is first introduced into the pancreatic duct and later injected i.v. No lesion occurs if the provocative i.v. injection is omitted. Histologic studies uniformly show capillary and venular hyaline thromboses such as also occur in clinical cases of hemorrhagic pancreatitis.

Johnstone et al. G21,295/58: With an *S. marcescens* endotoxin, highly effective in producing an SSP-L in the rabbit, no cutaneous lesions could be obtained in goats. However, one animal developed an SSP-G although the preparatory injection was given i.c.

GUINEA PIG

Gratia & Linz E70,317/31: An SSP-L can be obtained in the guinea pig by bacterial endotoxins (kind not stated) i.c., followed 24 hrs. later by the intracardiac injection of the same material.

Debonera et al. B78,075/32: In guinea pigs infected with the bacillus of Preisz-Nocard or with an avirulent tuberculosis culture (strain of Cheval-Vallée) s.c., the subsequent i.v. injection of *E. coli* endotoxin produces an SSP-L.

Gratia & Linz D6,544/32: Filtrates of cholera vibrios injected first i.c. and 24 hrs. later i.v., produce not only an SSP-L but also an SSP-G with hemorrhages in the intestine, peritoneal cavity and uterus. Pregnant animals abort.

Apitz D10,355/33: Extensive studies on the morphologic characteristics of the SSP-L produced by two injections of *B. typhosus*, *E. coli*, pneumococcus, nonhemolytic streptococcus and *B. cuniculisepticum* filtrates. All these produced a typical SSP-L in the rabbit, but only pneumococcus filtrates were effective in guinea pigs.

Freund B78,141/34: *B. typhosus* endotoxin, found highly potent in rabbits, produces no SSP-L when administered in the same manner in two injections to guinea pigs. On the other hand, guinea pigs given diphtheria toxin i.c. and then *B. typhosus* endotoxin i.v. exhibit an SSP-L. Similar reactions are sometimes also obtained when typhoid filtrate is given i.v. following preparation with silver nitrate i.c.

Gronchi & Carnielli 30,391/34; Gronchi 67,465/34: The production of an SSP-G by two i.v. injections of *E. coli* endotoxin elicits par-

ticularly conspicuous adrenal hemorrhages in the guinea pig.

Uyeda G25,123/34: An SSP-L can be obtained by two injections of *V. cholerae* filtrates, both in the rabbit and in the guinea pig. Young rabbits and guinea pigs are less susceptible than adults [exact ages not given (H.S.).]

Apitz E60,538/35: In the rat, guinea pig and mouse, no SSP-G could be obtained by two successive injections of *B. typhosus* agar-washings which proved regularly effective in the rabbit.

Vassiliadis D73,783/35: Filtrates of cholera vibrios elicit the SSP-L in rabbits when given in two injections according to the usual procedure. Filtrates of EL Tor vibrios are ineffective in rabbits, and neither filtrate elicits an SSP-L in the guinea pig.

Stolyhwo G21,662/35-36: A typical SSP-L can be produced in the guinea pig by two injections of typhoid or paratyphoid filtrate.

Gayta G26,873/36: In guinea pigs, an SSP-L cannot be produced by two injections of diphtheria endotoxin given at 24-hr. intervals, but the response is often positive if the critical period is prolonged to 48 hrs.

Laporte G23,881/36: Small amounts of live typhoid bacilli i.c. cause only transitory swelling of the skin in guinea pigs, while large doses produce hemorrhagic necrosis. If the i.c. administration of small doses of typhoid bacilli is accompanied by a simultaneous i.p. injection of typhoid-culture filtrate, hemorrhagic necrosis develops at the dermal injection site after 8-12 hrs. The response thus differs from the SSP-L in that there is no critical period between the two injections and that, following provocation, the dermal lesion is slower to develop. With this experimental arrangement, s.c. provocation yields inconstant results but if, instead of the filtrate, live typhoid bacilli are used for provocation, hemorrhagic necrosis invariably occurs at the site of preparation even if the provocative injection is given s.c. However, in this event, it may take 48 hrs. for the skin lesions to become evident. Similar results have been obtained with pneumococcus and pasteurella organisms.

Citarda B35,514/42: Guinea pigs are normally very resistant to the production of an SSP-L by two injections of *E. typhosa* endotoxin. However, they respond with a typical SSP-L when pretreated with thyroxin.

Heinlein G22,341/48: An SSP-L can be produced in guinea pigs by two injections of typhoid or Shiga endotoxin, though rabbits react much more regularly.

Valeton & Doeppfmer C5,901/54: It is possible to produce an SSP-L by two injections of *E. coli* endotoxin in the guinea pig if a concentrated filtrate is administered with an interval of only 10-14 hrs. This shortened critical period is held responsible for success, but no control experiments were made with longer intervals.

Wawersik C31,713/55: The SSP-L is elicited in the guinea pig by two injections of meningococcal endotoxin. In hypophysectomized animals treated with ACTH, adrenal hemorrhages were common although the preparatory injection was given i.c.

Johnstone et al. G21,295/58: Two injections of *S. marcescens* endotoxin (highly effective in rabbits) produced no skin hemorrhage in the guinea pig.

Kováts E99,030/61: Guinea pigs (and rats) sensitized 3-4 weeks previously with *S. typhosa* or *E. coli*, develop hemorrhagic skin lesions at sites prepared with endotoxin, on i.v. injection of endotoxin 24 hrs. later. Animals not pretreated with the bacteria do not develop hemorrhagic lesions. The endotoxin must not necessarily be derived from the bacteria used for sensitization. Rabbit antiserum, obtained by hyperimmunization with typhoid endotoxin, injected i.c. in guinea pigs (or rats) also results in hemorrhage, if followed 24 hrs. later by i.v. injection of endotoxin. Mixtures of typhoid endotoxin and colloidal silver i.c. followed by i.v. injection of the same material, also result in skin hemorrhages in guinea pigs. Normal rabbit, guinea pig or rat mononuclear peritoneal exudate cells injected i.c., and 24 hrs. later followed by endotoxin i.v., likewise elicit skin hemorrhage. The author believes to have "succeeded in demonstrating that the first phase of the Shwartzman phenomenon, that is, preparation of the skin by endotoxin, is a specific reaction depending on a well-characterizable immunological mechanism, namely, the phenomenon of local endotoxin hypersensitivity."

Kováts et al. D85,430/63: An "SSP-L" can be elicited in guinea pigs pretreated with colloidal silver i.v. and then given *E. coli* endotoxin plus colloidal silver intradermally. Both topical and systemic blockade of the RES by colloidal silver was necessary to elicit this reaction. An "SSP-G" with characteristic renal lesions also occurs in guinea pigs pretreated with colloidal silver i.v. and then given typhoid endotoxin i.v.

Scott & Blaszcynski G30,733/65: Guinea pigs did not respond with an SSP-G to two i.v. injections of *E. coli* endotoxin under conditions in which rabbits gave a typical result.

HAMSTER

Thomas & Good E59,874/51: Bilateral renal cortical necrosis is produced in cortisone-pre-treated rabbits and hamsters by a single i.v. injection of *S. marcescens* toxin.

Galton D58,259/63: A single i.p. injection of colchicine or *E. coli* endotoxin regularly elicits the SSP-G in the pregnant, but not in the nonpregnant hamster. "The superiority of colchicine, as opposed to foreign endotoxin, in the pregnant subject, may be attributed to the action of native endotoxin which is allowed parenteral access as a result of colchicine-induced injury to the intestinal mucosa."

Gustafson & Cronberg D61,874/63: In hamsters, an SSP-L could be produced in the cheek pouch by preparation with *E. coli* endotoxin followed by i.v. injections of the same agent. The mast cells showed no degranulation until the late stages, when other cells were also damaged.

Galton G9,002/64: An SSP-G can be produced in the pregnant hamster by a single i.p. injection of colchicine but not by *E. coli* endotoxin. Two properly spaced injections of endotoxin in a nonpregnant hamster were likewise ineffectacious.

Galton F51,263/65: During the THP-G elicited by colchicine in the pregnant hamster, India ink i.v. is trapped by some amorphous deposit in the glomerular capillaries.

MONKEY

Johnstone et al. G21,295/58: Using two injections of *S. marcescens* endotoxin, highly effective in rabbits, no corresponding response could be obtained in *Macacca mulatta* monkeys.

MOUSE

Heyrovsky G23,661/07: In mice treated with single or multiple i.p. or s.c. injections of filtrates of streptococcus mucosus (designated as "Stojan's strain"), there develops "especially at the naked parts of the body (ears, paws, tail, snout, genitalia), a localized hemorrhagic exanthema in the form of livid flat or slightly elevated round or irregularly circumscribed often confluent efflorescences." The hairy parts of the skin are not affected except for the place where the filtrate was injected and sites where the skin was mechanically traumatized. There is also bloody diarrhea with hemorrhages in the palate, lungs, intestine and urinary bladder, enlargement of the spleen and hyperemia of the kidney. Histologically, the hemorrhagic regions show signs of inflam-

mation. The condition is considered to be an experimental equivalent of the purpuric types of septicemia seen in man.

Stolyhwo G21,662/35-36: In the mouse, unlike in the rabbit and guinea pig, it is impossible to produce an SSP-L by two injections of typhoid or paratyphoid filtrate.

Homma G21,673/52: An SSP-L is produced in the mouse by two injections of filtrates from *Proteus vulgaris*, *Pseudomonas aeruginosa* and *E. coli*.

Takeda & Tsuchiya G21,674/53: Certain fractions of *E. coli* endotoxin produce abortion with manifestations of the SSP-G when given as single injections i.v. in the mouse.

Kelly et al. D3,776/57: Ten strains of mice were found to be non-reactive when tested for the production of an SSP-L by endotoxins of *S. marcescens*, *S. typhosa*, *Ps. aeruginosa* and *H. pertussis*. However, three strains and one F_1 hybrid subline developed hemorrhagic lesions at the site of injection of a single, relatively high i.c. dose of polysaccharide. When this dose was followed 24 hrs. later by an i.v. injection, the incidence was somewhat higher.

Arndt & Schneider D9,369/58: In certain strains of mice, it is possible to produce a typical SSP-L by *E. coli* endotoxin i.c. followed 24 hrs. later by i.p. administration of the same agent, as well as a THP by a single i.c. injection of (*E. coli* or *S. marcescens*) endotoxin. The lesions are described as the "Shwartzman-like reaction."

Antopol & Chryssanthou E30,599/59: Single injections of *E. coli* endotoxin i.c. rarely produce skin hemorrhages in mice but when human immune globulin is given i.p. 5 min. earlier, *E. coli* i.c. often produces intense local hemorrhagic reactions. γ -Globulin also increases the sensitivity of the mouse to an SSP-L elicited by an i.c. preparatory, followed by an i.p. provocative, *E. coli* endotoxin injection.

Arndt et al. C82,082/59: A typical SSP-L can be produced only in certain strains of mice by a preparing i.c. and a provoking i.p. dose of *E. coli* lipopolysaccharide.

Arndt & Schneider G21,207/60: In BSVS strain mice, an SSP-L can be elicited by an i.c. followed by an i.p. or i.v. injection of various bacterial endotoxins. Several types of antigen-antibody complexes can also be used for provocation. Some animals reacted in the usual manner to single i.c. injections of endotoxins but, in these, there was infection of the lungs with gram-negative microflora. Here, the latter apparently acted as the preparatory agent without there being any specific critical

period, since the animals were permanently responsive.

Ramos et al. G26,829/61: The SSP-L normally produced in the mouse by i.c. preparation and 24 hrs. later i.v. provocation with *S. typhosa* endotoxin is prevented if EACA is given i.p. before the provocative injection.

Antopol & Chryssanthou D56,730/63: In certain strains of mice, a single i.c. injection of *E. coli* lipopolysaccharide suffices to produce a typical SSP-L.

PIG

Hasselmann et al. G22,335/51: In pigs given repeated i.m. injections of BAL, subsequent infections with various bacteria produce thrombohemorrhagic necroses at the BAL injection sites. Similar observations have been made in patients treated with BAL for various infectious diseases. The phenomenon is ascribed to the SSP.

Johnstone et al. G21,295/58: Two injections of *S. marcescens* endotoxin (highly effective in rabbits) produce no skin hemorrhage in the pig.

RABBIT

Shwartzman G22,636/32: Certain rabbits are refractory to the SSP-L. Thus, *B. typhosus* endotoxin elicits positive reactions only in 85%, while meningococcal filtrates give positive results in nearly 100% of the rabbits tested. In some individuals the immunity to *E. coli* or *B. typhosus* endotoxin is specific; in others it is nonspecific.

RAT

Apitz D10,355/33: Extensive studies on the morphologic characteristics of the SSP-L produced by two injections of *B. typhosus*, *E. coli*, pneumococcus, nonhemolytic streptococcus and *B. cuniculisepticum* filtrates. All these produced a typical SSP-L in the rabbit, but only pneumococcus filtrates were effective in guinea pigs while rats were resistant to all filtrates.

Johnstone et al. G21,295/58: Two injections of *S. marcescens* endotoxin (highly effective in rabbits) produced no skin hemorrhage in the rat.

Kováts E99,030/61: Guinea pigs and rats sensitized 3-4 weeks previously with *S. typhosa* or *E. coli*, develop hemorrhagic skin lesions at sites prepared with endotoxin, on i.v. injection of endotoxin 24 hrs. later. Animals

not pretreated with the bacteria do not develop hemorrhagic lesions. The endotoxin need not necessarily be derived from the bacteria used for sensitization. Rabbit antiserum, obtained by hyperimmunization with typhoid endotoxin, injected i.c. in guinea pigs or rats also results in hemorrhage, if followed 24 hrs. later by i.v. injection of endotoxin. Mixtures of typhoid endotoxin and colloidal silver i.c., followed by i.v. injection of the same material, also result in skin hemorrhages in guinea pigs. Normal rabbit, guinea pig or rat mononuclear peritoneal exudate cells injected i.c., and 24 hrs. later followed by endotoxin i.v., likewise elicit skin hemorrhage. The author believes to have "succeeded in demonstrating that the first phase of the Schwartzman phenomenon, that is, preparation of the skin by endotoxin, is a specific reaction depending on a well-characterizable immunological mechanism, namely, the phenomenon of local endotoxin hypersensitivity."

Kaley et al. G21,294/62: A single i.v. dose of *E. coli* endotoxin produces a typical "SSP-G" in the rat when given during the last few days of pregnancy.

McKay & Wong E71,747/62: In pregnant rats maintained on a vitamin-E-deficient diet containing oxidized lipids, a typical SSP-G develops which in some respects resembles eclampsia.

Kaunitz et al. D59,756/63: In pregnant rats, a vitamin-E low diet containing oxidized cod-liver oil elicits an SSP-G. Dihydrostearic acid can replace oxidized cod-liver oil, although it is less effective.

Kováts et al. D85,430/63: Following i.c. injection of the serum of rabbits, hyperimmunized with typhoid endotoxin or vaccine (passive cutaneous anaphylaxis), *E. coli* or *E. typhosa* endotoxin i.v. produces an SSP-L at the site of preparation, both in guinea pigs and in rats. Essentially similar results are obtained if a mononuclear cell suspension, collected from the peritoneum of normal rabbits, guinea pigs or rats, is used for cutaneous preparation. The first experiment is interpreted as a cutaneous anaphylaxis due to endotoxin and the second as a cellular transfer of a delayed sensitivity to endotoxin. [It is not clear why the response induced by the mononuclears of the SSP-insensitive rat should be ascribed specifically to the transfer of hypersensitivity (H.S.).]

AGE

Data on the influence of age upon susceptibility to the SSP are conflicting; some investigators find young, others older rabbits more sensitive. These contradic-

tions may be due to chance variations, differences in the age-dependence of sensitivity in diverse strains or differences in the techniques used.

In the chick, a THP can be produced by single injections of endotoxins into the chorioallantoic membrane given at about the tenth day of incubation.

Gratia & Linz D6,544/32: The SSP-L elicited by two injections of *E. coli* filtrate is more constantly obtained in young rabbits than in old ones but, prior to the age of 3 weeks, the animals do not react.

Uyeda G25,123/34: An SSP-L can be obtained by two injections of *V. cholerae* filtrates, both in the rabbit and in the guinea pig. Young rabbits and guinea pigs are less susceptible than adults [exact ages not given (H.S.)].

Freund & Hosmer D85,443/35: Starch i.v. elicits an SSP-L at skin sites prepared with meningococcal toxin more regularly in rabbits weighing 2000 gm or more than in those weighing 1100-2000 gm. No such age-dependence was noted when meningococcal toxin was used for both injections.

Witebsky & Neter G24,318/36: Rabbits less than three weeks of age are almost totally refractory to the elicitation of an SSP-L by two injections of meningococcal or typhoid endotoxin. Refractory rabbits may become responsive as they grow.

Smith & Thomas C242/54: The SSP-G elicited by two i.v. injections of meningococcal endotoxin occurs in about 70% of young rabbits (average age 5 weeks, average weight 600 gm), but in only 10% of older rabbits

(average age 11 weeks, average weight 2500 gm). However, young rabbits are more easily affected by single i.v. injections of the endotoxin than old animals.

Smith & Thomas C97,047/56: Inoculation of various bacterial endotoxins into the chorioallantoic membrane or i.v., produces multiple hemorrhages, blood sludging and death of developing chick embryos. Injection of the same materials into the allantoic sac is ineffective. Susceptibility is greatest on the 10th day of incubation and absent in 6- or 16-day embryos as well as in fowl after hatching.

Stetson E74,348/59: There is a striking increase in susceptibility to endotoxins with age but the author was able to produce an SSP-L on the first day of life in the rabbit.

Bohle G34,275/60: In two cases of presumably criminal abortion, manifestation of the SSP-G (fibrin precipitates in the renal glomerular capillaries as well as in the microcirculation of the adrenals, lung and liver) were observed both in the maternal and the fetal organism.

Higginbotham & Bass F10,987/64: Extracts of *E. coli* and *S. aureus* produce hemorrhage and death in chick embryos but the latter, though highly toxic, elicits comparatively little bleeding. Cortisol exerts a protective action.

PREGNANCY

Pregnancy undoubtedly predisposes both experimental animals and women to the production of various forms of THP. The clinical implications of this fact will be discussed in Chapter VII; here, we shall deal merely with animal experiments.

A single injection of SSP-active microbial products suffices to produce a THP-G during pregnancy not only in the especially sensitive rabbit but also in the guinea pig, mouse and rat. This is true even if the active material is injected i.p. or s.c., although i.v. injections are generally more efficacious. It has been assumed that pregnancy induces a continuous state of preparation so that single provocative treatments suffice to elicit an "SSP-G."

Certain diets, especially those rich in highly oxidized lipids and poor in vitamin-E, can produce a THP during pregnancy in the rat. The resulting changes resemble eclampsia, but it is not yet known whether similar changes would be elicited by these diets in pregnant females of species other than the rat.

An eclampsia-like syndrome can also be produced by large doses of progesterone in late pregnant rats, especially if they are maintained on certain choline-de-

ficient diets. Yet choline itself does not appear to be the decisive factor, since supplements of it did not prevent the progesterone-induced changes. In such experiments, the induction of corticoid hypertension (by combined treatment with desoxycorticosterone + unilateral nephrectomy + NaCl-supplements) fails to augment the renal lesions, which are therefore thought to be largely independent of the blood pressure.

A single i.p. injection of *colchicine* causes a THP-G in the pregnant hamster and, in this respect, the drug is even more active than *E. coli* endotoxin. *Placenta extracts, thrombin, 5-HT and renal artery constriction* are also efficacious in eliciting eclampsia-like changes in pregnant animals.

NORMAL PREGNANCY

Fresh et al. G26,185/56: Extensive studies on normal pregnant women show an increase in the fibrinogen, proconvertin, prothrombin and possibly PTC-levels.

MICROBIAL PRODUCTS

Gratia & Linz D6,544/32: Filtrates of cholera vibrios injected first i.c. and 24 hrs. later i.v. produce not only an "SSP-L" but also an "SSP-G" with hemorrhages in the intestine, peritoneal cavity and uterus of the rabbit. In pregnant animals, they cause abortion.

Apitz E60,538/35: In pregnant rabbits, a single i.v. injection of various bacterial toxins suffices to produce an "SSP-G."

Zahl & Bjerknes A72,278/43; B36,113/44: I.p. injection of the endotoxins or *Sh. parady-enteriae*, *S. typhimurium* and *Rhodospirillum rubrum* in late-pregnant mice induces retro-placental hemorrhage with abortion or resorption of the embryos. The change is compared to hemorrhagic tumor necrosis.

Takeda & Tsuchiya G21,671/53: In pregnant rabbits, a single i.v. injection of meningococcal or *Sh. parady-enteriae* endotoxin produces an "SSP-G" with bilateral renal cortical necrosis, hepatic necrosis and hemorrhages in the placenta, often conducive to abortion.

Takeda & Tsuchiya G21,674/53: Certain fractions of *E. coli* endotoxin produce abortion with manifestations of the "SSP-G" when given as single injections i.v. in the mouse.

Galton et al. D14,237/60: In pregnant rabbits, a single injection of bacterial endotoxin (kind not stated) suffices to produce an "SSP-G." The state of capillary dilatation was checked by intra-aortal administration of India ink. "2 to 4 hrs. after endotoxin the glomerular capillaries were grossly dilated and packed with ink. The lungs contained large 'ischemic' areas devoid of ink alternating with blackened areas containing markedly di-

lated ink-filled capillaries. The liver showed ink confined to dilated periportal sinusoids. The sinusoids of the adrenal and splenic pulp were dilated and filled with ink." . . . "It is concluded that capillary dilatation precedes the deposition of fibrin thrombi in all the organs characteristically affected in the Schwartzman reaction in pregnant rabbits and thus plays an important part in 'preparation' for the reaction."

McKay et al. C83,052/60: In rabbits "prepared" through pregnancy, the provocation of an "SSP-G" by bacterial toxin (kind not stated) i.v., results in a localization of the microthrombi different from that seen in the classical SSP-G elicited by two endotoxin injections. "In the non-pregnant animal after the second injection of endotoxin, thrombi were found in the renal glomeruli (53%), sinusoids of the red pulp of the spleen (64%), lung vessels (76%) and in the central veins of the liver (69%). They were not observed in the adrenal. After the first injection in pregnant animals thrombi were found in the renal glomeruli (82%), Malpighian corpuscles of the spleen (64%), lung vessels (88%), peripheral sinusoids of the liver (76%) and adrenal sinusoids (41%)."

Rieder & Thomas C80,868/60: As little as 5 µg of *E. coli* lipopolysaccharide causes abortion in the mouse. In contradistinction to Takeda and Tsuchiya (G21,671/53, G21,674/53), this response is not considered to be an SSP in the placenta. Nor is it analogous to simple endotoxin shock or to the THP elicited by epinephrine in combination with endotoxins, because it is not blocked by cortisone (which inhibits endotoxin shock and the epinephrine THP), dibenzyline (which inhibits endotoxin shock and the epinephrine THP, though not the SSP), chlorpromazine (which inhibits endotoxin shock, the epinephrine THP, but not the SSP-G), 48/80 (which prevents endotoxin shock, the epinephrine THP and the SSP-G, though not the SSP-L), or heparin (which prevents the SSP-G).

Kaley et al. G21,294/62: A single i.v. dose of *E. coli* endotoxin produces a typical SSP-G in the rat when given during the last few days of pregnancy.

Wong E39,946/62: A single i.v. endotoxin injection produces a typical "SSP-G" in the pregnant rat. "From this study it can be stated that pregnant rats are susceptible to the generalized Shwartzman reaction, hence pregnancy 'prepares' for the reaction in a species which usually does not exhibit the reaction in the nonpregnant state." [It must be kept in mind, however, that the author confirmed previous investigators in showing that even two i.v. injections of endotoxin failed to produce an SSP-G in the nonpregnant rat. Hence, pregnancy must do more than merely substitute for the preparatory endotoxin injections (H.S.).]

McKay & Wong D11,799/63: i.v. injection of *E. coli* lipopolysaccharide during the 17th-18th day of pregnancy produces placental changes, fetal death and an "SSP-G" in the rat. The placental changes are very similar to (though not quite identical with) those observed in rats fed a low vitamin diet containing oxidized lipids, a ration which also causes an "SSP-G" with eclampsia-like manifestations in the pregnant rat.

Florek F12,519/64: Review of the literature on the preparation by pregnancy for the elicitation of an "SSP-G" by bacterial toxins in animals and by infections in women.

Galton G9,002/64: In pregnant hamsters, colchicine produces a typical THP-G with characteristic renal glomerular lesions, while vincaleukoblastine (another stathmokinetic drug) and *E. coli* endotoxin are inactive in this respect. Devitalization of intestinal segments is efficacious perhaps owing to the absorption of some special endotoxin from the intestinal flora. [Other stressors have not been tested (H.S.).]

Osborne & Smibert G28,866/64: "A fatal Sanarelli-Shwartzman reaction followed the single intravenous inoculation of *V. fetus* toxin in the gravid female rabbit. Certain features of the Sanarelli-Shwartzman reaction were evident in lethal reactions of the other species studied."

Rodriguez-Erdmann G31,454/64: An SSP-G with the typical coagulopathy and morphologic changes can be produced in pregnant rabbits by a single i.v. injection of *E. coli* endotoxin.

McKay E4,788/65: Review of the literature on the preparation by pregnancy for the production of thrombohemorrhagic lesions by bacterial endotoxins, RES-blocking agents, col-

chicine, progesterone, and diets deficient in vitamin E but rich in oxidized lipids.

Niesert & Schneider F32,779/65: A single i.v. injection of *S. abortus equi* endotoxin can produce an "SSP-G" in the rabbit.

Wilner G27,851/65: In pregnant rats, endotoxin (kind not stated) i.v. produces renal glomerular thrombosis and hepatic necrosis. Concurrent treatment with low molecular dextran increases the renal, but decreases the hepatic lesions.

DIETS

Stamler C14,364/56; C78,006/59: "Eclampsia" can be produced in pregnant rats when they are given a diet containing 61% corn starch, 20% casein, 10% brewers' yeast, 4% HMW salt mixture, and 5% cod-liver oil. The critical component appears to be cod-liver oil. Crude linoleic acid is approximately equally effective, while corn oil is nontoxic. Vitamin E counteracts the toxicity. The prominent autopsy findings are pulmonary edema, pleural effusions, adrenal hemorrhages and bilateral cortical renal necrosis with fibrinoid thrombi in the glomerular capillaries. [A possible relationship to the SSP-G is not mentioned (H.S.).]

Kaunitz et al. E67,900/62: In oxidized cod-liver oil, the factor responsible for the production of an "SSP-G" in vitamin-E-deficient pregnant rats, has been purified by molecular distillation. Esterification of the active fraction increased its activity.

McKay D15,443/62; *McKay & Wong* E71,747/62; *McKay & Goldenberg* G15,616/63: In pregnant rats, feeding of a vitamin-E deficient diet containing oxidized lipids induces the "SSP-G" in association with fibrin thrombi in the placenta, placentitis and fetal death. The response resembles pregnancy toxemia.

Kaunitz et al. D59,756/63; E29,696/63: In the diet producing eclampsia in the rat, di-hydroxystearic acid can replace oxidized cod-liver oil, although it is less effective.

McKay & Kaunitz E29,695/63; E29,694/63: Feeding a vitamin-E-deficient diet, rich in oxidized cod liver oil, produces an SSP-G only in pregnant rats, presumably because in these, lipid metabolism changes occur which sensitize the animals for this reaction.

Rothenberg et al. G26,181/63: Dietary lipids can partially block the phagocytic ability of the RES in the rat, and vitamin-E supplements prevent this blockade. However, pregnancy is associated with a slight increase in the phagocytic activity of the RES; hence, it presumably "prepares" for the production of a THP-G by diets (rich in oxidized lipids and

poor in vitamin E) through some mechanism other than blockade of the RES.

Goldstein & McKay G27,030/65: The fractions of cod liver oil which produce "experimental eclampsia" in pregnant rats are rich in lipid peroxides. Pregnant rats, fed fractions derived from molecular distillation of oxidized cod liver oil, had an excess of lipid peroxides in their kidneys, livers and placentas. The erythrocytes of these animals lysed upon contact with hydrogen peroxide and dialuric acid in a manner characteristic of vitamin-E deficiency. "It is concluded that a state of relative vitamin E deficiency exists in these toxemic rats and that the deficiency of the antioxidant properties of vitamin E may be the basis of cellular damage leading to the eclamptic state."

Rothenberg G27,059/65: Electron-microscopic studies of the glomerular capillary thrombi produced in pregnant rats by diets deficient in vitamin-E and rich in oxidized lipids showed that fibrin is present in two forms: 1) a fibrillar arrangement having 240 Å periodicity of the cross-striations, and 2) an irregular amorphous granular deposit. Thrombo-emboli were always present within capillary lumens, never mural deposits."

PROGESTERONE

Symeonidis B32,969/49: An eclampsia-like syndrome is induced in rats by large doses of progesterone given during the last third of pregnancy. There is abortion or resorption of the embryos, albuminuria, azotemia, edema, and hypertension. "The lesions in other organs, especially in the liver and the kidney were similar to those of human eclampsia. These were peripheral lobular necrosis of the liver, with capillary dilatation, fibrin thrombi, and hemorrhages, fibrin thrombi in glomeruli, thickening of the glomerular basement membrane, and tubular degeneration and necrosis in the kidney."

Waugh & Pearl C83,389/60: Contrary to earlier observations (performed on another strain of rats), progesterone produced no "eclampsia-like" changes in pregnant rats.

Moore D95,837/61: Periplacental hemorrhage and fetal death with renal cortical and/or liver necrosis occur in late-pregnant rats given progesterone. These changes are ascribed to vasoconstriction, and their resemblance to human abruptio placentae is noted.

Stamler D4,281/61: Progesterone elicits a THP-G in the late-pregnant rat.

Moore D34,394/62; D63,441/63: Renal cortical necrosis with thrombosis in the glomeru-

lar capillaries and intra-uterine hemorrhage with fetal death were observed in late-pregnant rats given progesterone and kept on a certain choline-deficient diet. However, choline itself does not appear to be the decisive factor since supplements of it did not prevent these changes. Still, some dietary factor was important as no such lesions were observed in similarly treated pregnant rats kept on ordinary rat meal.

Moore G28,594/65: In pregnant rats, fed an experimental diet and given progesterone during late pregnancy, the incidence of the renal lesions is not increased if steroid hypertension is produced by desoxycorticosterone + unilateral nephrectomy + NaCl-supplements. Apparently, renal cortical necrosis is independent of hypertension.

COLCHICINE

Galton D58,259/63: A single i.p. injection of colchicine or *E. coli* endotoxin regularly elicits the "SSP-G" in the pregnant, but not in the nonpregnant hamster. "The superiority of colchicine, as opposed to foreign endotoxin, in the pregnant subject, may be attributed to the action of native endotoxin which is allowed parenteral access as a result of colchicine-induced injury to the intestinal mucosa."

Innerfield et al. G27,038/64: A single i.p. injection of colchicine produces a THP-G with renal capillary thromboses in the pregnant golden hamster. This response is inhibited by the oral administration of streptokinase.

Galton F51,263/65: During the THP-G elicited by colchicine in the pregnant hamster, India ink i.v. is trapped by some amorphous deposit in the glomerular capillaries.

Galton F53,009/65: Colchicine produces an "SSP" in the pregnant hamster.

PLACENTA EXTRACTS

Kono G24,688/56: A single i.v. injection of placental extract produces abortion in the pregnant rabbit.

Magara G25,146/61: A water-soluble, alcohol-insoluble substance prepared from the human placenta produces an "SSP-G" when given either as the preparatory or the provocative i.v. injection in combination with *E. coli* endotoxin i.v. to nonpregnant rabbits. Pregnant rabbits respond similarly to a single i.v. injection of the placental extract. Apparently, pregnancy induces a continuous state of "preparation."

THROMBIN

Margareten & McKay G3,648/63; Margareten et al. G27,941/64: An "SSP-G" with renal

glomerular thrombosis can be produced in rats by slow i.v. infusion of thrombin. In nonpregnant rats, unlike in pregnant ones, these thrombi rapidly disappear as a consequence of fibrinolysis.

5-HT

Waugh & Pearl C83,389/60: Various forms of renal cortical necrosis and acute nephrosis can be produced by different doses of 5-HT in the rat. The severity of these changes was not influenced by pregnancy, but widespread glomerular intercapillary thrombi and focal necrosis of the liver, which occurred rarely, were observed only in pregnant rats. Contrary to earlier studies (performed on another strain

of rats), progesterone produced no "eclampsia-like" changes in pregnant rats.

OTHER AGENTS

Dill & Erickson 91,301/38: An eclampsia-like syndrome occurs in pregnant dogs and rabbits following renal artery constriction.

Galton G9,002/64: In pregnant hamsters, colchicine produces a typical THP-G with characteristic renal glomerular lesions, while vincaleukoblastine (another stathmokinetic drug) and *E. coli* endotoxin are inactive in this respect. Devitalization of intestinal segments is efficacious perhaps owing to the absorption of some special endotoxin from the intestinal flora. [Other stressors have not been tested (H.S.).]

IMMUNE REACTIONS

The possible relationship between the THP, particularly the SSP, and various forms of immune reactions has long been the subject of intensive study. As outlined in the historic introduction, Sanarelli first considered his reaction to be a hemorrhagic form of allergy and, for want of any better place to mention it, the SSP is listed in most texts among the immunologic hypersensitivity reactions, although usually with some remark indicating that actually it does not belong there. The observations on the effect of immune responses upon various forms of the THP will be dealt with here in two subsections, one concerned with their induction (or aggravation), the other with their inhibition.

Production of THP. Under certain conditions, immune phenomena can elicit a THP or at least facilitate its production by other agents. Anaphylatoxin i.v. causes thrombocytopenia but no THP. Antiplatelet serum i.v. induces thrombocytopenia with multiple hemorrhages, but the organ lesions do not appear to correspond to those of the THP. However, an SSP-L produced by two injections of *E. coli* endotoxin in the rabbit is greatly aggravated by the concurrent administration of antiplatelet immune serum.

In tuberculous guinea pigs sensitized to egg white, reinjection of the same antigen i.p. causes death with intense hemorrhages in the tuberculous lesions. The changes are similar to those of the SSP and also reminiscent of the Bordet phenomenon. (It will be recalled that the latter is elicited by killed *E. coli* organisms in guinea pigs sensitized to BCG vaccine several weeks earlier, and manifests itself by hemorrhagic lesions in the peritoneal lymph nodes. If the killed *E. coli* are injected s.c., a topical hemorrhage appears which eventually leads to necrosis.)

Shwartzman observed that rabbits, sensitized to various animal proteins (blood serum, egg white, etc.), and given bacterial endotoxin i.c., respond to i.v. reinjection of the antigenic animal protein (24 hrs. after the dermal preparation) with an SSP-L at the prepared site. It is even possible to elicit an SSP-L in prepared skin sites of nonsensitized rabbits if they are given i.v. injections of antigen and antibody (passive transfer).

Various modifications of this type of interaction between true allergic phe-

nomena and the SSP-L have been observed. However, this does not prove the participation of any immunologic phenomenon in the ordinary SSP. It merely indicates that allergic responses can sensitize tissues to endotoxin-induced non-allergic changes. Apparently, tuberculin-induced allergies are especially effective in eliciting this type of sensitization. However, various other antigen-antibody reactions, including the Arthus phenomenon, can be made hemorrhagic by such techniques. Indeed, several investigators pointed out that even the ordinary Arthus phenomenon is related to the SSP in that it is often associated with hemorrhage and necrosis.

In rabbits which have received a single i.v. injection of *E. coli* endotoxin, subsequent i.c. administration of *E. coli* or *S. typhosa* endotoxin produces a greatly accelerated and intensified cutaneous inflammatory response which resembles the Arthus reaction both in its appearance and in that it becomes evident within an hour. This accelerated reactivity is detectable 6 hrs. after the i.v. injection and remains demonstrable for as long as a month. Rabbits prepared with one endotoxin i.v. responded with accelerated reactions to skin-testing with other endotoxins, perhaps as a consequence of the formation of cross-reacting antibodies which allegedly may play a role in the SSP.

Ledingham G24,703/14: An antiplatelet serum obtained by immunizing rabbits with guinea-pig platelets, elicits a purpura when given i.v., i.p., or s.c. to guinea pigs. The multiple hemorrhages in the skin, lung, epicardium, intestinal serosa and lymph nodes are associated with erythrocyte agglutination thrombi and a decrease in the red-cell count.

Bedson G21,641/22: In rabbits the anaphylatoxin of "agar-serum" (agar incubated with serum) i.v., causes a transitory fall in blood platelets in the rabbit, but "on no occasion was this accompanied by the production of haemorrhages." In guinea pigs given antiplatelet serum i.v., the resulting drop in blood platelets is associated with multiple hemorrhages in the skin, muscles, mesentery, intestine, epididymis, lung, and peritoneal cavity. [No mention is made of thromboses (H.S.).]

Dienes E71,742/29-30: If guinea pigs are injected i.p. with slightly virulent or killed tubercle bacilli and, 3 to 8 days later, receive an injection of egg white, they develop a strong skin sensitivity to egg white. If, 9 to 14 days later, these guinea pigs are reinjected with egg white i.p., they die in shock with intense hemorrhages in the tuberculous lesions. The phenomenon is compared to the SSP.

Bordet G23,543/31: A suspension of killed *E. coli*, which is normally well tolerated by guinea pigs, kills them if they have received BCG vaccine i.p. 2-3 weeks earlier. The animals die with hemorrhages in the peritoneal lymph nodes. If the killed *E. coli* are injected s.c. a topical hemorrhage appears which

eventually leads to necrosis. A number of other foreign proteins and bacteria are ineffective in producing such lesions in BCG-treated guinea pigs. The phenomenon is presumably related to those described by Sana-relli and Shwartzman respectively. [This response subsequently became known as the Bordet phenomenon (H.S.).]

Gratia & Linz E70,317/31; D6,544/32: An SSP-L produced by two injections of *E. coli* endotoxin in the rabbit is greatly aggravated by the concurrent administration of anti-platelet immune serum.

Shwartzman G24,353/31-32: In rabbits prepared by *B. typhosus* endotoxin i.c., the i.v. injection 24 hrs. later of the following serum precipitates induces an SSP-L: 1. Normal horse serum with anti-horse rabbit serum. 2. Antimeningococcus horse serum with anti-horse rabbit serum. 3. Antimeningococcus horse serum with anti-horse goat serum. 4. Antimeningococcus anti-human horse serum with normal human serum.

Shwartzman E82,480/32: Rabbits sensitized to animal proteins (blood serum, egg albumin, etc.) received an i.c. injection of bacterial toxin (kind not stated). Twenty-four hours later they were given the same animal protein i.v. and developed hemorrhagic necrosis at the prepared skin site. It is also possible to elicit an SSP-L in prepared skin sites of nonsensitized rabbits receiving separate i.v. injections of antigen and antibody (i.e., passive transfer).

Shwartzman G23,070/32: Precipitates de-

rived from mixtures of serum precipitinogen with precipitating antiserum, cause an SSP-L in rabbits at sites prepared by typhoid endotoxin i.c. The provocative potency did not depend upon the size of the aggregates formed, and even clear supernatant fluids obtained by centrifugation were effective, while a variety of colloidal suspensions (India ink, silicic acid, etc.) were ineffective. Hence it was concluded that the "potency of serum precipitates is not due to the mechanical effect of colloidal particles in the blood stream but to some toxic factors liberated or formed in the serum through the colloidal disturbance induced by the process of precipitation."

Freund D37,522/32-33: In tuberculous guinea pigs which had previously received an i.c. injection of bovine tuberculin, the i.v. administration of typhoid endotoxin produces a hemorrhagic necrosis at the site of the tuberculin reaction.

Apitz G24,112/33: Depending upon the technique of its elicitation, the Arthus phenomenon induced by repeated i.c. injections of horse serum in the rabbit may assume a strongly hemorrhagic character.

Apitz D10,355/33: Following repeated i.c. injections of horse serum at different sites, an Arthus phenomenon is eventually obtained. At this time, i.v. injection of the same antigen can elicit hemorrhages in the prepared skin sites and the reaction becomes identical with the SSP-L. Following preparation with a single i.c. injection of horse serum, no SSP-L can be elicited by a subsequent i.v. injection of the same antigen. If a precipitating antiserum is injected i.c., topical hemorrhages result, even when horse serum is given i.v. 2-3 hrs. after the passive sensitization.

Bordet G23,083/33: In guinea pigs infected with tuberculosis, the subsequent i.v. injection of an *E. coli* endotoxin extract produces widespread SSP-G lesions. The author points out that Roemer was the first to show, in 1891, that tuberculous guinea pigs are hypersensitive to various microbial products in that they react to them with lesions similar to those elicited by tuberculin.

Michelazzi D92,869/33: In rabbits prepared by *E. coli* endotoxin i.c., subsequent i.v. injection of guinea-pig erythrocytes and anti-guinea-pig hemolytic serum elicit no THP-L. Under the same circumstances, i.v. injection of hemolytic antirabbit serum does not act as a provocative factor.

Shwartzman G22,681/33: Rabbits sensitized by a single i.v. injection of horse serum, received (one week later) *B. typhosus* endotoxin i.c. and 24 hrs. after that a second injection of horse serum i.v. An "SSP-L" developed at

the i.c. injection site. There was no apparent parallelism, however, between the precipitin titers of the various sera and the incidence of "SSP-L" reactions.

Wadsworth & Sickles G24,320/33: "Rabbits sensitized to serum were injected intradermally with bacterial products, such as bile-lysed pneumococci, pneumococcus carbohydrate, and streptococcus toxin, or with live bacteria. Twenty-four hours later, 1 cc of horse serum was injected intradermally in the same area, and 24 hrs. later an intravenous dose of meningococcus toxin was given. In some animals a marked hemorrhagic reaction appeared before the intravenous dose was given. In the remaining animals the intravenous inoculation was followed within 5 hrs. by marked hemorrhagic changes in the edematous area."

Freund B78,141/34: Typhoid endotoxin i.v. produces hemorrhagic necrosis in tuberculous guinea pigs but not in normal ones at the site of tuberculin injections. On the other hand, in guinea pigs sensitized to horse serum and challenged with horse serum i.c., no hemorrhage is produced by typhoid endotoxin i.v.

Freund B78,142/34: Guinea pigs were infected with virulent bovine or human tubercle bacilli, and then injected i.c. with old tuberculin. This skin test, followed 1-2 days later by *B. typhosus* endotoxin i.v., elicited a positive tuberculin reaction which became hemorrhagic within about 4 hrs. At autopsy, hemorrhages were also found in the organs containing tubercles. Tuberculin does not prepare the skin of the non-tuberculous guinea pig for this hemorrhagic reaction. In guinea pigs infected with B.C.G. or virulent tubercle bacilli, subsequent sensitization with horse serum and challenge by horse serum i.c. produces local hemorrhagic necrosis at the challenged skin sites.

Bordet G23,542/35: In tuberculous rabbits, the dermal tuberculin reaction becomes hemorrhagic and similar in appearance to the SSP-L if, 24 hrs. after the administration of tuberculin i.c., *E. coli* endotoxin is given i.v. In tuberculous guinea pigs, the cutaneous tuberculin reaction is often hemorrhagic in itself, thereby raising the question whether in this species the SSP might not participate even in ordinary tuberculin reactions.

Michelazzi G26,872/35; G26,871/35: A skin area, pretreated by *E. coli* endotoxin i.c. 2-3 days earlier, becomes refractory to the production of an SSP-L by two injections of *E. coli* endotoxin. Other skin areas in the same animal retain their reactivity.

Polettini G25,136/35: In rabbits sensitized by an i.v. injection of horse serum, 8 days later *E. coli* endotoxin was injected i.c. The

same site was injected with horse serum 24 hrs. later and simultaneously two new skin sites were injected with horse serum or *E. coli* endotoxin respectively. Without i.v. provocation, hemorrhagic reactions occurred at the site where either horse serum alone or horse serum and endotoxin were injected. Repeated s.c. injections of horse serum may also result in hemorrhagic necrotic types of the Arthus phenomenon which are indistinguishable from the SSP-L. Repetition of these experiments in dogs only rarely gave positive results.

Shwartzman E58,441/35: "Mixtures of *B. typhosus* culture filtrates with homologous antisera possess a high phenomenon-producing and low lethal potency." [No experimental details given (H.S.).]

Shwartzman G24,102/35: If a rabbit, sensitized to some animal protein (blood serum, ovalbumen, etc.), receives meningococcus or typhoid endotoxin i.c. and 24 hrs. later the same animal protein i.v., there develops an SSP-L at the site prepared by the endotoxin. However, the serum of chickens immunized with Rous sarcoma contains no antibodies demonstrable by this test.

Bordet D1,280/36: Erythrocytes of goats sensitized by a corresponding hemolytic serum provoke an "SSP-L" in the rabbit previously prepared by microbial endotoxins i.c.

Gerber C95,662/36: Rabbits sensitized by normal horse serum i.v., were given 6 days later, an i.v. injection of meningococcal or typhoid toxin, followed after another 24 hrs. by a second i.v. injection of normal horse serum. This caused an SSP-G with hemorrhagic necrosis in various organs, but renal lesions were not specifically mentioned.

Shwartzman G23,097/36: In rabbits sensitized by a single i.v. injection of horse serum, an SSP-L could be produced 6 days later by an i.c. injection of horse serum preceded by 1 hr., or followed 18-24 hrs. later by an i.v. injection of a potent bacterial filtrate.

Veratti G26,189/36: In attempting to reproduce the Apitz phenomenon, the most reliable procedure consisted in administering 5-6 i.v. injections of *E. coli* endotoxin at 3-4-hr. intervals in ascending doses, each injection doubling the preceding one. Thrombohemorrhagic lesions occurred primarily in the lung and intestine, accompanied by fibrin thromboses of the renal glomerular capillaries. Passive transfer of the phenomenon by transfusion of large amounts of blood, from an animal about to develop the lesions to a new one, gave negative results. Pretreatment with small amounts of endotoxin offered immunity.

Gougerot & Hamburger G22,527/37: In a syphilitic patient, tuberculin i.c. produced a

topical necrosis of the tuberculin-reaction type. At the same time a purpuric response occurred in an old syphilitic scar at a distance from the injection site. This is interpreted as a Shwartzman-Sanarelli-Bordet type of response.

Horster & Müller G25,124/37: In rabbits sensitized to pig serum, it is possible to elicit an SSP-L with two injections of meningococcal endotoxin, even if the critical period is extended to 48 hrs. Furthermore, after i.c. injection of endotoxin to such serum-sensitized rabbits, i.v. administration of the sensitizing serum produces a THP-L at the endotoxin-prepared site. The Arthus phenomenon can also be made intensely hemorrhagic by an i.v. injection of endotoxin.

Kourilsky et al. G28,158/37: Review of the literature on hemorrhages in the stomach, duodenum, small intestine, lung, pleura and endocardium during anaphylactic shock in various animal species and man. These changes were first described by Charles Richet in 1902 and have since been confirmed by many others.

Shwartzman G18,862/37: Review of the literature and personal observations suggest that "the complexes of Forssman antigen and antibody may be endowed with provocative potency" in the production of the SSP-L as judged by observations on rabbits prepared by bacterial endotoxins.

Albus & Fischer E63,720/38: In rabbits and guinea pigs sensitized by pretreatment with native plant pollen, the same pollen was injected i.c. at one site and *E. coli* endotoxin at another site. Subsequent i.v. provocation with *E. coli* endotoxin resulted in hemorrhagic lesions typical of the SSP-L at both sites. In animals not sensitized with pollen but otherwise similarly treated, the pollen injection site did not respond, while the skin pretreated with endotoxin developed a typical SSP-L. Conversely, *E. coli* endotoxin i.c. followed by the i.v. injection of pollen-antigen—pollen-antibody complex produced an SSP-L at the site of preparation in the guinea pig and rabbit. It is concluded that pollen-antigen—pollen-antibody complexes can act both as preparatory and as provocative stimuli in eliciting the SSP-L in conjunction with *E. coli* endotoxin.

Albus & Schwarz G28,160/38: In rabbits sensitized with horse serum, subsequent horse-serum injections i.c., followed by the i.v. administration of the same material, produce a typical "SSP-L." These findings confirm those of Horster and Müller (G25,124/37) and show that the SSP-L can be elicited without the use of endotoxin. The authors agree with Schmidt (G28,194/37) who considers the

Arthus phenomenon and the SSP as essentially related immunologic-allergic phenomena.

Angevine & DeGara G22,365/41: In rabbits immunologically sensitized to various bacterial filtrates or heat-killed organisms, an SSP-L can more easily be produced by two injections of these agents given in the usual way than in nonsensitized controls.

Ogata G22,362/41: An Arthus phenomenon induced by repeated i.c. injections of ovalbumen in the rabbit is rendered necrotic and SSP-like by the i.c. injection of an SSP-active endotoxin filtrate (kind not stated), into the ovalbumen-treated region.

Black-Schaffer et al. G22,334/50: In rabbits rendered hypersensitive to beef gamma-globulin, a single inoculation of homologous antigen mixed with *E. coli* or meningococcus endotoxin "may lead to the production of a Shwartzman reaction which functions as an amplifier of the antigen-antibody tissue response."

Schlang B69,777/52: An SSP-L can be elicited in the rabbit by an antigen-antibody reaction *in vivo*. Meningococcus, *E. coli* or *S. typhimurium* i.c. is used for preparation in rabbits sensitized to human serum and challenged by the same antigen 24 hrs. after i.c. preparation.

Alechinsky G22,361/53: If, simultaneously with the usual i.c. preparatory injection of *E. coli* endotoxin, the same material is injected i.v., provocation with *E. coli* endotoxin i.v. 24 hrs. later causes neither local nor generalized SSP-manifestations. However, in animals previously sensitized to protein antigens (horse serum, egg white, milk), the same experiment performed after a 21-day rest (during which no antigen is given) results in both SSP-L and SSP-G lesions. Similarly, admixture of nonspecific proteins with the i.c. and i.v. preparatory injections, or even administration of such proteins i.m. at a distance from the preparatory injection site, annuls the resistance to the SSP normally induced by the double preparatory injection.

Rempt G23,511/54; Rempt & Julius G23,512/54; Rempt G23,068/56: A rabbit is sensitized with horse serum and injected parenterally with *E. coli* filtrate. Upon i.c. injection of horse serum, it develops an Arthus phenomenon with a central hemorrhage, indistinguishable from the SSP-L. "The result is a combined phenomenon of Arthus-Shwartzman. Without previous contact with coli filtrate only the Arthus' phenomenon is induced."

Stetson G22,085/55: In rabbits rendered hypersensitive to BCG, i.c. injection of old tuber-

culin prepares the skin for the production of an SSP-L by the subsequent i.v. injection of meningococcal endotoxin. The results somewhat resemble those reported by Freund (B78,142/34), using tuberculous guinea pigs. If BCG-sensitized rabbits are given an i.c. injection of meningococcal endotoxin and 24 hrs. later tuberculin i.v., an SSP-L appears at the site of endotoxin treatment. Following i.c. preparation with either meningococcal endotoxin or tuberculin, the topical application of epinephrine to the prepared skin site resulted in hemorrhagic necrosis in these sensitized animals. No such response was obtained in rabbits that were not made hypersensitive to BCG.

Arhelger et al. C49,043/57: "Simultaneous injection of nephrotoxic serum and minute amounts of Gram-negative bacterial endotoxin resulted in acute death in a high percentage of rats and renal lesions resembling those of the generalized Shwartzman reaction." The glomerular capillaries were filled with PAS-positive thrombi.

Fehr & Brunson G21,900/57: Rabbits prepared by six daily s.c. injections of bovine gamma-globulin were given *E. coli* endotoxin or sodium polyanethol-sulfonate i.v. 72 hrs. after the last globulin injection. They developed fibrinoid lesions involving the heart, lungs, spleen, liver and kidneys. In the coronary arteries the lesions resembled polyarteritis. "The renal lesions observed in the present experiments are similar to those of 'focal' or 'embolic' glomerulonephritis in humans, and in some respects resemble the changes of acute proliferative glomerulonephritis. The focal glomerular accumulation of large amounts of fibrinoid, with obliteration of capillary loops, is similar also to the lesion of diabetic glomerulosclerosis."

Hugues et al. G21,632/57: In rabbits sensitized to ovalbumen, subsequent topical application of the same antigen to the mesentery produces a local hemorrhagic reaction with leukocytic infiltration which is reminiscent of the SSP-L and of the Arthus phenomenon.

McKinnon et al. G26,513/57: Anaphylactic shock, induced in rabbits by large amounts of antigen and antibody, is associated with the appearance of intravascular amorphous "thrombi" especially in the pulmonary and the hepatic circulation. Apparently, "the intravascular 'thrombi' are antigen-antibody precipitates, since the 'thrombi' were fluorescent only when the challenging fluorescein-labeled antigen was the antigen to which the animal had been sensitized."

Waksman & Adams C39,574/57: Experimental allergic encephalomyelitis (EAE) was produced in rabbits by a single injection of nervous tissue in adjuvant. An "SSP-G" was elicited by two properly spaced i.v. injections of meningococcal endotoxin or by a single dose following pretreatment with Thorotrast. Fifteen of the 63 rabbits receiving this combined treatment "showed full-blown Shwartzman lesions, with hemorrhage and necrosis of the nervous parenchyma, usually superimposed on the pre-existing lesions of EAE. Such hemorrhagic or necrotic lesions were not observed in the control group given toxin alone and occurred in only 2 of the 92 EAE rabbits not given toxin. There was no correspondence between the occurrence of lesions in the central nervous system and the presence or severity of Shwartzman lesions in the major viscera."

Gatling C58,378/58: In rabbits made hypersensitive to horse serum, epinephrine i.c. given soon after an additional dose of horse serum i.v. produces a THP-L at the site of catecholamine treatment. A similar response is obtained by norepinephrine but not by ephedrine. The response shows individual variations but its intensity parallels that of an Arthus reaction elicited in the same rabbit. Epinephrine injected into an Arthus lesion so alters the latter that it becomes similar to an epinephrine lesion. Epinephrine i.c. is ineffective if given to sensitized rabbits which have not received a simultaneous i.v. injection of horse serum. Apparently, the "epinephrine lesion does not occur in the skin of the hypersensitive rabbit in the absence of circulating antigen, residual or injected." This response to epinephrine is prevented by heparin but not modified by chlorpromazine.

Robbins & Stetson G26,023/59: Several antigen-antibody systems can shorten blood-clotting time of the rabbit in vitro. Addition of specific antigens to the blood of actively immunized rabbits, or addition of antigen-antibody mixtures to the blood of normal animals, produced the same effect.

Arndt & Schneider G21,207/60: In BSV strain mice, an SSP-L can be elicited by an i.c. followed by an i.p. or i.v. injection of various bacterial endotoxins. Several types of antigen-antibody complexes can also be used for provocation. Some animals reacted in the usual manner to single i.c. injections of endotoxins but, in these, there was infection of the lungs with Gram-negative microflora. Here, the latter apparently acted as the preparatory agent without there being any specific critical period, since the animals were permanently responsive.

Gatling C83,022/60: Epinephrine or norepinephrine, given i.v. to hypersensitive rabbits in the presence of circulating specific antigen, produce topical hemorrhage with fibrinoid necrosis of arteries. Ephedrine, histamine and atropine i.c. are ineffective under the same conditions.

Lee & Stetson G21,653/60: Single i.c. injections of *E. coli* or *S. typhosa* endotoxin produce delayed inflammatory reactions in the rabbit. Moderate erythema and leukocytic infiltration appear after 6-12 hrs., reaching a maximum at 20-24 hrs. By contrast, in rabbits which first received a single i.v. injection of *E. coli* endotoxin, the subsequent i.c. administration of *E. coli* or *S. typhosa* endotoxin produced a greatly accelerated and intensified cutaneous response. Within 1 hr., there was bleb formation with pronounced edema, erythema and leukocytic infiltration although extravasation of erythrocytes and necrosis were rarely conspicuous. The response resembled the Arthus reaction both in general appearance and in being visible within an hour. This accelerated reactivity is detectable 6 hrs. after the i.v. injection and, in some animals, weak but definite accelerated reactivity was demonstrable for as long as a month. Although the reaction was specific for endotoxins as a group, rabbits pretreated with one endotoxin i.v., responded with accelerated reactions to skin testing with other endotoxins. The capacity for accelerated reactivity can be transferred from a rabbit given *E. coli* endotoxin i.v. to another, unpretreated, rabbit in which the skin test is performed. These findings suggested that accelerated reactivity might be an Arthus phenomenon, due to interactions between antigen and precipitating antibody. However, in various experimental arrangements, no parallelism was found between the appearance of precipitating antibodies and accelerated skin reactivity. Besides, the precipitating antibodies found were highly antigen-specific. On the other hand, a cross-reacting nonprecipitating antibody appeared within 3 days after the i.v. injection of endotoxin concurrently with the accelerated skin reactivity. "The possibility that such antibodies may be involved in the non-specific immunity elicited by endotoxin would seem to deserve investigation." These cross-reacting antibodies may play a role in the production of the SSP-G and SSP-L.

McCluskey et al. D82,558/60: Glomerulonephritis with arteritis in the lungs, stomach, heart, muscles and urinary bladder was produced in mice by the i.v. injection of soluble antigen-antibody complexes. Cortisone dimin-

ished the glomerulonephritis but caused deposition of amorphous eosinophilic material in the glomerular capillary loops which contained antigen and antibody, as judged by the fluorescent antibody technique.

Kováts E99,030/61: Guinea pigs and rats, sensitized 3-4 weeks previously with *S. typhosa* or *E. coli*, develop hemorrhagic skin lesions at sites prepared with endotoxin upon i.v. injection of endotoxin 24 hrs. later. Animals not pretreated with the bacteria do not develop hemorrhagic lesions. The endotoxin must not necessarily be derived from the bacteria used for sensitization. Rabbit antiserum, obtained by hyperimmunization with typhoid endotoxin, injected i.c. in guinea pigs or rats also results in hemorrhage, if followed 24 hrs. later by i.v. injection of endotoxin. Mixtures of typhoid endotoxin and colloidal silver i.c., followed by i.v. injection of the same material, also result in skin hemorrhages in guinea pigs. Normal rabbit, guinea pig or rat mononuclear peritoneal-exudate cells injected i.c., and 24 hrs. later, followed by endotoxin i.v., likewise elicit skin hemorrhage. The author believes to have "succeeded in demonstrating that the first phase of the Shwartzman phenomenon, that is, preparation of the skin by endotoxin, is a specific reaction depending on a well-characterizable immunological mechanism, namely, the phenomenon of local endotoxin hypersensitivity."

Salmon et al. G34,273/62: A thrombopenic purpura can be produced in the rat by the i.v. injection of anti-rat platelet rabbit serum.

Michael D68,994/63: Anaphylaxis elicited by repeated injections of horse serum in mice produces necrosis in sarcoma-37 transplants. This effect is not influenced by pretreatment with pertussis vaccine.

Antopol & Chryssanthou D56,730/63: Human immune globulin i.v. aggravates the SSP-L produced by *E. coli* endotoxin in the rabbit and mouse.

Prevention of THP. The SSP-L normally produced by various bacterial endotoxins can be prevented by homologous antisera. This procedure has even been recommended for the titration of antimeningococcus and antityphoid sera. However, the practical applicability of this technique is limited because the neutralization is by no means wholly specific.

An SSP-L can be elicited in the rabbit by meningococcal endotoxin i.c. followed 18 hrs. later by agar i.v. Within limits this phenomenon also lends itself to the titration of antimeningococcus serum.

In rabbits which have received i.c. injections of endotoxin, an SSP-L can be

Kováts et al. D85,430/63: Following intradermal injection of the serum of rabbits, hyperimmunized with typhoid endotoxin or vaccine (passive cutaneous anaphylaxis), *E. coli* or *E. typhosa* endotoxin i.v. produces an SSP-L at the site of preparation, both in guinea pigs and in rats. Essentially similar results are obtained if a mononuclear cell suspension, collected from the peritoneum of normal rabbits, guinea pigs or rats, is used for cutaneous preparation. The first experiment is interpreted as a cutaneous anaphylaxis due to endotoxin and the second as a cellular transfer of a delayed sensitivity to endotoxin. [It is not clear why the response induced by the mononuclears of the insensitive rat should be ascribed specifically to the transfer of hypersensitivity (H.S.).]

Lee G26,187/63: After RES-blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the appearance of "heparin precipitable fibrinogen" in the circulation.

Levin & Cluff G25,182/65: *E. coli* endotoxin i.c. followed 18 hrs. later by antiplatelet serum i.v. elicited no cutaneous thrombohemorrhagic lesions in the rabbit. However, an "SSP-G" with renal capillary thromboses can be produced in rabbits by combined treatment with Thorotrast i.v. followed by antiplatelet serum i.v.

Mckay E4,788/65: Review of literature on THP in relation to immunity.

Renaud G31,557/65: In rats kept for several weeks on a high fat low protein diet, anti-rat-erythrocyte serum produces disseminated thrombosis affecting various organs, particularly the portal veins of the liver. This is noteworthy because in rats kept on the same diet, endotoxins induced thrombosis in the hepatic, but not in the portal, veins.

induced either by i.p. or by i.v. provocation. However, repeated i.p. injections of the endotoxin prior to preparation can make it impossible to elicit an SSP-L by i.p. provocation while i.v. administration of the provocative endotoxin remains effective. Allegedly, this type of immunity is purely topical and limited to the peritoneum.

Local desensitization against the SSP-L can also be produced by injecting bacterial endotoxins repeatedly into the same skin site prior to the i.c. preparation that will be followed by i.v. provocation. However, this type of protection is transient and probably nonspecific, since many irritants can duplicate it.

Certain normal and immune blood sera possess "reactivating" potency in that they restore the provocative ability of endotoxins that have been completely neutralized by homologous antisera. The reactivating factor is apparently non-specific, heat labile and unrelated to complement.

In rabbits in which an SSP-L is elicited by two injections of endotoxin in the usual manner, a certain degree of immunity develops, since the same treatment becomes ineffective in eliciting the reaction during the next few weeks, unless much higher doses are given. To obtain this type of immunity it is not even necessary to elicit an SSP-L; a single i.v. injection of endotoxin given outside the critical period (a few hours before or after the preparatory i.c. injection) can offer a similar transitory protection.

In rabbits which have become immune to the SSP-L by repeated administration of endotoxin, responsiveness can be restored by the i.v. administration of RES-blocking agents. This phenomenon has been ascribed to an inhibition of the removal of endotoxin by the RES.

The production by endotoxins of hemorrhagic necrosis in transplantable tumors is inhibited in mice immunized to unrelated endotoxins, or even to moccasin venom. This observation further supports the concept that the endotoxin immunity thus obtained is nonspecific.

Shwartzman E68,670/28-29: The SSP-L normally produced by various bacterial endotoxins can be prevented by the corresponding antisera.

Shwartzman G21,640/28-29; E65,451/29; E61,721/29; Reiner & Shwartzman G24,354/29-30: The SSP-L normally produced by two injections of *B. typhosus* filtrates can be prevented if the serum of rabbits or goats immunized with *B. typhosus* filtrates is mixed with the preparatory i.c. dose of endotoxin. "It appears from these studies that a new method is available for quantitative titration of substances in the serum which neutralize the skin preparatory factors of the phenomenon of local skin reactivity to *B. typhosus* culture filtrates."

Shwartzman E42,529/29; G25,696/30: The potency of antimeningococcus serums can be titrated by their ability to inhibit the SSP-L produced in the rabbit by two injections of meningococcus toxin.

Frisch E95,434/30: "Rabbits in which the intraperitoneal injection of *B. typhosus* culture filtrate was able to elicit the Shwartzman phenomenon in previously prepared skin sites were rendered negative to this phenomenon by repeated injections of this culture filtrate intraperitoneally. It was then shown that this skin reaction could still be produced if the reacting factors were introduced intravenously. It must thus be concluded that the immunity produced under these circumstances was of a distinctly local character involving only the peritoneum."

Shwartzman E53,222/30: In the production of an SSP-L by various bacterial endotoxins, "a toxic filtrate of a given bacterium consistently neutralized by a homologous serum loses its ability to elicit reactions not only in areas prepared with the filtrate of the same bacterium but also in areas prepared with antigenically unrelated filtrates."

Shwartzman G23,664/30: Using various strains of *B. typhosus* "transformation of 'stock' strain into 'rough' brought about the formation of reacting factors of new specificity. The 'rough' reacting factors were neutralized by homologous sera and also differed in their neutralizability" by specific antisera.

Burnet E42,707/31: Local desensitization against the SSP-L, produced by various bacterial endotoxins, can be accomplished in the rabbit by injecting the prepared area with active material just before the i.v. injection. However, no evidence of any lasting general immunization has been obtained. Repeated reactions can be elicited in rabbits without diminishing reactivity. A transient desensitization, however, has been induced by an i.v. injection 24 hrs. or less before the i.c. test injection.

Gross D51,461/31: Pretreatment of rabbits with *E. coli* or meningococcus antisera specifically prevents the production of an SSP-L by two injections of the corresponding bacterial endotoxins.

Powell & Jamieson D20,132/31: The SSP-L elicited in the rabbit by two injections of meningococcal toxin can be neutralized if antimeningococcal serum is added to the provocative i.v. injection of toxin.

Shwartzman G24,359/31: A special antibody auxiliary to the neutralization of meningococcus reacting factors plays a role in the serological prevention of the SSP-L induced by meningococcal toxin.

Shwartzman G22,587/31: Tests with the SSP-L, induced by two injections of *B. typhosus* endotoxin, showed that passive immunity can be conferred by normal or immune homologous neutralizing antibodies best administered about 30 min. prior to the i.v. injection of the provocative factor.

Shwartzman G23,363/31; G23,379/31; G24,104/31: The SSP-L normally elicited by two injections of meningococcal endotoxin can be inhibited by the corresponding antiserum.

Klein E65,246/31-32: The SSP-L normally produced in rabbits by two injections of meningococcal or *B. dysenteriae* toxin can be prevented if, just prior to the i.v. provocative injection, these same toxins are injected into the prepared skin site. It has previously been thought that this local inhibition might be due to some immunological phenomenon. However, the author found that many substances (epinephrine, pituitrin, normal saline, phenolized saline, formalinized saline, sterile egg-white solution, immune rabbit serum, normal human serum), injected i.c. just prior to

the provocative i.v. injection, exhibit the same inhibitory effect. Indeed, even compression of the skin site with padded clamps can protect it. Hence "it is believed that these agents produce their effects by creating a local ischemia which shields the prepared skin tissue from the injurious agents circulating in the blood stream."

Grati & Linz D6,544/32: After a more or less prolonged rest, an SSP-L can be produced repeatedly by two injections of *E. coli* endotoxin. Apparently, one SSP-L does not immunize permanently against another. On the other hand, if a small amount of endotoxin is injected i.c. just before the full preparatory dose of the same agent, then topical desensitization can be obtained. Anaphylaxis produced in the sensitized guinea pig by horse serum does not desensitize against the production of an SSP-L by two injections of *E. coli* filtrate. Treatment with anaphylatoxin likewise fails to significantly affect the SSP-L produced by *E. coli* filtrate, but the resulting anaphylactoid response is altered by the SSP-L in that the lungs are not emphysematous but atelectatic and hemorrhagic.

Ogata D27,637/32: Pretreatment with bacterial endotoxins prevents the SSP-L normally produced by two injections of endotoxin in the rabbit.

Powell & Jamieson E64,217/32: The protective activity of antimeningococcus serum against the production of an SSP-L by two injections of meningococcal endotoxin can be used for the quantitative titration of the antiserum.

Shwartzman D70,950/32: The ability of specific antisera to neutralize the provocative power of meningococcal or *E. coli* endotoxins in the production of the SSP-L can, in turn, be blocked by the serum of normal human beings, horses, rabbits or guinea pigs.

Shwartzman G22,588/32; G24,306/32: Technical details concerning the neutralizability of meningococcal endotoxin by antimeningococcus serum, using the SSP-L in the rabbit as a test object.

Shwartzman G22,636/32: *B. typhosus* endotoxin i.c. can induce an immunity to the subsequent production of an SSP-L by two injections of the same material, whereas two injections of meningococcal endotoxin can still produce an SSP-L. Immunization with *B. typhosus* and meningococcal endotoxin renders rabbits immune to both these factors, while two injections of *E. coli* can still elicit an SSP-L.

Shwartzman G23,072/32: Certain normal and immune blood sera of various species possess a

"reactivating" potency: they restore the provocative ability of meningococcal and *E. coli* endotoxins completely neutralized by the corresponding antisera. This property is apparently nonspecific, heat labile, and has no relationship to complement.

Pabst & Braham G16,000/33: "Serum neutralization of the Shwartzman phenomenon produced by filtered meningococcus washings is not restricted to antimeningococcal sera, but also occurs with antipneumococcal, antidysenteric, and antigenococcal sera and with diphtheria antitoxin, as well as with normal horse and rabbit sera. This nonspecific neutralization is so frequent and so marked that it seems to limit the usefulness of the Shwartzman phenomenon in the evaluation of therapeutic antimeningococcal sera."

Sickles D36,865/33: An SSP-L can be elicited in the rabbit by meningococcal endotoxin i.c. followed 18 hrs. later by 0.2% agar i.v. The technique lends itself to the titration of the neutralizing potency of antimeningococcus serum.

Sickles D94,462/33: An SSP-L, produced in the classical way by an intracutaneous, followed by an i.v. injection of meningococcus toxin, can be prevented with antimeningococcus serum, and the latter can be thus titrated.

Boquet B18,399/35: A typical SSP-L can be elicited in the rabbit by two injections of filtrates of *B. lepisepticum*. Animals made resistant by pretreatment with repeated i.v. injections of killed *B. lepisepticum* cultures remain sensitive to the production of an SSP-L by *B. lepisepticum* filtrates. The response is non-specific, since *E. coli* filtrate can be used for preparation or provocation when *B. lepisepticum* is administered as the other injection.

Linton et al. G23,261/35: An SSP-L can be produced by various vibrios (including *El Tor*). The effect of the filtrates is neutralized by incubating them with homologous anti-serum.

Michelazzi G26,191/35: Rabbits infected with live staphylococci develop a particularly severe SSP-L following two injections of *E. coli* endotoxin. No such accentuation of the phenomenon is seen in animals pretreated with killed staphylococci or staphylococcus filtrate. Rabbits infected with bovine tuberculosis are almost completely refractory to the production of an SSP-L by *E. coli* endotoxin but no such protection is offered by pretreatment with killed human or bovine tubercle bacilli. Pretreatment with washed *E. coli* bacilli offers considerable resistance to the SSP-L.

Stolyhwo G21,662/35-36: In rabbits in which an SSP-L is elicited by two injections of typhoid or paratyphoid filtrate, a certain degree of immunity develops, since the same treatment is ineffective in eliciting the reaction during the next few weeks unless much higher doses are given. Even a single i.v. injection of such filtrates may induce an immunity which lasts up to 55 days.

Ogata G21,285/36: An SSP-L, produced by two injections of various bacterial toxins, can be inhibited by an i.v. injection of the same or even an unrelated bacterial toxin given a few hrs. before or after the preparatory i.c. injection. This inhibition is transitory and probably not of anaphylactic nature.

Veratti G23,476/36: Apitz phenomenon is elicited by repeated i.v. injections of *E. coli* endotoxin given at intervals of about 5-6 hrs. three times a day in gradually increasing dosages. It is characterized by fibrin deposition in the glomerular capillaries with hemorrhages into Bowman's capsule in the kidney, followed in a second stage by capillary hemorrhages, unaccompanied by fibrin deposition, in the lungs. Death ensues usually on the second day. Pretreatment by repeated i.v. or s.c. injections of the same bacterial extract induces an immunity to this phenomenon.

Moritz & Weir G22,344/37: In rabbits prepared by *B. aertrycke* endotoxin injected directly into the left renal artery, a subsequent i.v. injection of the same material produced an SSP-G with typical manifestations in the right kidney also, while the left kidney remained unimpaired. Even removal of the contralateral kidney did not prevent this "local refractory state" in the injected kidney. The observations are in contradiction to the statement of Shwartzman (E53,222/30) who claims to have produced an SSP-L through preparation of one rabbit kidney by the injection of endotoxin into its artery, followed by the i.v. injection of the same material.

Sanarelli G22,253/38; G28,164/39: The SSP normally elicited by repeated i.v. injections of sterilized human saliva in the rabbit can be prevented by pretreatment with the same material.

Stolyhwo G28,157/38; G22,093/39: Pretreatment with typhoid filtrate i.c. immunizes the rabbit against the subsequent production of an SSP-L by two injections of typhoid endotoxin. This immunity is not limited to the pretreated region but affects the entire integument. Similar immunization can be obtained by the prophylactic administration of the endotoxin i.m., s.c. or intracerebrally. Following applica-

tion of bandages soaked in filtrate, only the treated area becomes resistant to the production of an SSP-L, presumably because insufficient endotoxin is absorbed into the general circulation.

Ogata G27,947/39: General review on the inhibition of the SSP-L in rabbits pretreated with various substances which normally produce an SSP-L.

Zahl et al. G22,087/43: The hemorrhagic necrosis of Sarcoma-180 transplants, normally induced by *Sh. paradyssenteriae* endotoxin i.p., does not occur in animals previously immunized with this antigen.

Zahl et al. G21,528/43: Mice, immunized with endotoxins of *Sh. paradyssenteriae*, *S. typhimurium* and *Rhodospirillum rubrum*, were protected against the induction of hemorrhage in sarcoma-180 transplants by any one of these endotoxins. Apparently, "a common antigenic toxic component is characteristic of gram-negative bacteria generally."

Zahl & Hutner E41,878/44: Mice, immunized with moccasin (*Agirostodon piscivorus*) venom, were protected against otherwise lethal doses of *S. typhimurium* endotoxin, and inversely salmonella-immunized mice were protected against the venom. "This cross-protection may be due to the presence in gram-negative organisms and moccasin venom of a common factor characterized by hemorrhagic action, antigenicity, and a lack of serological specificity."

Beeson B64,425/47: In rabbits which had become immune to the SSP-L by repeated administration of cutaneous and i.v. injections of *E. typhosa* filtrate washings, as well as in naturally immune rabbits, i.v. injection of Thorotrast or trypan blue restored reactivity, presumably by blocking the RES. "Consideration of these results leads to the assumption that immunity to the Shwartzman reaction depends on ability of the R-E system to remove the bacterial toxin from the blood stream to such an extent that the tissues at the site of skin preparation are spared serious injury. R-E blockade permits the toxin to be delivered to the prepared skin area in a concentration sufficient to produce capillary damage and hemorrhagic necrosis."

Beeson D2,409/47: Following repeated injections of various bacterial endotoxins, their pyrogenic response in the rabbit diminished considerably. This resistance is ascribed to an activation of the RES because: "Pyrogenic substances disappeared from the circulating blood more rapidly in rabbits rendered pyrogen-tolerant than in normal animals. Lack of spe-

cificity was shown by the fact that rabbits previously injected with *Eberthella typhosa* bacterial vaccine were able to remove the pyrogens of *Serratia marcescens* and *Pseudomonas aeruginosa* from their blood more rapidly than normal animals." Blockade of the RES by trypan blue or Thorotrast retarded the speed of disappearance of pyrogens from the circulating blood of tolerant animals and abolished their pyrogen resistance.

Cluff & Bennett B61,183/51: Resistance to the SSP-L develops when the reaction is elicited repeatedly at short intervals, but disappears after a 3-4 week rest period. This resistance is effective against materials from heterologous bacterial species, and can be produced even by repeated i.v., i.c., or i.m. inoculation of bacterial substances; hence it is not dependent on the development of skin hemorrhage. It can be overcome by increasing the provocative i.v. dose, but not by increasing the preparatory i.c. dose. Attempts to transfer this resistance passively with homologous serum were unsuccessful.

Bennett G21,296/52: Review of the literature on the gradual induction of resistance to the SSP-L during attempts to elicit the reaction repeatedly in the same rabbit. Thorotrast or colloidal organic iodide abolishes this resistance when administered before the provocative injection. This sensitizing effect is ascribed to a blockade of the RES.

Bennett & Cluff B77,767/52: Various bacterial endotoxins in doses too small to produce an SSP-L in the rabbit induce a state of non-reactivity to subsequent treatment with endotoxins which are effective in producing an SSP-L in unpretreated animals.

Alechinsky G22,361/53: If simultaneously with the usual i.c. preparatory injection of *E. coli* endotoxin, the same material is injected i.v., provocation with *E. coli* endotoxin i.v. 24 hrs. later causes neither local nor generalized SSP manifestations. However, in animals previously sensitized to protein antigens (horse serum, egg white, milk), the same experiment performed after a 21-day rest (during which no antigen is given) results in both SSP-L and SSP-G lesions. Similarly, admixture of non specific proteins with the i.c. and i.v. preparatory injections, or even administration of such proteins i.m. at a distance from the preparatory injection site, annuls the resistance to the SSP normally induced by the double preparatory injection.

Thomas B92,009/54: On the basis of a review of the literature, "two generalizations can be stated: (a) When animals are made resistant to the endotoxin of one species of

bacteria, they are resistant to other endotoxins. (b) When animals are made resistant to one effect of endotoxin, they are resistant to other effects."

Eichenberger et al. C13,546/55: An SSP-L can be elicited in the rabbit by two injections of *S. abortus equi* polysaccharide (Pyrexal). Previous immunization with this endotoxin prevents the response.

Meier et al. C57,198/57: Polysaccharides, obtained from various species of proteus, could be used for the production of an SSP-L in the rabbit. Alechinsky (G15,976/52) reported that coli filtrates, injected i.v. simultaneously with the preparatory i.c. dose, largely inhibited the SSP-L. This has now been confirmed with the proteus polysaccharide.

Fine et al. D98,173/59: Rabbits, made resistant to *E. coli* endotoxin by repeated i.v. injections of sublethal doses, also become highly resistant to hemorrhagic shock. However, if such animals are given Thorotrast i.v., they die with manifestations of the SSP-G. It is assumed that Thorotrast induces shock by blocking the endotoxin-destroying power of the RES.

Freedman E52,651/59: The serum of rabbits rendered tolerant by a brief schedule of endotoxin administration protects mice against the

lethal effect of homologous or heterologous endotoxin. This protective effect is not attributable to blood-borne antibodies. "Preliminary experiments indicate that the protective serum of tolerant donors stimulates the reticuloendothelial system of the recipient, as measured by carbon-clearance in the latter."

Gaiginschi et al. G22,148/64: In guinea pigs infected with tuberculosis, the production of an SSP-L by two injections of *E. coli* endotoxin is inhibited.

Levin & Cluff G25,182/65: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit was not prevented by repeated i.v. injections of antiplatelet serum, although the latter elicited a severe thrombocytopenia.

Nowotny et al. G29,062/65: "Reaction of endotoxic O-antigens with rabbit O-antisera results in a neutralization of toxic effects, determined in mice by lethality, pyrogenicity, and Shwartzman skin-reactivity assays, while the enhancement of non-specific resistance of these preparations remains unchanged." SSP-L-activity was tested in rabbits by i.c. preparation with endotoxic O-antigen isolated from *S. marcescens* cells given as such or after complexing with the corresponding antibody.

THE RES

RES-blocking agents exert a very potent effect upon THPs induced either by microbial or by nonmicrobial agents.

Microbial Agents. It was observed as early as 1928 that blockade of the RES by India ink, trypan blue or colloidal silver i.v. makes it possible to produce a "Sanarelli reaction" by a single i.v. injection of a microbial agent (e.g. *E. coli* endotoxin) given 24 hrs. later. Subsequent investigations have amply confirmed and extended this finding by showing that various other RES-blocking agents possess the same enhancing potency not only for single i.v. injections of various other endotoxins but also for the SSP-L and the SSP-G produced in the routine manner by two properly spaced injections. Indeed, even rabbits rendered resistant by repeated endotoxin injections again become sensitive to the production of an SSP if their RES is thus blocked. It is essential, however, to administer the RES-blocking agents before the microbial products. In rabbits prepared by endotoxins i.c., the subsequent i.v. injection of RES-blocking agents has no provocative potency. These findings are consonant with the assumption that blockade of the phagocyte system enhances sensitivity because it impedes the removal either of the causative microbial factors themselves, or of the resulting fibrin precipitates. Treatment of the site of the preparatory i.c. injection by RES-blocking agents is ineffective in preventing or enhancing the development of an SSP-L.

According to a few isolated reports, chlorazol fast pink and Congo red pre-treatment actually prevent the SSP-L. These reports require confirmation on a

larger experimental material, besides, it is possible that certain dyes possess a particular enhancing effect of their own which overcompensates for their RES-blocking action.

Ugriumow D20,561/28: In rabbits pretreated with an i.v. injection of India ink, trypan blue or colloidal silver, a single i.v. injection of *E. coli* endotoxin, given 24 hrs. later, suffices to produce a "Sanarelli reaction." [The nature of the resulting organ changes is not described (H.S.).]

Shwartzman E53,222/30: Treatment of the site of the preparatory i.c. injection with various RES-blocking agents, including India ink, failed to prevent the SSP-L produced by two injections of *B. typhosus* endotoxin. Apparently, topical blockade of the RES does not prevent the SSP-L.

Sickles B78,436/31: SSP-L may be elicited in the rabbit by meningococcal toxin i.c. followed by agar i.v. Local reactions did not occur at the sites of i.c. agar injections followed by the bacterial toxin i.v. Galactose, gelatin, serum or India ink i.v. following meningococcal toxin i.c., failed to elicit the SSP-L.

Shwartzman G23,070/32: In rabbits prepared with *B. typhosus* endotoxin i.c., the following colloidal suspensions were found to have no provocative potency: charcoal, infusorial earth, Witte's peptone, silicic acid and gelatine.

Giuffré G27,055/37: The SSP-L normally elicited by two injections of typhoid endotoxin in rabbits can no longer be obtained if the RES of the animals is blocked by trypan blue injection. [It is questionable whether the dose of dye applied has in fact produced a blockade or a stimulation of the RES (H.S.).]

Trizzino & Caffarelli G27,500/39: The SSP-G normally elicited by two i.v. injections of typhoid filtrate in the rabbit can be inhibited by pretreatment with repeated i.v. injections of lithium carmine. Allegedly, this inhibition is due to blockade of the RES. [Whether the dye actually blocked or stimulated the RES at the dose given has not been verified (H.S.).]

Beeson B64,425/47: In rabbits which had become immune to the SSP-L by repeated administration of cutaneous and i.v. injections of *E. typhosa* filtrate washings, as well as in naturally immune rabbits, i.v. injection of Thorotrast or trypan blue restored reactivity, presumably by blocking the RES. "Consideration of these results leads to the assumption that immunity to the Shwartzman reaction depends on ability of the R-E system to remove the bacterial toxin from the blood stream to such an extent that the tissues at the site of the skin preparation are spared serious injury. R-E blockade permits the toxin to be de-

livered to the prepared skin area in a concentration sufficient to produce capillary damage and hemorrhagic necrosis."

Beeson D2,409/47: Following repeated injections of various bacterial endotoxins, their pyrogenic response in the rabbit diminished considerably. This resistance is ascribed to an activation of the RES because: "Pyrogenic substances disappeared from the circulating blood more rapidly in rabbits rendered pyrogen-tolerant than in normal animals. Lack of specificity was shown by the fact that rabbits previously injected with *Eberthella typhosa* bacterial vaccine were able to remove the pyrogens of *Serratia marcescens* and *Pseudomonas aeruginosa* from their blood more rapidly than normal animals." Blockade of the RES by trypan blue or Thorotrast retarded the speed of disappearance of pyrogens from the circulating blood of tolerant animals and abolished their pyrogen resistance.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by trypan blue, Niagara sky blue, Congo red or India ink.

Costa B60,775/51: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit can be inhibited by Congo red i.v. administered prior to the provocative i.v. injection.

Costa B63,283/51: The SSP is allegedly inhibited by chlorazol fast pink i.v. [This brief report mentions no experimental details (H.S.).]

Filipp & Kelenhegyi G23,257/51: Blockade of the RES by Congo red i.v., 10 hrs. after the preparatory injection, prevents the production of an SSP-L by two injections of live *E. coli* organisms given in the usual manner. It is concluded that "blockade of the RES by Congo red can consistently prevent the production of a Sanarelli-Shwartzman phenomenon." [This finding is directly opposed to the majority of pertinent observations and requires confirmation (H.S.).]

Bennett G21,296/52: Review of the literature on the gradual induction of resistance to the SSP-L during attempts to elicit the reaction repeatedly in the same rabbit. Thorotrast or colloidal organic iodide abolishes this resistance when administered before the provocative injection, presumably owing to blockade of the RES.

Good et al. B69,366/52: "A single injection of meningococcal or *S. marcescens* toxin, 6 hrs.

after an injection of Thorotrust, regularly produced the following results: 1) The lethal effect of toxin was enhanced 500-fold; 2) Bilateral cortical necrosis of the kidneys occurred in a high percentage; 3) An intradermal injection of toxin caused local skin hemorrhage as well as renal cortical necrosis. Identical results were obtained when trypan blue was used for 'blockade.' Neither Thorotrust nor trypan blue caused illness or tissue lesions when given alone, or when given a few hours after, instead of before, toxin."

Good & Thomas B80,500/52: The i.v. injection of meningococcal or *S. marcescens* toxin in amounts which were without apparent ill effect in normal rabbits was followed by bilateral renal necrosis and death in a high proportion of animals which were given Thorotrust or (to a lesser extent) trypan blue, several hours before the toxin. If, after Thorotrust or trypan blue i.v., meningococcal or marcescens toxin is injected i.c., an SSP-L (often accompanied by bilateral cortical necrosis) appears. Apparently here, the blockade of the RES imitates the previously observed effect of cortisone, in that it permits the induction of an SSP-L by a single injection of bacterial toxin. At the same time, it so enhances the absorption of the latter from the skin that an SSP-G results. When the Thorotrust or trypan blue are given after the bacterial toxin, neither cutaneous nor renal lesions develop. Other RES-blocking agents such as glycogen, starch, PVP, tissue extracts and antigens failed to prepare rabbits so that subsequent i.v. injection of suitable bacterial toxins would have produced an SSP-G. "The foregoing experiments do not furnish evidence concerning the specificity of the action of Thorotrust or trypan blue on the reticulo-endothelial system. They indicate, however, that other types of colloidal or particulate materials do not affect the susceptibility to bacterial toxin in the same manner."

Thomas & Good B79,249/52: Earlier work had shown that the SSP-L can be provoked by i.v. injection of colloidal and particulate suspensions of non-bacterial materials such as starch, glycogen, serum, tissue extracts, kaolin and antigen-antibody complexes in rabbits prepared by meningococcal endotoxin i.c. In the present experiments, kaolin, starch, a 10% suspension of rabbit liver tissue, glycogen and human serum (given after sensitization with the same antigen) i.v. were found to be ineffective in eliciting an SSP-G in rabbits prepared on the preceding day by meningococcal toxin i.v. "It is evident that the provoking action of toxin is not imitated by non-bacterial materials in the generalized Shwartzman reaction,

although the substances are highly active in the local Shwartzman reaction."

Bennett & Beeson B95,351/53: The resistance to the SSP-L which develops following repeated courses of two injections of *S. marcescens* endotoxin each, can be annulled by Thorotrust i.v.

Race & Reed G23,063/53: Pretreatment with Thorotrust i.v. at the time of the preparatory injection or 6 hrs. later aggravates the SSP-L normally produced by two injections of meningococcal endotoxin in the rabbit.

Smith et al. B82,232/53: Blockade of the RES with colloidal carbon or Fe-OS i.v. so alters the responsiveness of the rabbit that it develops a THP-L upon i.c., and a THP-G (with renal cortical necrosis) upon i.v. administration of *S. marcescens* or meningococcal toxin.

Thomas B89,551/53: In rabbits pretreated with Thorotrust or trypan blue, a single i.v. injection of meningococcal endotoxin elicits bilateral renal cortical necrosis.

Hestrin & Davies C23,684/56: The native levan of *Aerobacter levanicum*, given i.c. and then i.v., produces a typical SSP-L in the rabbit. The response is inhibited by native levan or native dextran given i.v. just before the preparatory i.c. dose of toxin. Since i.v. injection of the levan or dextran produced leukopenia, "the leucopenogenic activities of polymers and their ability to depress diapedesis and block skin preparation in the Shwartzman reaction are seen to be correlated properties. The findings support the view that induction of skin reactivity in the Shwartzman phenomenon requires infiltration of the prospective site by leucocytes during the phase of skin preparation."

Cremer & Watson C37,986/57: The distribution of *S. typhosa* endotoxin in the RES was determined in rabbits by its ability to complex with fluorescein-tagged gamma globulin. Pretreatment with cortisone and X-irradiation did not affect the initial phagocytosis of toxin by the RES-cells of the liver, spleen and lung but inhibited its degradation and elimination after a single i.v. injection, as judged by the rate of its disappearance from the RES-cells. Pretreatment with Thorotrust and preliminary injection of toxin caused depression of initial phagocytosis following a subsequent second injection of toxin. "Thorotrust and the first injection of toxin by incapacitating the initial phagocytic ability of the RES, probably keeps the provoking dose of toxin in the systemic circulation where it can effect its deleterious action at its primary site for a longer period of time."

Thomas D1,020/57: An SSP-G can be produced in the rabbit by a single injection of bacterial endotoxin if this is preceded, but not if it is followed by the i.v. administration of RES-blocking agents. In rabbits pretreated by Thorotrust or Fe-OS i.v., the i.c. injection of endotoxin does not produce the usual immediate inflammatory reaction but, after approximately 18 hrs., numerous petechiae appear which coalesce and develop into hemorrhagic necrosis indistinguishable from that of the typical SSP-L. It is also assumed that, normally, the endotoxin is retained at the injected skin site while, after RES blockade, it is absorbed into the general circulation so that systemic manifestations of an SSP-G are superimposed upon the SSP-L.

Zweifach et al. G22,062/57: The toxicity of *E. coli* endotoxin in rats is greatly increased by previous blockade of the RES with colloidal carbon or ferric oxsaccharate (Fe-OS). In rats rendered resistant to *E. coli* endotoxin by repeated injections, the tolerance is abolished by these RES-blocking agents, so that hemorrhagic infarctions of the intestine, lymph nodes, liver and kidney occur after treatment with previously well tolerated amounts of endotoxin.

Fine et al. D85,444/59: A typical "SSP-G" can be produced in the rabbit by pretreatment with Thorotrust i.v. and subsequent induction of a hemorrhagic shock terminated after 90 min. by transfusion of all the shed blood. The animals then recover, but die 24 hrs. later with diffuse hemorrhagic lesions. A similar "SSP-G" is produced in the rabbit by Thorotrust i.v. followed by endotoxin or by two successive injections of Thorotrust. "Thus, we had produced what we regard as endotoxic shock, without giving endotoxin, and achieved this simply by eliminating the endotoxin-detoxifying power of the reticuloendothelial system."

Wong et al. D10,406/61: As judged by observations on rabbits, using Shear's polysaccharide, it is concluded that "Thorotrust, in spite of its ability to 'prepare' an animal for the generalized Shwartzman reaction, is incapable of substituting for endotoxin as the

second or 'provoking' dose." This may be due to the inability of Thorotrust to produce intravascular clotting.

Lee E41,395/62: A single i.v. injection of *E. coli* endotoxin produces an "SSP-G" in the rabbit if given just before or after blockade of the RES.

Kováts et al. D85,430/63: An "SSP-L" can be elicited in guinea pigs pretreated with colloidal silver i.v. and then given *E. coli* endotoxin plus colloidal silver intradermally. Both topical and systemic blockade of the RES by colloidal silver was necessary to elicit this reaction. An "SSP-G" with characteristic renal lesions can also be elicited in guinea pigs pretreated with colloidal silver i.v. and then given typhoid endotoxin i.v.

Scott E45,724/63: The production of an SSP-G by two i.v. injections of *E. coli* endotoxin is enhanced by pretreatment with trypan blue i.v. The incidence of renal cortical necrosis and thrombi in the liver is augmented, and particularly pronounced fibrinoid deposition occurs in the intima of the pulmonary arteries.

Levin & Cluff G25,181/65: In rabbits pretreated with Thorotrust or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, this response differs from the SSP in that it is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment. The adrenal hemorrhages are also prevented by certain adrenergic blocking agents such as phenoxybenzamine, alderlin, or 1(3',4'-dichlorophenyl)-2-(isopropylamino)ethanol. Since ACTH, Thorotrust and *E. coli* endotoxin all increase the blood-cortisol level of the rabbit, it is assumed that the localization of the hemorrhages is connected with increased adrenocortical activity.

Levin & Cluff G25,182/65: An "SSP-G" with characteristic fibrinoid thrombi in the renal glomerular capillaries can be produced in rabbits by a single i.v. injection of *E. coli* endotoxin following Thorotrust i.v.

Nonmicrobial Agents. The production of a THP by nonmicrobial agents is likewise facilitated by RES-blocking agents. The ability of thrombin i.v. to produce a THP is greatly augmented by pretreatment with Thorotrust or other RES-blocking agents. Indeed, in rabbits, repeated i.v. injections of lithium carmine suffice by themselves to produce hyaline thrombi in the renal glomerular capillaries and thrombohemorrhagic necroses in other organs. Essentially similar changes have been noted after i.v. injections of Thorotrust in rabbits and dogs.

Reyna E24,151/36: In rabbits repeated daily i.v. injections of lithium carmine, given over a period of 2-6 days, produce hyaline thrombi in the renal glomerular capillaries with bilateral cortical necrosis. There are also hemorrhages and necroses, sometimes with hyaline thrombi, in the liver, lung and adrenals. [The author emphasizes the similarity of these changes to those characteristic of eclampsia and bilateral cortical necrosis in man, but he does not mention the possibility of a relationship to the SSP (H.S.).]

Ravin et al. G27,057/58: The toxin that appears in the blood of dogs and rabbits during irreversible hemorrhagic shock resembles bacterial endotoxin in many of its pharmacologic and chemical properties. Concentrates of this toxin can act as the provocative factor of the SSP-G in rabbits prepared by *E. coli* endotoxin or Thorotrast i.v. It is concluded "that the circulating toxin in shock is similar to, or identical with, bacterial endotoxin."

Fine et al. D98,173/59; D85,444/59: In rabbits, transient hemorrhagic shock was produced by bleeding into a heparinized reservoir and then restoring their own blood to effect recovery. If Thorotrast was given i.v. prior to the bleeding, immediate recovery still occurred but was followed, within a few hours, by a second period of shock which terminated in death. At autopsy, multiple focal hemorrhages were found in the lungs, kidneys, liver and retroperitoneal space. There was also severe bilateral cortical necrosis of the kidneys which was regarded as indicative of the SSP-G. Hemorrhagic necrosis of the gut was observed in dogs under similar conditions but this was not considered to be an SSP-G. A single large dose of Thorotrast i.v. suffices to produce an SSP-G in the rabbit. A small dose i.v. followed by a sublethal dose i.v. produces a typical "SSP-G" in the rabbit. Two spaced injections of India ink given in this manner are ineffective. Neomycin or polymyxin can cause an "SSP-G" when given orally 2-8 hrs. prior to Thorotrast. This effect is ascribed to an increased absorption of endotoxin from the gut. Thorotrast i.v. after trypan blue, trypan blue after Thorotrast, and two spaced injections of trypan blue are ineffective in eliciting the "SSP-G" in the rabbit.

Selye et al. C70,942/59: Topical injection of cortisol into one hind paw of the rat protects the pretreated region selectively against the

angiotactic sequestration of blood-borne India ink particles during an anaphylactoid inflammation induced by dextran i.v.

Lee E41,395/62: The ability of thrombin i.v. to produce an "SSP-G" in the rabbit is greatly augmented by pretreatment with Thorotrast, denatured albumin or *E. coli* endotoxin i.v., all of which depress the function of the RES. It is assumed that blockade of the RES increases susceptibility to the production of an SSP-G by interfering with the removal of fibrin (not, as had previously been thought, through the removal of endotoxin). This view was further supported by the finding that epsilon-aminocaproic acid, or EACA (which likewise enhances the development of an SSP-G after a single injection of *E. coli* endotoxin or thrombin) interferes with carbon clearance by the RES. Presumably, EACA likewise acts through blockade of the RES rather than through the activation of fibrinolysis.

Lee G26,187/63: After RES blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the appearance of "heparin precipitable fibrinogen" in the circulation.

Rothenberg et al. G26,181/63: Dietary lipids can partially block the phagocytic ability of the RES, and vitamin-E supplements prevent this blockade in the rat. However, pregnancy is associated with a slight increase in the phagocytic activity of the RES; hence, it presumably "prepares" for the production of a THP-G by diets rich in oxidized lipids and poor in vitamin E through some mechanism other than blockade of the RES.

Rodriguez-Erdmann G30,256/65: Following blockade of the RES by Thorotrast, the i.v. injection of homogenized fibrin produces renal cortical necrosis with thrombosis of the glomerular capillaries in the rabbit.

Rodriguez-Erdmann G34,859/65: In rabbits pretreated with Thorotrast, i.v. injection of phospholipids, containing platelet factor 3 or Inosithin (soya bean phospholipid) there developed an SSP-G associated with the typical alterations of the clotting mechanism.

FACTORS INFLUENCING BLOOD COAGULATION

Since blood coagulation plays a particularly important role in all forms of THP, we shall devote a special section to the factors influencing blood coagula-

tion. Under this heading we shall discuss conjointly natural body constituents (thrombin, thromboplastin, heparin) and drugs which exert especially potent effects upon blood clotting (heparinoids and related compounds, epsilon-aminocaproic acid, antiplatelet serum).

Thrombin, Thromboplastin. Continuous i.v. infusions or repeated i.v. injections of thrombin or thromboplastin (including thromboplastin-containing placental extracts) produce multiple capillary fibrin thrombi especially in the renal glomerular capillaries, thrombocytopenia, hypofibrinogenemia, leukopenia, and incoagulability of the blood. The resulting "consumption coagulopathy" is reminiscent of the SSP-G and of eclampsia. This effect of thrombin is greatly augmented by EACA (epsilon-aminocaproic acid) and RES-blocking agents.

Fulton & Page G20,921/48: Thromboplastin-containing human placental extracts i.v. normally produce an eclampsia-like condition with multiple necroses in the mouse. Following sublethal doses, the blood becomes incoagulable, and the animals resist otherwise lethal doses of thrombin or thromboplastin i.v. Refractoriness is "abolished by restoring fibrinogen to the circulating blood, indicating that prothrombin is still present."

Jürgens & Studer D38,953/48: Following slow i.v. infusion of thrombin in the rabbit, the blood becomes incoagulable, and there is leukopenia, thrombocytopenia and hypofibrinogenemia. Multiple capillary fibrin thrombi develop, especially in the renal glomerular capillaries, the liver and the lung. Polymorphonuclear leukocytes tend to accumulate in these same organs. [The possible implications of this observation in the pathogenesis of the SSP are not discussed (H.S.).]

Schneider B56,544/50: In rabbits, thromboplastin-containing rabbit placental extracts i.v. cause pulmonary thromboembolism, cerebral hemorrhages and liver necrosis, especially in pregnant animals. Similar results are obtained by trauma to the placenta. Perhaps "following placental damage, material from the placenta might gain access to the maternal blood circulation, and initiate clotting. Thromboplastin is considered to be the chief one of these activators." The changes thus produced may represent an experimental counterpart of obstetrical shock and eclampsia.

Basinger & Allen G24,124/51: When beef-lung thromboplastin or bovine thrombin are infused i.v. for an hour in dogs, fibrinogen disappears from the blood, prothrombin activity is reduced and there is thrombocytopenia. "Autopsy sections taken four hours after defibrination disclosed no evidence of fibrin deposits in the lung, liver, kidneys, or spleen." . . . "It is concluded that intravascular defi-

brination is possible and compatible with life under these conditions."

Page et al. G22,348/51: Thromboplastin-containing human placental extract i.v. produces fibrin deposition in the renal glomerular capillaries and in the hepatic vessels with blood sludging in arterioles, particularly those of the lungs. Sometimes, there are scattered hepatic necroses. These changes are ascribed to a coagulation defect similar to that seen in abruptio placentae. [Possible relations to the SSP are not considered (H.S.).]

Schneider & Engstrom C6,038/54: Acute disseminated occlusion of the pulmonary arterial vasculature was induced in dogs by thromboplastin (crude bovine lung extract) i.v.

Johnstone & McCallum G21,668/56: In rabbits, repeated i.v. injections of thromboplastin produce fibrin thrombi in the renal glomerular capillaries and pulmonary vessels, combined with hypofibrinogenemia.

Quick et al. D18,347/59: When thrombin is rapidly injected i.v. in the dog, thrombosis occurs but, if the solution is diluted and given slowly, occult clotting without thrombosis ensues. Studies of the resulting clotting defect "suggest that thrombin not only clots fibrinogen, but acts as a catalyst that sets off the clotting reaction which results in a marked consumption of several clotting factors, thereby bringing about a state of hypocoagulability. It may be postulated that most of the injected thrombin is adsorbed promptly to filaments of fibrin which are filtered by the capillary beds, thereby preventing sufficient accumulation of thrombin which could eventuate in massive thrombosis."

Hardaway et al. G26,426/60: Intra-aortic injection of thrombin causes intravascular clotting in the abdominal organs and the lung of the dog. This is associated with a decrease in blood fibrinogen and an increase in heparin-like substances and fibrinolysins. The results

essentially duplicate those produced by incompatible blood, except for the marked fibrinolysis production noted in the present experiments.

Robbins & Collins E85,082/61: The SSP-G elicited by two i.v. injections of bacterial endotoxin (kind not stated) is prevented or reduced by the injection of thrombin into the renal arteries. "These results are additional evidence that the initiation of blood coagulation by endotoxin has a basic role in the pathogenesis of the Shwartzman reaction."

Hardaway D12,907/62: Intra-aortic injection of thrombin induces hemorrhagic necrosis in the gastro-intestinal mucosa of the dog. Microscopically, thrombi could also be detected in the gastro-intestinal mucosa, lungs, liver, kidneys and pancreas.

Henry G33,285/62: Review on the production of thromboses with thrombin i.v.

Lee E41,395/62: Thrombin i.v. produces renal cortical necrosis, fibrin thrombi in the glomeruli and, less constantly, hemorrhage and necrosis in the liver, spleen and lung of the rabbit. Apparently, "thrombin could duplicate all of the pathologic features usually associated with the generalized Shwartzman phenomenon." The ability of thrombin i.v. to produce an SSP-G in the rabbit is greatly augmented by pretreatment with EACA, Thorotrast and other RES-blocking agents.

Margaretten & McKay G3,648/63: Glomerular capillary thrombi similar to those of the SSP-G have been produced in pregnant and nonpregnant rats by thrombin i.v.

Vassalli et al. G14,966/63: Electron-microscopic studies show the deposition of fibrin and fibrinoid in the glomerular capillaries of rabbits injected with Liquoid, thromboplastin or thrombin.

Vassalli et al. E56,313/64: Description of ultrastructural changes in the platelets within in the glomerular capillaries of rabbits, fol-

lowing intravenous infusion of thromboplastin or injection of thrombin into the renal artery. Fibrin deposition occurs only secondarily around damaged platelets.

Margaretten et al. F3,924/64: Prolonged infusion of thrombin i.v. elicits no adrenal hemorrhage in the rat (changes in other organs are not mentioned). However, if ACTH or EACA is simultaneously infused, adrenal hemorrhages result.

Margaretten et al. G27,941/64: An "SSP-G" with renal glomerular thrombosis can be produced in rats by slow i.v. infusion of thrombin. However, in nonpregnant, unlike in pregnant rats, these thrombi rapidly disappear as a consequence of fibrinolysis.

Solum & Stormorken F56,817/65: In experiments on washed human blood platelets, it was found that thrombin and collagen, unlike ADP and epinephrine, require externally added fibrinogen for the induction of platelet aggregation. The participation of these phenomena in the production of thromboses is discussed.

Beller & Mitchell G27,060/65: An "SSP-G" is produced in rabbits by the simultaneous i.v. infusion of thrombin and either EACA or other protease inhibitors (e.g., Trasylol, soya bean trypsin inhibitor, lima bean trypsin inhibitor and ovomucoid). The response disappears after the injection of streptokinase, suggesting that the intravascular deposits are fibrin which can undergo lysis.

Margaretten et al. G26,896/65: Hemorrhagic thrombosis of the adrenals, often combined with renal cortical necrosis can regularly be obtained in rats by combined treatment with ACTH, EACA and thrombin. It is assumed that thrombin induces a generalized predisposition for thrombosis, while ACTH is responsible for the adrenal localization and EACA prevents fibrinolysis. Treatment with thrombin and EACA or thrombin and ACTH have a similar but less constant effect.

Heparin. Heparin pretreatment prevents the SSP-L, the SSP-G and various other THPs, including those produced by single injections of bacterial endotoxin.

On the other hand, the THP induced by epinephrine i.c. + endotoxin i.v., or by mixtures of epinephrine and endotoxin i.c., is allegedly not prevented by heparin, nor does this anticoagulant significantly affect the direct toxic effects of bacterial endotoxins.

Doses of epinephrine, norepinephrine, phenylephrine, ephedrine, isopropyl-arterenol or *E. coli* endotoxin i.c., which are in themselves well tolerated, produce topical necrosis (without hemorrhage) in rabbits exposed to "rotational shock" in the Noble-Collip drum. These changes cannot be prevented by heparin.

Such observations suggested some fundamental difference between the THPs

elicited by catecholamines and those produced by other means, particularly microbial products. However, the bilateral renal cortical necrosis produced by a single i.v. injection of staphylococcal endotoxin likewise fails to be prevented by heparin. Furthermore, in rabbits made tolerant to epinephrine by repeated pretreatment with this catecholamine, heparin prevents the SSP-L (normally elicited by two injections of *E. coli* endotoxin) only if it is given at the time of the preparatory injection, but not when administered concurrently with the provocative injection. This is the reverse of what occurs in rabbits not made resistant to epinephrine.

Vincke B24,876/47: According to the method of Dietrich (E55,223/41), jugular vein thrombosis is produced in rabbits by partially constricting the vessel and then giving *E. coli* bacilli into the ipsilateral ear vein, followed 24-48 hrs. later by the i.v. administration of *E. coli* filtrate into the contralateral ear vein. This thrombosis is inhibited by pretreatment with heparin or neodiumium nicotinate.

Lawrence et al. G26,851/52: Intravenous injection of suspensions of the transplantable V₂ carcinoma of the rabbit causes thrombosis in the right side of the heart and in the pulmonary vessels owing to the thromboplastic property of the neoplasm. Heparin, dicoumarol, and soybean trypsin inhibitor protect against this effect, while Benadryl is ineffective.

Berthrong & Cluff D83,712/53: Observations on tissue culture fragments from the buffy coats of centrifuged blood, using the glass slide method, revealed that *S. marcescens* and *Sh. flexneri* endotoxins i.v. inhibit the migration of leukocytes. The response is obtained both when an SSP-L is produced by two injections and when a single dose is given i.v. Inhibition of the SSP-L by heparin fails to alter this response.

Cluff & Berthrong D79,023/53: The SSP-L normally produced by *S. marcescens* or meningococcus endotoxin in the rabbit can be inhibited by heparin.

Good & Thomas B86,937/53: Heparin given at the time of the provocative injection prevents both the SSP-L and the SSP-G produced by two injections of meningococcal endotoxin in the rabbit. After i.c. injection of meningococcal toxin, the subsequent i.v. administration of glycogen, rabbit liver suspension, or human serum suffices to elicit an SSP-L. In all these instances, heparin administered at the time of the provocative injection prevents the SSP-L. The bilateral renal cortical necrosis normally produced by a single i.v. injection of meningococcal toxin in Thorotrast or cortisone-pretreated rabbits is also prevented by heparin given before the provocative injection. However, the prostration and death caused by large doses of meningococcal

toxin i.v. in rabbits, were not influenced by heparin.

Crowell et al. G24,212/55: When brief periods of circulatory arrest are induced in dogs by fibrillating and defibrillating the heart electrically, a syndrome of intravascular clotting develops which can be prevented by heparinization.

Rall et al. C2,777/55: Pretreatment with heparin or Tromexan (ethyldicoumarol acetate) prevents the SSP-L normally produced by two injections of *S. marcescens* endotoxin.

Thomas et al. E52,778/55: Liquid, given i.v. 2 hrs. before an i.v. injection of bacterial endotoxins (*meningococcus*, *S. marcescens*, *Shigella paradyseteriae*), produces an "SSP-G" with disappearance of blood fibrinogen in the rabbit. The response (attributed to intravascular precipitation of fibrinogen) is prevented by heparin but not by nitrogen mustard or cortisone.

Thomas et al. G21,281/55: In rabbits prepared by a single i.v. injection of various Gram-negative bacterial endotoxins, subsequent i.v. injection of several acidic polymers (Liquid, dextran sulfate or sodium polyvinyl alcohol sulfonate) elicits an "SSP-G." Heparin protects against this response.

Gronvall & Brunson C50,109/56: The "SSP-G" produced in the rat by the i.p. administration of bacterial toxins + Liquid is prevented by heparin, although the lethal effect of the treatment is not abolished.

Rall & Gaskin C13,122/56: In rabbits given *S. marcescens* endotoxin i.c., the subsequent injection of epinephrine or norepinephrine into the prepared skin sites produces a local hemorrhagic necrosis. This response is prevented by SY 28, but atropine and heparin (both of which inhibit the classic SSP-L) are ineffective. "These data support the hypothesis that sympathetic nerve-mediated vasoconstriction is an important factor in the local Schwartzman reaction."

Thomas & Zweifach C13,964/56; Thomas C27,073/56; C15,187/56: Epinephrine i.c. produces extensive skin hemorrhages in rabbits

when given one hour after *E. coli*, *E. typhosa*, or *S. marcescens* endotoxin i.v., presumably because the hormone elicits an unusually prolonged local ischemia. This response is prevented by chlorpromazine or cortisone, but not affected by heparin, or nitrogen mustard.

Eichbaum G27,048/57: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit can be prevented by dicoumarol or heparin. However, since, in the SSP-L, hemorrhage occurs before thrombosis, the effect of the anticoagulants cannot be ascribed to the prevention of blood clotting. It is presumably due to some of their other pharmacologic properties such as antiemetic activity or inhibition of platelet agglutination.

Rall & Kelly C36,395/57: The "SSP-L" normally produced by *S. marcescens* endotoxin i.c., followed 24 hrs. later by the injection of epinephrine into the prepared skin sites, is not prevented (and is, indeed, perhaps aggravated) by heparin given i.v. just before or a few hrs. after epinephrine.

Thomas D1,020/57: The production of an "SSP-G" (with the characteristic fall in blood fibrinogen) by combined treatment with bacterial endotoxins and acidic polymers (e.g., Liquoid) in the rabbit can be prevented by heparin.

Gatling C58,378/58: If epinephrine or norepinephrine are injected i.c. into hypersensitized rabbits immediately after a challenge dose of horse serum i.v., a THP-L results at the site of catecholamine administration. This response is prevented by heparin but not modified by chlorpromazine.

Hardaway & McKay G26,419/59: The shock produced by i.v. injection of amniotic fluid in dogs is completely (that elicited by incompatible blood only partially) prevented by heparinization. Presumably, heparin acts by preventing intravascular clotting.

Hardaway & McKay G33,251/59: A type of pseudomembranous enterocolitis with multiple thromboses in the microcirculation of the bowel can be produced in dogs by transfusion of incompatible blood. Heparin prevents this phenomenon.

Schrader et al. G22,067/59: Following abdominal x-irradiation, there is a gradual rise in the blood fibrinogen of the rabbit. When *E. coli* endotoxin is given 24 hrs. following x ray, there is an immediate sharp rise, followed by a precipitous drop within 4-8 hrs. These changes correlate well with the fibrinoid lesions of the resulting "SSP-G." The pattern is very similar to that seen after two injections

of endotoxin. Heparin i.v. following abdominal x ray in conjunction with the endotoxin administration prevents the fibrinoid lesion but, when heparin was given only at the time of radiation, no inhibition was observed. "No heparin-precipitable fibrinogen (HPF) was demonstrated following abdominal x ray, but the prevention of development of the lesions by the administration of heparin at the time of administration of endotoxin suggest that similar mechanisms operate in the production of x-ray endotoxin lesions and in those of the generalized Shwartzman phenomenon."

Sheehan & Davis G21,362/59: Compression of the renal pedicle for 3 hrs. causes ischemic death of the parenchyma and blood vessels of the rabbit kidney. If at this stage, the vascular occlusion is released, the dead arteries become greatly dilated and numerous hemorrhages occur in their media, but circulation is not re-established. The glomerular capillaries are first dilated with red corpuscles which are then pushed into the intertubular capillaries by a finely vacuolated "microfoam." After about 2 hrs., fibrin is laid down in the microfoam along the endothelial surfaces, and eventually it may completely occlude the capillaries. Thrombi may also occur in interlobular arteries. Heparinization prevents fibrin deposition in arteries, but not the formation of glomerular thrombi.

Evers & Brunson C97,146/60: In themselves well tolerated i.c. doses of epinephrine, norepinephrine or *E. coli* endotoxin produce topical necrosis without hemorrhage in rabbits exposed to the "rotational shock" in the Noble-Collip drum. The response was more constant when the rotation preceded, than when it followed, the i.c. injections. Similar changes were obtained by phenylephrine, ephedrine and isopropylarterenol administered during rotational shock. These lesions could not be prevented by nitrogen mustard or heparin. They were prevented or attenuated, however, by pretreatment with mixtures of promethazine and promazine.

Gans & Kravit D16,680/60: In dogs given a single i.v. injection of *E. coli* endotoxin, death occurs from extensive hemorrhages in the lungs, gastro-intestinal tract and kidneys, associated with a drop in blood fibrinogen. All these changes are prevented by heparin. However, "the dog does not develop the complex which is so characteristic for the Shwartzman reaction."

Gatling C83,022/60: The topical hemorrhage and fibrinoid necrosis of arteries, produced by i.c. injection of epinephrine or norepinephrine in hypersensitive rabbits, is inhibited by

heparin and cortisone but not by nitrogen mustard, chlorpromazine or sodium salicylate.

Rieder & Thomas C80,868/60: As little as 5 µg of *E. coli* lipopolysaccharide causes abortion in the mouse. This response is not blocked by heparin.

Hardaway et al. D18,362/61: Intra-aortic injection of incompatible blood, thrombin, or *E. coli* endotoxin, produces hemorrhagic necrosis with intravascular fibrin-clot formation in the dog. The changes resemble pseudo-membranous enterocolitis in man and can be largely prevented by heparin pretreatment.

Hardaway et al. E96,214/61: A single intra-aortic infusion of *E. coli* endotoxin produced an SSP-G-like syndrome in the dog with a decrease in blood coagulability which was ascribed to the consumption of blood-clotting factors, mainly fibrinogen. Heparin pretreatment largely prevents the morphologic changes.

Koutský et al. E52,939/61: The THP normally produced by i.v. injection of amniotic fluid in the mouse can be prevented by pretreatment with heparin.

Hardaway et al. G26,292/62: Irreversible hemorrhagic shock with intravascular coagulation is produced in dogs by bleeding them through an ion-exchange resin for decalcification without the administration of any anti-coagulant. The gastrointestinal, renal, hepatic, and other thrombohemorrhagic lesions produced in this manner are essentially similar to those elicited by intra-aortic injection of thrombin or *E. coli* endotoxin. The body responds to this form of hemorrhage by heparin-, and (in some cases) fibrinolysin-production, but the adaptive changes are too slow to offer significant protection. Exogenous heparin, however, prevents these changes.

Lee G26,187/63: After RES blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the appearance of "heparin precipitable fibrinogen" in the circulation.

Nakai & Margaretten E45,655/63: The bilateral renal cortical necrosis produced by a single i.v. injection of staphylococcal endotoxin cannot be prevented either by heparin or by nitrogen-mustard pretreatment. Thus, this lesion differs from the typical SSP-G in its responsiveness.

Bouissou et al. D19,954/64: A single i.v. injection of *E. coli* endotoxin suffices to produce an "SSP-G" with glomerular capillary throm-

boses and renal cortical necrosis in rabbits pretreated with cortisone i.m. Heparin (route of administration not stated) prevents this response.

Hall et al. G9,421/64: In rabbits made tolerant to epinephrine, the administration of heparin at the time of the provocative injection fails to prevent the SSP-L normally elicited by two injections of *E. coli* endotoxin. However, the SSP-L was prevented when heparin was given at the time of the preparatory injection of endotoxin. This is the reverse of what had previously been found in rabbits not made resistant to epinephrine.

Levin & Cluff G25,181/65: In rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, this response differs from the SSP in that it is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment.

McKay E4,788/65: The hypotension and shock produced in dogs by bacterial endotoxins can be lessened by heparinization. "Since these differences are minor and occur prior to the appearance of fibrin thrombi in the small vessels, it appears that endotoxin exerts its immediate hypotensive action through mechanisms other than disseminated intravascular coagulation."

Niesert & Schneider F32,779/65: Heparin is highly effective in preventing the SSP-G normally produced by two i.v. injections of *S. abortus equi* endotoxin.

Renaud G31,668/65: In rats made hyperlipemic by prolonged maintenance on a special diet, *S. typhosa* or *E. coli* endotoxin i.v. consistently produce thromboses in the large hepatic veins with consequent red infarcts of the liver. Heparin, hirudin or acenocoumarin given just before the endotoxin considerably lowered the incidence of thrombosis and the mortality rate.

Cochrane E5,332/65: A survey of the literature shows many similarities between the SSP and the Arthus phenomenon. "Both reactions develop in the several hours following challenge, both are marked by an influx of polymorphs, and in at least the severe Arthus reactions in which large quantities of immune reactants are employed, leucocyte-platelet thrombi occur in both. However, at least one difference apparently exists, and that is the dependence of the Shwartzman phenomenon on thrombosis, for the reaction is preventable with heparin."

Liquoid (Sodium Polyanetholesulfonate). In rabbits, a single i.v. dose of Liquoid causes multiple hemorrhages in various internal organs, as well as hyaline thrombosis of the renal glomerular capillaries. These changes are even more readily obtained if Liquoid is given shortly before or after endotoxin i.v.

In rabbits pretreated by repeated s.c. injections of bovine γ -globulin, Liquoid i.v. elicits fibrinoid lesions involving the heart, lungs, spleen, liver and kidneys. The changes induced in the coronary arteries resemble polyarteritis nodosa.

Demole & Reinert E57,753/30: A syndrome characterized by multiple hemorrhages, especially in the kidneys, adrenals, thymus, lungs, small intestine, and lymph nodes, can be elicited by a single i.v. injection of Liquoid in the rabbit. In the kidney, the changes are accompanied by signs of "nephritis." The lesions are ascribed to the anticoagulant effect of the compound. [There may be a relationship between these changes and Jaques' "hemorrhagic stress syndrome" or the SSP (H.S.).]

Hausman & Dreyfus C99,073/53: A single i.v. dose of Liquoid causes hyaline thrombosis of the renal glomerular capillaries, as well as similar lesions in the lungs and adrenals of the rabbit. In the kidneys, these thrombi often "lined the walls of the capillaries and formed casts which resembled to some extent the 'wire-loop' lesions seen in disseminated lupus erythematosus."

Brunson et al. C14,440/55: Liquoid i.v., given 12 hrs. after meningococcal endotoxin i.v., produces an "SSP-G" in the rabbit. There is cortical necrosis and thrombosis of the glomerular capillaries by a hyaline, highly birefringent material.

Thomas et al. E52,778/55: Liquoid given i.v. 2 hrs. before an i.v. injection of bacterial endotoxins (meningococcus, *S. marcescens*, *Sh. paradyserteriae*) produces an "SSP-G" with disappearance of blood fibrinogen in the rabbit. The response (attributed to intravascular precipitation of fibrinogen) is prevented by heparin but not by nitrogen mustard or cortisone.

Thomas et al. G21,281/55: In rabbits prepared by a single i.v. injection of various Gram-negative bacterial endotoxins, subsequent i.v. injection of several acidic polymers (Liquoid, dextran sulfate or sodium polyvinyl alcohol sulfonate) elicits an "SSP-G."

Gronvall & Brunson C50,109/56: An "SSP-G" is rarely produced by a single i.p. injection of *E. coli* or meningococcal endotoxin in the rat. It does occur more regularly, however, when these endotoxins are administered conjointly with Liquoid. It is seen even after large amounts of Liquoid alone.

Fehr & Brunson G21,900/57: Rabbits prepared by six daily s.c. injections of bovine

γ -globulin were given *E. coli* endotoxin or Liquoid i.v. 72 hrs. after the last globulin injection. They developed fibrinoid lesions involving the heart, lungs, spleen, liver and kidneys. In the coronary arteries the changes resembled polyarteritis. "The renal lesions observed in the present experiments are similar to those of 'focal' or 'embolic' glomerulonephritis in humans, and in some respects resemble the changes of acute proliferative glomerulonephritis. The focal glomerular accumulation of large amounts of fibrinoid, with obliteration of capillary loops, is similar also to the lesion of diabetic glomerulosclerosis."

Rodriguez-Erdmann et al. G22,083/60; Rodriguez-Erdmann & Lasch G24,133/61: A single i.v. injection of Liquoid suffices to produce an "SSP-G" in the rabbit. This syndrome (like that elicited by two i.v. injections of endotoxin) is associated with a decrease in the activity of the factors prothrombin, V (accelerator globulin), VII and IX/X-complex with severe acute thrombocytopenia. However, the pronounced loss of antihemophilia globulin characteristic of the SSP is not demonstrable. Protamine sulfate largely prevents these changes, including the pathologic lesions. "The similarity between the classical Sanarelli-Shwartzman phenomenon and the coagulopathy induced by Liquoid suggests that, in both cases, an analogous mechanism induces intravascular precipitation of fibrin in various organs."

Berken & Wolman D85,445/62: A typical "SSP-G" can be produced in the rabbit by *E. coli* endotoxin i.v. followed by Liquoid i.v. However, a single large dose of Liquoid i.v. suffices to produce an "SSP-G" with bilateral renal cortical necrosis, possibly due to the precipitation of serum lipoproteins with coprecipitation of other protein fractions.

Vassalli et al. G14,966/63: Electron-microscopic studies show the deposition of fibrin and fibrinoid in the glomerular capillaries of rabbits injected with Liquoid, thromboplastin or thrombin. Particularly pronounced lesions are obtained following simultaneous treatment with EACA + Liquoid i.v. Phagocytosed fibrin was occasionally observed in swollen endothelial and intercapillary cells.

Other Heparinoids. Changes reminiscent of the SSP-G can be produced by the i.v. injection of various heparinoid substances given alone, or even more easily when followed by bacterial endotoxins i.v.

Astrup G23,059/53: The following heparin substitutes were found to agglutinate platelets in vitro: a hyaluronic acid sulfuric acid ester, a xylan sulfuric acid ester (Thrombocid), and an alginic acid sulfuric acid ester (Paritol). In addition, some of these preparations even precipitate fibrin, and the thromboembolic effects, produced by them in vivo, may result from these properties.

Brunson et al. C14,440/55: An "SSP-G" can be elicited in the rabbit by polyvinyl alcohol polysulfonic acid ester (PVAS) or dextran sul-

fate followed by meningococcal endotoxin i.v. Less pronounced changes can be obtained by PVAS or dextran given alone.

Schallock G27,499/55: Brief abstract stating that a thrombotic microangiopathy can be produced by "synthetic heparinoids" (kind not stated) in "animals" (kind not stated).

Niesert & Schneider F32,779/65: SP 54 (a vasoactive sulfated polyanion with heparinoid action), fails to protect the rabbit against the production of an SSP-G by two i.v. injections of *S. abortus equi* endotoxin.

Dicoumarol and Related Substances. Contrary to earlier observations, it has been noted that dicoumarol pretreatment prevents the SSP-L normally produced by two injections of bacterial endotoxins in the rabbit, although the associated thrombocytopenia is not prevented.

Coumadin (Warfarin) prevents not only the SSP-G produced by two injections of bacterial endotoxins in the rabbit, but also the SSP-L induced by various bacterial endotoxins in susceptible strains of mice.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by dicoumarol.

Lawrence et al. G26,851/52: Intravenous injection of suspensions of the transplantable *V₂* carcinoma of the rabbit causes thrombosis in the right side of the heart and in the pulmonary vessels owing to the thromboplastic property of the neoplasm. Heparin, dicoumarol, and soybean trypsin inhibitor protect against this effect, while Benadryl is ineffective.

Rothfeld et al. B99,672/54: Unlike heparin, dicoumarol does not prevent the SSP-L produced by two injections of meningococcal endotoxin in the rabbit. It would seem, therefore, that the SSP-L-inhibiting effect of heparin, if it is due to interference with the clotting mechanism, is not due to any property which it has in common with dicoumarol.

Rall et al. C2,777/55: Pretreatment with heparin or Tromexan (ethyldicoumarol acetate) prevents the SSP-L normally produced by two injections of *S. marcescens* endotoxin.

Spanoudis et al. G21,524/55: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit can be inhibited by pretreatment with dicoumarol. "Temporary thrombocytopenia occurs in dicoumarol-inhibited Shwartzman-negative rabbits, in Shwartzman-positive animals, and also

after a single intravenous injection of *Serratia marcescens* toxin, without previous dermal preparation. . . . This indicates that the thrombocytopenia, following the toxin injections, depends on the direct action of the toxin without any relation at all to the positivity or negativity of the Schwartzman reaction."

Eichbaum G27,048/57: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit can be prevented by dicoumarol or heparin. However, since in the SSP-L hemorrhage occurs before thrombosis, the effect of the anticoagulants cannot be ascribed to the prevention of blood clotting. It is presumably due to some of their other pharmacologic properties such as antienzymatic activity or inhibition of platelet agglutination.

Kelly et al. D3,776/57: The SSP-L produced by various bacterial endotoxins in susceptible strains of mice can be blocked by the anticoagulant drug coumadin (Warfarin).

Shapiro & McKay D15,422/58: In rabbits rendered hypoprothrombinemic by i.v. injection of Warfarin, two i.v. injections of Shear's polysaccharide no longer produce the usual SSP-C. "It is concluded that the prothrombin complex is necessary for the production of the generalized Shwartzman reaction by bacterial endotoxins and that this phenomenon is essentially a process of disseminated intravascular coagulation."

Stamler D4,281/61: The eclampsia-like THP-G elicited by progesterone overdosage in late-pregnant rats is not inhibited by dicoumarol.

Stacher E33,582/63: Review of the literature and personal observations indicate that various dicoumarol and indandione derivatives can cause widespread cutaneous necroses which are presumably related to the SSP.

Lieb F2,046/64: In patients treated with coumarol, there sometimes develop hemorrhagic necroses with microthrombi in the skin and subcutaneous tissue. These "coumarol necroses" are interpreted as manifestations of the "SSP."

Colombo F41,024/65: In patients treated with coumarin or indandione derivatives, cutaneous infarcts, often with necrosis of the subcutaneous tissue and musculature, are occasionally seen. No such lesions occur after

treatment with heparin or heparinoids. [There is no indication of any relationship between these infarcts and the THP (H.S.).]

Nalbandian et al. F39,666/65: In patients treated with coumarin congeners for various reasons, a syndrome of cutaneous petechiae, ecchymoses and necroses may appear. Histologically, thrombi are found in the capillaries and venules and the lesions are considered to be hemorrhagic infarcts.

Renaud G31,668/65: In rats made hyperlipemic by prolonged maintenance on a special diet, *S. typhosa* or *E. coli* endotoxin i.v. consistently produce thromboses in the large hepatic veins with consequent red infarcts of the liver. Heparin, hirudin or acenocoumarin given just before the endotoxin considerably lowered the incidence of thrombosis and the mortality rate.

EACA (Epsilon-aminocaproic Acid). EACA (an antifibrinolytic agent) fails to prevent the SSP-G produced by two injections of bacterial endotoxin in the rabbit. Indeed, even a single i.v. injection of *E. coli* endotoxin which rarely produces a THP in rabbits does so quite readily if the animals are simultaneously given EACA i.v. On the other hand, this compound protects the dog against the lethal effects of single i.v. injections of *E. coli* endotoxin.

Lasch et al. E64,434/61: When fibrinolysis is inhibited by pretreatment with EACA, two i.v. injections of bacterial endotoxin (kind not stated) still elicit a typical SSP-G. At the same time, there is a decrease in the prothrombin factor VII and factor V and platelet content of the blood both in the control and in the experimental animals. On the other hand, the fibrinogen content of the blood is higher in the animals pretreated with EACA. Apparently, fibrinolysis plays no role in the causation of the drop in prothrombin factors VII and V and of blood platelets.

Naeye G26,518/61: In one patient, a prostatic carcinoma was releasing tissue thromboplastin, thus inducing a hemorrhagic diathesis due to consumption of blood-clotting factors. However, the blood proteolytic activity removed the unwanted fibrin and thereby prevented thrombosis. When EACA was given, the plasmin activity was inhibited and removal of this defense mechanism led to diffuse thromboses, especially in the digits of both feet.

Ramos et al. G26,829/61: The SSP-L normally produced in the mouse by i.c. preparation, and 24 hrs. later i.v. provocation with *S. typhosa* endotoxin, is prevented if EACA is given i.p. before the provocative injection.

Spink & Vick E42,906/61: Pretreatment of

dogs with EACA protected many of them against lethal doses of *E. coli* endotoxin.

Zweifach et al. E95,298/61: A THP is elicited in the rabbit by *E. coli* endotoxin i.c. combined with epinephrine given either i.v. or topically in combination with the endotoxin, both agents being administered at the same time. Both these forms of THP were prevented by such classical inhibitors of proteolytic activity as EACA, tosylarginine methyl ester (TAME), and soybean trypsin inhibitor (SBTI). No effect was observed on the classical SSP-L induced by two injections of *E. coli* endotoxin.

Lee E41,395/62: A single i.v. injection of *E. coli* endotoxin often produces an "SSP-G" in rabbits simultaneously given EACA i.v., presumably owing to the activation of fibrinolysis by the latter compound.

Vassalli et al. G14,966/63: Electron-microscopic studies show the deposition of fibrin and fibrinoid in the glomerular capillaries of rabbits injected with Liquoid, thromboplastin or thrombin. Particularly pronounced lesions are obtained following simultaneous treatment with EACA + Liquoid i.v. Phagocytosed fibrin was occasionally observed in swollen endothelial and intercapillary cells.

Margareten et al. G26,896/65: Hemorrhagic thrombosis of the adrenals, often combined

with renal cortical necrosis, can regularly be obtained in rats by combined treatment with ACTH, EACA and thrombin. It is assumed that thrombin induces a generalized predisposition for thrombosis, while ACTH is responsible for the adrenal localization and EACA prevents fibrinolysis. Treatment with thrombin and EACA or thrombin and ACTH have a similar but less constant effect.

Galton F53,009/65: No "SSP-G" could be produced in a hamster by combined treatment with EACA and 5-HT.

Antiplatelet Serum. Antiplatelet serum does not protect the rabbit against the production of an SSP-L by two injections of bacterial endotoxins, nor does it produce a typical THP.

Bedson G21,641/22: In guinea pigs given antiplatelet serum i.v., the resulting drop in blood platelets is associated with multiple hemorrhages in the skin, muscles, mesentery, intestine, epididymis, lung, and peritoneal cavity. [No mention is made of thromboses (H.S.).]

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by antiplatelet serum.

Platelet factors. *Rodriguez-Erdmann G34,859/65:* In rabbits pretreated with Thorotrast, i.v. injection of phospholipids, containing platelet factor 3 or Inosithin (soya bean phospholipid) there developed an SSP-G associated with the typical alterations of the clotting mechanism.

Hirudin. *Loeb et al. D85,463/10:* In rabbits, dog serum i.v. produces hemolysis with erythrocyte agglutination and fibrin thrombi, especially in the lungs and the heart. In the lungs, this is accompanied by periarterial hemorrhages. Hirudin i.v. prevents this response. Cattle serum produces only erythrocyte aggregation and its effect is not prevented by hirudin.

Amantea 43,781/33: In rabbits deprived of their complement by hirudin or arsenobenzol, an SSP-L can still be produced by bacterial endotoxins and, hence, the response differs from anaphylaxis.

Renaud G31,668/65: In rats made hyperlipemic by prolonged maintenance on a special diet, *S. typhosa* or *E. coli* endotoxin i.v. consistently produce thromboses in the large hepatic veins with consequent red infarcts of

Haustein & Markwardt G33,841/65: The THP-L elicited by two injections of *E. coli* endotoxin in the rabbit can be prevented by the thrombin inhibitor hirudin, but not by p-aminomethylbenzoic acid (PAMBA) nor by the trypsin, kallikrein and plasmin inhibitor Contraykal.

Niesert & Schneider F32,779/65: EACA given i.v. simultaneously with the second (provocative) i.v. injection of *S. abortus* endotoxin, fails to protect the rabbit against the production of an SSP-G.

the liver. Heparin, hirudin or acenocoumarin given just before the endotoxin considerably lowered the incidence of thrombosis and the mortality rate.

Haustein & Markwardt G33,841/65: The THP-L elicited by two injections of *E. coli* endotoxin in the rabbit can be prevented by hirudin.

Blood clots, fibrin. *Muirhead & Montgomery E83,590/51:* Human amniotic fluid and autogenous blood clots injected i.v. in rabbits, produce widespread acute necrotizing pulmonary arteritis. Following multiple injections, subacute and chronic lesions (characterized by fibrosis and hyalinization of the arterial wall) result in the picture of endarteritis obliterans and pulmonary vascular sclerosis.

Rodriguez-Erdmann G30,256/65: Following blockade of the RES by Thorotrast, the i.v. injection of homogenized fibrin produces renal cortical necrosis with thrombosis of the glomerular capillaries in the rabbit.

Protamin. *Koutský et al. E52,939/61:* The THP normally produced by amniotic fluid i.v. in the mouse can be prevented by protamin pretreatment.

Rodriguez-Erdmann & Lasch G24,133/61: A single i.v. injection of Liquoid produces an SSP-G-like generalized hemorrhagic diathesis in the rabbit. "The haemorrhages are due to the loss of activity of factor V, prothrombin factor IX, fibrinogen and PTA in the sense of a 'coagulopathy by consumption.' . . ." "In addition, there is thrombocytopenia and a diminution of platelet factors I and III. Protamin sulfate, given simultaneously with Liquoid, prevents these changes."

HORMONES AND HORMONE-LIKE SUBSTANCES

Among the classical hormones, the catecholamines, ACTH and the corticoids are most effective in modifying susceptibility to THPs. However, in this respect,

several hormone-like substances (histamine, serotonin, kallikrein) and a variety of tissue extracts also play important roles.

Catecholamines. It has long been known that, following inoculation with living or killed microorganisms, a rabbit may respond with hemorrhagic necrosis to normally well-tolerated doses of epinephrine i.c. A similar hyperreactiveness to the topical actions of epinephrine has also been seen in patients with diverse allergic conditions; this was ascribed to "adrenaline hypersensitivity." However, depending upon dosage and timing, the THP-activity of catecholamines is subject to great variations.

For example, if an SSP-L is produced in rabbits and epinephrine is injected into the prepared skin site, one to three hours after provocation, the local response is inhibited, although small petechiae may develop in a corona surrounding the site of preparation. Histamine exerts the same protective effect. On the other hand, in BCG-vaccinated rabbits, following i.c. preparation with endotoxins, topical application of epinephrine to the prepared skin site produces hemorrhagic necrosis.

In rabbits prepared by endotoxin i.c., neither epinephrine nor norepinephrine given i.v. 24 hrs. later produces the THP-L, but if the catecholamines are injected directly into the prepared skin sites, a topical hemorrhagic necrosis results. Epinephrine also produces a topical THP when injected i.c. together with the endotoxins without any systemic provocation.

These seemingly contradictory results obtained by early investigators are probably explained by the fact that the catecholamines are most effective when given almost simultaneously with the endotoxins. Extensive dermal hemorrhagic necrosis is produced in rabbits, for example, by the i.c. injection of as little as 5 µg of epinephrine or norepinephrine followed within 4 hours by 1 µg of various endotoxins i.v. This reaction is highly specific, since serum, ovalbumen, glycogen or Fe-OS could not substitute for the i.v. injection of endotoxins, whereas ephedrine, vasopressin, histamine, 5-HT and ferritin were unable to replace the i.c. injection of epinephrine or norepinephrine. Certain polysaccharides of plant or animal origin likewise failed to substitute for endotoxins when given i.v. shortly before epinephrine i.c.

In rabbits exposed to "rotational shock" in the Noble-Collip drum, the concurrent i.c. administration of endotoxin, phenylephrine, ephedrine or isopropylarterenol produces topical necrosis without hemorrhage.

The induction of epinephrine tolerance by graded daily i.v. injections allegedly inhibits the SSP-G, but not the SSP-L.

Marcus G23,205/21: First demonstration of the fact that, following infection with streptococci, s.c. injection of epinephrine into the rabbit ear produces local hemorrhagic necrosis. In control rabbits, epinephrine had no such effect, except in one animal which proved to have a spontaneous infection. Since gangrene frequently develops in patients with latent Raynaud's disease under the influence of infection, it is assumed that here adrenergic mechanisms may also play a role.

Schmidt-Weyland G24,461/32: Following infection with live streptococci or tubercle bacilli, as well as after inoculation with killed E. coli, rabbits become hypersensitive to epinephrine injected s.c. into the ear. Unlike control rabbits, they develop hemorrhagic necrosis with leukocytic and hyaline thrombi in the capillaries and veins (less frequently in the arteries). These changes are compared to those of thromboangiitis obliterans and it is suspected that some adrenergic mechanism

may play a role not only in this disease, but also in the thromboembolic phenomena frequently observed in the course of severe infections (e.g., cholera, dysentery).

Kielanowski & Selzer G23,077/34; D71,895/35: Rabbit skin prepared by *E. coli* endotoxin i.c. responds like normal skin, with vasoconstriction, to the topical application of epinephrine. In the event of subsequent i.v. provocation, hemorrhages occur around the zone of epinephrine anemia, but not within it. If epinephrine is injected into a skin site in which, as a result of provocation, petechiae are beginning to form, the region becomes anemic and new petechiae do not develop. Apparently, preparation does not involve a paralysis of the microcirculatory system.

Cohn A31,000/39: In four asthmatic patients, "slow epinephrine" (epinephrine crystals suspended in peanut oil) s.c. produced vesicular urticaria, cyanosis, swelling and edema of the forearm, nausea, vomiting and chills.

Cohen & Waterstone G18,745/40: Local inflammation and necrosis frequently occur at sites of epinephrine or norepinephrine treatment, especially in asthmatic patients. In one such case, when a small amount of epinephrine was injected i.v., activation of previous s.c. epinephrine injection site occurred. This is interpreted as a "Shwartzman phenomenon."

Franke D45,064/44: Toxic doses of *S. marcescens* lipopolysaccharide produced hemorrhagic necrosis in the intestine, lymphatic tissue and liver of the dog. "Adrenalin administered after polysaccharide injection augmented the intestinal congestion and hemorrhage and the subendocardial hemorrhages."

Waters & DeSoto-Nagy B64,578/49-50: Essentially identical arteriolar necroses with hemorrhages are produced in dogs by i.v. injections of large doses of epinephrine, N-amylamine, citrated compatible canine blood or epinephrine + large amounts of canine blood. Similar lesions are obtained by treatment of nephrectomized dogs with pressor renal extracts. The epinephrine-induced lesions can be prevented by dibenamine.

Herxheimer B57,564/51: In a man with asthma, injections of synthetic epinephrine caused an urticarial rash all over the body, while the asthma subsided. Norepinephrine produced no urticaria.

Mitchell B87,135/52: Local inflammation and necrosis occasionally occur at sites where epinephrine of animal origin is injected s.c., particularly in asthmatic patients. "The use of the same site for inoculation over a period of time was found to be necessary for development of the phenomenon. Absence of mani-

festations of sensitivity to artificial epinephrine and its derivatives was confirmed." . . . "It is suggested that the phenomenon is a type of local fixed tissue sensitivity."

Stetson G22,085/55: In BCG-vaccinated rabbits, following i.c. preparation with either meningococcal endotoxin or tuberculin, the topical application of epinephrine to the prepared skin site resulted in hemorrhagic necrosis.

Rall & Gaskin C13,122/56: In rabbits prepared by *S. marcescens* endotoxin i.c., neither epinephrine nor norepinephrine given i.v. 24 hrs. later produces an "SSP-L," but if these catecholamines are injected directly into the prepared skin sites, a local hemorrhagic necrosis results. Vasopressin (Pitressin) is also active locally, while 5-HT is not.

Thomas & Zweifach C13,964/56: Epinephrine i.c. produces extensive skin hemorrhages in rabbits when given one hour after *E. coli*, *E. typhosa*, or *S. marcescens* endotoxin i.v., presumably because the hormone causes an unusually prolonged local ischemia. When epinephrine is mixed with various bacterial endotoxins and injected i.c., "hemorrhagic lesions resembling local Shwartzman reactions occur within a few hours."

Thomas C27,073/56; C15,187/56; D1,020/57: Extensive dermal hemorrhagic necrosis is produced in rabbits by the i.c. injection of as little as 5 µg of epinephrine or norepinephrine, followed within 4 hrs. by 1 µg of various endotoxins i.v. The response is apparently specific for endotoxins, since human or horse serum, ovalbumen, rabbit liver glycogen, and Fe-OS i.v. did not provoke hemorrhagic reactions at the sites of dermal epinephrine injections. The action of epinephrine and norepinephrine is also specific since, in rabbits given i.v. injections of *E. coli* endotoxin, i.c. administration of ephedrine, vasopressin, histamine, 5-HT and ferritin produce no hemorrhages at the dermal injection sites. On the other hand, epinephrine produces hemorrhagic skin necrosis even when injected i.c. together with the bacterial endotoxins without any systemic provocation.

Landy & Shear G21,289/57: A great variety of polysaccharides isolated from various animal and plant sources can substitute for bacterial endotoxins when given either as the preparatory or as the provocative injection in conjunction with *S. typhosa* or *S. marcescens* endotoxin in rabbits. These animal tissue polysaccharides, unlike those of plants, are also capable of provoking dermal hemorrhagic necrosis at the site of epinephrine injection when they are administered 4 hrs. prior to the hormone.

Rall & Kelly C36,395/57: In rabbits prepared by an i.c. injection of *S. marcescens* endotoxin, the i.v. injection of epinephrine or norepinephrine 24 hrs. later results in no "SSP-L." On the other hand, if these catecholamines are injected directly into the prepared skin site 24 hrs. after the endotoxin, a high incidence of local hemorrhagic necroses ensues.

Gatling C58,378/58: If epinephrine or norepinephrine are injected i.c. in hypersensitized rabbits immediately after a challenge dose of antigen (horse serum) i.v., a THP-L results at the site of catecholamine administration. This response is prevented by heparin but not modified by chlorpromazine. Injection of epinephrine or norepinephrine directly into the challenged area of an Arthus reaction causes the latter to assume a hemorrhagic aspect.

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, and rises in hematocrit and plasma hemoglobin. These changes "apparently result from a sympathomimetic action of endotoxin on the bowel." The syndrome is inhibited by adrenergic blocking agents (chlorpromazine, dibenzyline), artificial hypothermia and, to a lesser extent, by cortisol. Previous sterilization of the intestinal contents by sulfasuxidine and neomycin has no effect, while vasoconstrictor drugs (norepinephrine, metaraminol) "actually potentiate the shock caused by endotoxin by increasing intestinal ischemia."

Mezzano & Peluffo D9,326/60: In rabbits given *S. typhosa* filtrate i.c. and 1-2 hrs. later norepinephrine i.v., there develops a central ischemic necrosis surrounded by a halo of hemorrhagic necrosis at the site of the filtrate injection. Intravascular blood clots are never observed; hence, the response differs essentially from the SSP-L.

Evers & Brunson C97,146/60: In themselves well tolerated, doses of epinephrine, norepinephrine or *E. coli* endotoxin i.c. produce topical necrosis without hemorrhage, in rabbits exposed to "rotational shock" in the Noble-Collip drum. The response was more constant when the rotation preceded the i.c. injections than when it followed. Similar changes were obtained by phenylephrine, ephedrine and isopropylarterenol, administered during rotational shock. These lesions could not be prevented by nitrogen mustard or heparin. They were prevented or attenuated, however, by pretreatment with mixtures of promethazine and promazine.

Gatling C83,022/60: Epinephrine or norepinephrine, given i.c. to hypersensitive rabbits

in the presence of circulating specific antigen, produce topical hemorrhage with fibrinoid necrosis of arteries. Ephedrine, histamine and atropine i.c. are ineffective under the same conditions.

Gilbert C88,049/60: Detailed review of the literature suggesting that epinephrine and norepinephrine are involved in the mediation of endotoxin-induced vascular disturbances. 1. Many observations show morphologic similarities in the lesions induced by catecholamines and by endotoxins. 2. The catecholamine content of the blood increases sharply following endotoxin administration, while the epinephrine content of the adrenals drops. 3. Following endotoxin i.v., epinephrine produces intense topical vascular disturbances with hemorrhages and necrosis *in vivo* and *in vitro*. 4. Increased sympathoadrenal activity may act adversely in different types of shock. 5. Large doses of epinephrine can produce bilateral cortical necrosis in themselves. 6. Protection against various types of shock and THPs has been obtained by dibenamine and ganglionic blocking agents, which would be expected to reduce vascular tone.

Neter et al. C85,418/60: A purified and polysaccharide-free "lipoid A component of *E. coli* 0111:B4 endotoxin" i.v., in amounts as small as 2 µg per kg so alters the reactivity of the rabbit that epinephrine (100 µg) i.c. causes topical hemorrhagic necrosis. This reaction is inhibited by dibenzyline (phenoxybenzamine hydrochloride).

Neter et al. C97,516/60: Following i.v. injection of living *S. aureus* organisms or their endotoxins, epinephrine i.c. produces hemorrhagic lesions in the abdomen or back, but not in the ear of the rabbit. The changes can be prevented by dibenzyline.

Zweifach et al. E95,298/61: A THP is elicited in the rabbit by *E. coli* endotoxin i.c. combined with epinephrine given either i.v. or topically in combination with the endotoxin, both agents being administered at the same time. Both these forms of THP were prevented by such classical inhibitors of proteolytic activity as EACA, tosylarginine methyl ester (TAME), and soybean trypsin inhibitor (SBTI). No effect was observed on the classical SSP-L induced by two injections of *E. coli* endotoxin.

Antopol & Chryssanthou D56,730/63: The Thomas reaction can be elicited in the rabbit by injecting 100 µg-1mg of epinephrine i.c. at different sites and concurrently 250 µg of *Proteus vulgaris* lipopolysaccharide i.v.

Douglas et al. G33,267/63: The serum of patients with septic abortion given i.v. sensitizes

the rabbit to the production of a THP-L by epinephrine in the same manner as preparation by *S. enteritidis* endotoxin.

Gustafson & Cronberg D61,874/63: *E. coli* endotoxin i.v. followed by the injection of epinephrine into the cheek pouch of the hamster produced local necrosis similar to that of the SSP-L. The local mast-cell population did not appear to be much more damaged under these conditions than when epinephrine was injected in otherwise untreated animals.

Patterson et al. D58,647/63: In rabbits, injection of *E. coli* toxin into the rectum followed by an i.v. injection of the same toxin results in an SSP-L in the treated intestinal region. This effect is aggravated when epinephrine or norepinephrine is mixed with the *E. coli* toxin injected into the rectum. The lesions could not be long maintained by repeating the reacting dose or the preparatory dose.

Shimanoto & Ishioka D57,197/63: In preparations of the rabbit aorta perfused in vitro, addition of small doses of epinephrine to the perfusion fluid causes a release of thromboplastin activity from the vessel wall. Norepinephrine and large doses of epinephrine are ineffective. The release of thromboplastin activity by epinephrine can be blocked by a MAO inhibitor such as nialamide.

Hall et al. G9,421/64: In the rabbit, the induction of epinephrine tolerance by graded daily i.v. injections had no inhibitory effect on the SSP-L but it did inhibit the SSP-G induced by two successive doses of *E. coli* endotoxin. Inhibition of the SSP-G was dose-dependent and related to failure of development of a heparin-precipitable fraction in the plasma.

Kováts et al. D9,550/64: An SSP-L was produced by two injections of typhoid endotoxin. Dibenamine applied at the site of i.c. preparation simultaneously with the i.v. dose of endotoxin diminished the skin hemorrhage, but epinephrine given in the same manner did not aggravate it; indeed, it delayed its appearance.

ACTH, Adrenalectomy and Corticoids. The SSP-L normally produced by two injections of meningococcal endotoxin in rabbits can be inhibited by cortisone or ACTH given a few hours before the provocative injection. These hormones are ineffective when administered prior to the preparatory injection and their effect could not be duplicated under any conditions by desoxycorticosterone, oxytocin or vasopressin. After a single injection of endotoxin i.c., ACTH can provoke petechial hemorrhages at the prepared skin sites, although these differ essentially from the SSP-L.

Cortisone fails to influence the THP produced by a single i.v. injection of

Atropine failed to influence the SSP-L. In all these respects, the effect of the drugs upon the SSP-L differs from their influence upon the "Thomas reaction," induced by giving epinephrine i.c. and typhoid endotoxin i.v. in rabbits.

Solum & Stormorken F56,817/65: In experiments on washed human blood platelets, it was found that thrombin and collagen, unlike ADP and epinephrine, require externally added fibrinogen for the induction of platelet aggregation. The participation of these phenomena in the production of thromboses is discussed.

Nordøy & Rørvik F56,815/65: After a review of the literature on the probable role of stress and epinephrine in the production of thromboembolic disorders, the authors describe observations showing that in heparinized platelet-rich plasma aggregation, adhesion of platelets occurs upon incubation with epinephrine. "In plasma from rats given adrenaline in oil to induce a state of 'adrenaline stress,' a higher total platelet count was found than in control animals." Intravenous injection of an LD₅₀ of ADP elicits pulmonary platelet thrombi in control rats while in "adrenaline-stressed" animals, the mortality is reduced and platelet thrombi are absent.

McKay E4,788/65: Subcutaneous infusion of large amounts of epinephrine or norepinephrine causes topical gangrene in experimental animals and in man. Norepinephrine i.v. can cause focal myocardial necrosis and fibrinoid necrosis in the coronary and gastrointestinal arteries, sometimes with hemorrhagic necrosis of the intestinal mucosa. These changes are largely due to prolonged vasoconstriction, but disturbances of blood coagulation may also be involved since epinephrine shortens the platelet lifespan and platelet agglutination may occur on endothelial cells damaged by the local ischemia.

Niesert & Schneider F32,779/65: Norepinephrine i.v., given simultaneously with the second i.v. injection of *S. abortus* endotoxin, does not prevent the SSP-G in the rabbit.

The SSP-L normally produced by two injections of meningococcal endotoxin in rabbits can be inhibited by cortisone or ACTH given a few hours before the provocative injection. These hormones are ineffective when administered prior to the preparatory injection and their effect could not be duplicated under any conditions by desoxycorticosterone, oxytocin or vasopressin. After a single injection of endotoxin i.c., ACTH can provoke petechial hemorrhages at the prepared skin sites, although these differ essentially from the SSP-L.

endotoxin + Liquoid or other acidic polymers, yet this response is prevented by heparin. Conversely, the THP induced by epinephrine i.c. and endotoxin i.v. is allegedly prevented by cortisone but not by heparin.

The lethal THP, elicited in chick embryos by single endotoxin injections, can likewise be prevented by various glucocorticoids.

On the other hand, cortisone can also *sensitize* for a THP. Thus it prevents the development of resistance to the SSP-L that normally occurs following repeated courses of two injections of endotoxin. Even a fully established resistance of this kind can be annulled by cortisone.

Both in the rabbit and in the hamster, a single i.v. injection of endotoxin can produce bilateral renal cortical necrosis with hyaline thrombosis of the glomerular capillaries, following pretreatment with cortisone. Furthermore, under these conditions, i.c. injections of endotoxin can cause both an "SSP-L" and an "SSP-G" simultaneously, perhaps because of improved toxin absorption from the skin. Prolonged pretreatment with ACTH or cortisone also aggravates the SSP-G produced by two properly spaced i.v. injections of endotoxin.

Prolonged infusion of thrombin i.v. produces adrenal hemorrhages in the ACTH-pretreated, but not in the normal rat. Hypophysectomized ACTH-treated guinea pigs, unlike normal controls, also respond with adrenal hemorrhages when given two injections of endotoxin to produce an SSP-L.

The fact that, depending upon conditions, ACTH and glucocorticoids can either aggravate or prevent THPs, has never been fully explained. The evidence at hand suggests that dosage and timing are the decisive factors, yet, dexamethasone prevents both the SSP-L and the SSP-G normally produced by two injections of endotoxin, whether it be given for four days prior to the experiment, or only once, just before the provocative injection.

As judged by experiments with fluorescein-tagged γ -globulin complexed with *S. typhosa* endotoxin, pretreatment with cortisone does not affect the initial phagocytosis of toxin by the RES-cells. In this respect, its effect differs from that of Thorotrast.

An interesting "*eclampsia-like syndrome*" with multiple thrombohemorrhagic lesions in various organs can be elicited by renin in rats rendered hypertensive by desoxycorticosterone + unilateral nephrectomy + NaCl. (This response has been referred to as the "Masson phenomenon.")

Pashaei B10,243/37: The SSP-L normally elicited by two injections of *E. coli* endotoxin in the rabbit is somewhat depressed by adrenalectomy but, since the animals become moribund as a consequence of adrenal insufficiency, this observation is difficult to interpret.

de Navasquez E63,407/38: Following a review of the earlier literature on the production of bilateral renal cortical necrosis by single injections of staphylococcal toxin, the author describes the histology of the underlying lesions in detail. These changes (unlike the

associated hypertension, hyperglycemia and glycosuria) are not abolished by adrenalectomy.

Shwartzman et al. D71,760/50: The SSP-L elicited by two injections of meningococcal toxin in rabbits is inhibited by cortisone but not by desoxycorticosterone given i.m. 2 hrs. prior to the provocative injection.

Soffer et al. B47,030/50: The SSP-L normally produced by two injections of meningococcal endotoxin in the rabbit can be inhibited by ACTH given before the provocative injection. The hormone has no effect when administered prior to the preparatory injection. Neither

oxytocic nor pressor posterior-lobe extracts reproduce this inhibitory effect of ACTH.

Thomas & Mogabgab B50,101/50: The gross hemorrhage characteristic of the SSP-L produced by two injections of meningococcal endotoxin can be prevented by ACTH. However, the prepared skin areas become extremely pale within a few hours after ACTH treatment and many small petechiae appear in them. To determine whether the latter lesion merely represents partial inhibition of the SSP-L or is actually brought about by ACTH after preparation, the effect of ACTH and cortisone was examined in rabbits merely given a single preparatory dose of endotoxin. Unlike in otherwise untreated rabbits, the prepared skin sites developed hemorrhagic lesions, but these "differed from the typical Shwartzman reaction in that they were flat and possessed irregular margins, and the spots of hemorrhage were usually distributed unevenly through the involved area, in contrast with the diffusely swollen, uniformly purple appearance of the Shwartzman phenomenon."

Vita G22,817/50: Combined treatment with desoxycorticosterone and vitamin C i.v. largely inhibits the SSP-L normally produced by two injections of *E. coli* endotoxin. [This finding requires confirmation (H.S.).]

Hoigné et al. B63,813/51: ACTH administered prior to the provocative injection of *E. coli* toxin inhibits the SSP-L in the rabbit by diminishing the drop in thrombocytes and capillary resistance as well as the rise in anti-thrombin level that normally characterize this reaction.

Shwartzman B63,812/52: ACTH given before the preparatory bacterial toxin (kind not stated) did not influence the SSP-L. However, if the hormone was injected a few hours preceding the provocative injection, the local response was completely prevented.

Thomas & Good E59,874/51: Bilateral renal cortical necrosis is produced in cortisone-pre-treated rabbits and hamsters by a single i.v. injection of *S. marcescens* toxin.

Marcus & Donaldson B87,419/52: The SSP-L normally elicited by two injections of *S. aertrycke* endotoxin is inhibited by ACTH and cortisone, especially if hormone treatment is started before the i.c. injection of endotoxin. However, in the protected animals, the provocative injection elicited small petechiae at the site of preparation.

Masson et al. B70,138/52: In rats rendered hypertensive by desoxycorticosterone + unilateral nephrectomy + NaCl, renin-containing extracts elicit an "eclampsia-like syndrome" as-

sociated with wide-spread thrombohemorrhagic lesions in various organs. Fibrin thrombi occlude the renal glomerular capillaries as well as capillaries and arterioles in other parts of the body. Many arterioles show homogenization of their walls. There were hemorrhages in the kidney, heart, intestines, bladder, adrenals, and brain, as well as edema of the pancreas, mesoappendix, stomach and brain.

Thomas G26,184/52: In cortisone-treated rabbits, a single i.c. injection of meningococcal toxin produces a local hemorrhagic necrosis reminiscent of the SSP-L, while a single i.v. injection of this toxin elicits an "SSP-G" with thrombohemorrhagic lesions in the internal organs and characteristic hyaline thrombi in the renal glomerular capillaries.

Thomas G21,667/52: General reviews on the somewhat contradictory literature concerning the effect of ACTH and cortisone upon the SSP.

Thomas & Good B79,249/52: In rabbits prepared and challenged by meningococcal toxin i.v., pretreatment with ACTH or cortisone aggravates the ensuing renal cortical necrosis and mortality. Indeed, following cortisone pretreatment, a single i.v. injection of meningococcal toxin suffices to produce an "SSP-G."

Thomas & Good E56,605/52: A single i.v. injection of *S. marcescens* or meningococcal toxin is followed by bilateral cortical necrosis and hyaline thrombosis of the renal glomerular capillaries in the cortisone pretreated rabbit. There are also hemorrhages in the lung, spleen, liver and gastrointestinal tract. In cortisone-treated rabbits, *S. marcescens* toxin i.c. can cause both an SSP-L and an SSP-G simultaneously, perhaps because toxin absorption from the skin is increased under the influence of the glucocorticoid.

Bennett & Beeson B95,351/53: Cortisone prevents the development of resistance to the SSP-L that normally occurs in the rabbit following repeated courses of two injections of *S. marcescens* endotoxin each. (Yet, the resistance to the pyrogenic effect cannot be thus prevented.) Even an already fully established resistance to the SSP-L effect is annulled by subsequent cortisone treatment. However, topical application of cortisone to the prepared skin site is ineffective.

Race & Reed G23,063/53: The SSP-L produced by two injections of meningococcal endotoxin in the rabbit is incompletely suppressed by ACTH given 2 hrs. prior to the provocative i.v. injection.

Thomas B89,551/53: Especially intense renal cortical necrosis is produced in cortisone-pre-

treated rabbits by a single i.v. injection of meningococcal or *S. marcescens* endotoxin.

Mazzei & de Benedetti C6,078/54: The inhibition by ACTH of an SSP-L produced by two injections of *B. typhosus* endotoxin depends upon timing. "The Sanarelli-Shwartzman phenomenon was found to be inhibited by ACTH, provided a daily dosage of 2 mg/kg was administered during a space of time extending from 72 hrs. before the primary or preparatory injection till 8 hrs. after the secondary or reaction-producing injection. A mere abatement in intensity of the reaction pattern was observed if administration of ACTH covered only the 72 hrs. preceding the preparatory injection or was confined to the 24 hrs. intervening between the preparatory and the reaction-producing injections."

Quattrochi & Rao C464/54: The SSP-L normally produced by two injections of typhoid endotoxin is inhibited by cortisone and aggravated by desoxycorticosterone pretreatment.

Thomas & Smith E23,202/54: In rabbits given Fe-OS 2 hrs. before meningococcal toxin i.v., there is high mortality with renal cortical necrosis. Cortisone pretreatment diminishes the mortality but increases the incidence of renal cortical necrosis. In rabbits pretreated with cortisone, a single i.v. injection of meningococcal endotoxin produces bilateral renal cortical necrosis.

Verge & Paraf B96,396/54: ACTH given i.v. 24 hrs. after preparation with *E. coli* endotoxin i.c. causes a typical "SSP-L" in the rabbit.

Thomas et al. E52,778/55: Liquoid, given i.v. 2 hrs. before an i.v. injection of bacterial endotoxins (meningococcus, *S. marcescens*, *Shigella paradyenteriae*), produces an "SSP-G" with disappearance of blood fibrinogen in the rabbit. The response is prevented by heparin but not by nitrogen mustard or cortisone. This "SSP-G" is attributed to intravascular precipitation of fibrinogen by the polymer.

Thomas et al. G21,281/55: In rabbits prepared by a single i.v. injection of various Gram-negative bacterial endotoxins, subsequent i.v. injection of several acidic polymers (Liquoid, dextran sulfate or sodium polyvinyl alcohol sulfonate) elicits an "SSP-G." Cortisone does not influence this response.

Wawersik C31,713/55: The SSP-L elicited in the guinea pig by two injections of meningococcal endotoxin is not significantly influenced by hypophysectomy, ACTH or hypophysectomy + ACTH. However, in hypophysectomized animals treated with ACTH, adrenal

hemorrhages were common, although the preparatory injection was given i.c.

Smith & Thomas C97,047/56: Inoculation of various bacterial endotoxins into the chorioallantoic membrane or i.v., produces multiple hemorrhages, blood sludging and death of developing chick embryos. Injection of the same materials into the allantoic sac is ineffective. Susceptibility is greatest on the 10th day of incubation and absent in 6- or 16-day embryos as well as in fowl after hatching. The lethal effect is prevented by various glucocorticoids.

Thomas C15,187/56; C27,073/56; Thomas & Zweifach C13,964/56: Epinephrine i.c. produces extensive skin hemorrhages in rabbits when given one hour after *E. coli*, *E. typhosa*, or *S. marcescens* endotoxin i.v., presumably because the hormone produces an unusually prolonged local ischemia. This response is prevented by cortisone or chlorpromazine, but not affected by heparin or nitrogen mustard.

Cremer & Watson C37,986/57: The distribution of *S. typhosa* endotoxin in the RES was determined in rabbits by its ability to complex with fluorescein-tagged gamma globulin. Pretreatment with cortisone and x-irradiation did not affect the initial phagocytosis of toxin by the RES-cells of the liver, spleen and lung but inhibited its degradation and elimination after a single i.v. injection, as judged by the rate of its disappearance from the RES-cells.

Lohel C50,024/57: An SSP-G, elicited by two i.v. injections of *E. coli* endotoxin, is inhibited by concurrent ACTH administration.

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, and rises in hematocrit and plasma hemoglobin. The syndrome is inhibited by adrenergic blocking agents (chlorpromazine, dibenzylamine), artificial hypothermia and, to a lesser extent, by cortisol.

D'Angelo et al. C86,715/59: Apparently contradictory reports concerning the influence of cortisone upon the SSP are due to differences in the timing of hormone treatment. Rabbits were treated for the production of an SSP-L or SSP-G by two injections of *E. coli* endotoxin in the customary manner. If the rabbits were given a single i.m. dose of 19 mg of cortisone one hr. prior to the provocative endotoxin injection, both the SSP-L and the SSP-G were prevented. Conversely, daily treatment with 25 mg of cortisone beginning three days prior to the preparatory endotoxin injection increased the susceptibility of the animals so that they

responded with an SSP-L or SSP-G even after the first injection (i.c. and i.v. respectively) of endotoxin.

Merrian & McKay C66,400/59: In rabbits pretreated for three days with 25 mg of cortisone per day, a single i.v. injection produces renal lesions with marked dilatation of the renal glomerular capillaries which become replete with carbon particles if India ink is injected i.v. This is "an observation compatible with the theory that glomerular capillary dilation is in part responsible for lodgement of fibrin in these vessels in the Shwartzman reaction."

Bianco et al. C91,522/60: The SSP-L or SSP-G normally produced in rabbits by two injections of *E. coli* endotoxin is prevented by dexamethasone irrespective of whether the hormone is given daily for four days prior to the experiment, or only once 1 hr. before the provocative injection. In this respect dexamethasone differs fundamentally from cortisone, which sensitizes in the event of prolonged pretreatment and protects when given only once before the provocative injection.

Gatling C83,022/60: The topical hemorrhage and fibrinoid necrosis of arteries, produced by i.c. injection of epinephrine or norepinephrine in hypersensitive rabbits, is inhibited by heparin and cortisone but not by nitrogen mustard, chlorpromazine or sodium salicylate.

Kaley et al. G27,361/60: In rats rendered hypertensive by treatment with desoxycorticosterone + unilateral nephrectomy + dietary NaCl-supplements according to a previously described technique (Selye et al. A58,748/43), treatment with renin produces "an eclampsia-like syndrome accompanied by a degenerative glomerular lesion." Chronic treatment with *E. coli* endotoxin "produced a striking occlusive glomerular lesion associated with fibrinoid degeneration of glomerular basement membranes in 18 of 24 animals. The histologic lesion seen in these kidneys had the salient features of human eclampsia and reproduces some of the changes seen in the generalized Shwartzman phenomenon." 5-HT produced no detectable lesions.

McCluskey et al. D82,558/60: Glomerular nephritis with arteritis in the lungs, stomach, heart, muscles and urinary bladder can be produced in mice by the i.v. injection of soluble antigen-antibody complexes. Cortisone diminished the glomerular nephritis but caused deposition of amorphous eosinophilic material in the glomerular capillary loops which contained antigen and antibody, as judged by the fluorescent antibody technique.

Rieder & Thomas C80,868/60: As little as 5 µg of *E. coli* lipopolysaccharide causes abortion in the mouse. This response is not blocked by cortisone, which inhibits both endotoxin shock and the epinephrine-THP.

Berken & Wolman D85,445/62: In prednisolone-pretreated rabbits, two i.v. injections of *E. coli* endotoxin, too small to elicit an SSP-G in themselves, suffice to elicit the typical response.

Hoak et al. E33,389/63: In rabbits injected with ACTH or crude anterior pituitary extract s.c., thromboses developed in isolated jugular-vein segments, simultaneously with a 5 to 7-fold increase in plasma-free fatty acids. Thrombi were also found in branches of the pulmonary artery, liver, kidney and the cardiac cavities. "These results suggest that rapid lipid mobilization resulting in high plasma-free fatty acids can be associated with a thrombotic state and acute heart failure in the rabbit."

Nakai & Margaretten E45,655/63: The bilateral renal cortical necrosis produced by a single i.v. injection of staphylococcal endotoxin cannot be prevented either by heparin or by nitrogen mustard pretreatment. Thus, this lesion differs in its responsiveness from the typical SSP-G. Pretreatment with cortisone, on the other hand, protected rabbits both against the renal cortical necrosis and the lethal effects of a single i.v. injection of staphylococcal toxin.

Bouissou et al. D19,954/64: A single i.v. injection of *E. coli* endotoxin suffices to produce an "SSP-G" with glomerular capillary thromboses and renal cortical necrosis in rabbits pretreated with cortisone i.m.

Higginbotham & Bass F10,987/64: Extracts of *E. coli* and *S. aureus* produce hemorrhage and death in chick embryos but the latter, though highly toxic, elicits comparatively little bleeding. Cortisol exerts a protective action.

Levin & Cluff G8,713/64: Massive bilateral adrenal cortical hemorrhages are produced in rabbits prepared with Thorotrast and injected a few hours later with endotoxin (kind not stated) or ACTH. Administration of multiple doses of cortisol, soon after the Thorotrast or ACTH injections, suppress the adrenal hemorrhagic reaction, otherwise elicited by endotoxin. It is concluded "that adrenal hemorrhage observed during sepsis, as in the Waterhouse-Friderichsen syndrome, may be attributable to endotoxemia occurring during or shortly after stimulation of the adrenal cortex by infection."

Margaretten et al. F3,924/64: Prolonged infusion of thrombin i.v. elicits no adrenal hemorrhage in the rat (changes in other organs are not mentioned). However, if simultaneously ACTH or EACA is infused, adrenal hemorrhages result.

Thomas F738/64: A THP-L can be elicited in the skin of the rabbit by i.c. injection of the granule fraction obtained from peritoneal granulocytes followed by i.v. provocation with *E. coli* endotoxin. "It is suggested that one or more of the acid hydrolases contained in granules may be implicated in the pathogenesis of vascular damage." Cortisol i.v. prevents this response, allegedly because of its stabilizing effect upon the lysosomes.

Gabbiani et al. G19,450/65: In rats pretreated with ACTH, fluorocortisol or stress (restraint), a single i.v. injection of Thorotrast produced thrombohemorrhagic lesions with necrosis in the adrenals and liver, as well as hyaline glomerular capillary thromboses in the kidneys.

Levin & Cluff G25,181/65: In rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, unlike the SSP, this response is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment. The adrenal hemorrhages are also prevented by cortisol and by certain adre-

nergic blocking agents such as phenoxybenzamine, alderlin, or 1(3',4'-dichlorophenyl)-2-(isopropylamino) ethanol. Since ACTH, Thorotrast and *E. coli* endotoxin all increase the blood-cortisol level of the rabbit, it is assumed that the localization of the hemorrhages is connected with increased adrenocortical activity.

Margaretten et al. G26,896/65: Hemorrhagic thrombosis of the adrenals, often combined with renal cortical necrosis, can regularly be obtained in rats by combined treatment with ACTH, EACA and thrombin. It is assumed that thrombin induces a generalized predisposition to thrombosis. ACTH is responsible for the adrenal localization (owing to dilatation of the sinusoids), while EACA prevents fibrinolysis. Treatment with thrombin and EACA or thrombin and ACTH have a similar but less constant effect.

Moore G28,594/65: Previous experiments have shown that pregnant rats, fed an experimental diet and given progesterone during late pregnancy, develop intra-uterine hemorrhage with fetal death and, occasionally, renal cortical necrosis (Moore D95,837/61; D34,394/62; D63,441/63). The incidence of the renal lesions is not increased under these conditions if steroid hypertension is produced by desoxycorticosterone + unilateral nephrectomy + NaCl-supplements. Apparently, renal cortical necrosis is independent of hypertension.

Other Pituitary Hormones and Hypophysectomy. The influence of the pituitary upon responsiveness to THPs is not dependent only upon ACTH. In guinea pigs, *hypophysectomy* prevents the usual topical and adrenal hemorrhagic necrosis following a single s.c. dose of diphtheria toxin. If the toxin is given simultaneously with *gonadotrophic hormone*, hemorrhagic necrosis occurs in the gonads.

STH (the somatotrophic or growth hormone) has not been found to affect the SSP-G, but this problem has as yet received little attention.

Neither *vasopressor* nor *oxytocic posterior lobe extracts* appear to inhibit the SSP-L. Unlike epinephrine and norepinephrine, vasopressin (despite its vasoconstrictor action) fails to produce a THP-L in rabbits given endotoxin i.v.; however, vasopressin can replace epinephrine or norepinephrine in the production of topical hemorrhagic necroses when it is injected mixed with endotoxins i.c.

Greene G25,944/39: Certain rabbits are subject to a spontaneous disease of pregnancy reminiscent of eclampsia and characterized by bilateral renal cortical necrosis and lesions in the liver and kidneys. Treatment with crude anterior pituitary extracts towards the end of pregnancy elicited this disease with great frequency.

Tonutti B48,825/49; B48,887/49; B48,892/50: The hemorrhagic, necrotizing and inflammatory responses that normally occur in the adrenals and at the site of injection following a single s.c. dose of diphtheria toxin, are prevented by hypophysectomy. In the absence of the hypophysis, the topical reaction to skin burns and the associated adrenal stimulation

are likewise prevented. Apparently, the pituitary conditions nonspecific tissue reactivity through the regulation of corticoid secretion. In guinea pigs simultaneously treated with diphtheria toxin and gonadotrophic hormone, hemorrhagic necrosis occurs in the ovaries and testes, presumably as the consequence of a specific sensitization of these organs.

Shwartzman B63,812/52: Neither vasopressin nor oxytocin inhibits the SSP-L produced with bacterial toxins (kind not stated) in the rabbit.

Thomas & Good B79,249/52: Pretreatment with STH does not influence the course of an SSP-G elicited by two injections of meningococcal toxin in the rabbit.

Rall & Gaskin C13,122/56: In rabbits prepared by *S. marcescens* endotoxin i.c., neither epinephrine nor norepinephrine given i.v. 24 hrs. later produce an SSP-L, but if these catecholamines are injected directly into the prepared skin sites, a local hemorrhagic necrosis results. Vasopressin (Pitressin) is also active locally, while 5-HT is not.

Gonadal Hormones (Female). Following estradiol pretreatment, a single injection of diphtheria toxin elicits hemorrhagic necrosis in the uterus of the castrate guinea pig. This response can be prevented by progesterone although the typical SSP-L is apparently not modified either by estradiol or by progesterone. When administered to late pregnant rats, progesterone can produce an eclampsia-like syndrome with renal lesions similar to those of the SSP-G, intra-uterine hemorrhage and fetal death. This effect of progesterone is especially evident in animals kept on certain diets, but the nature of the sensitizing food factor has not yet been clarified.

Pashaei B10,243/37: The SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit is not significantly influenced by ovariectomy.

Symeonidis B32,969/49: An eclampsia-like syndrome is induced in rats by large doses of progesterone given during the last third of pregnancy. There is abortion or resorption of the embryos, albuminuria, azotemia, edema, and hypertension. "The lesions in other organs, especially in the liver and the kidney, were similar to those of human eclampsia. These were peripheral lobular necrosis of the liver, with capillary dilatation, fibrin thrombi, and hemorrhages, fibrin thrombi in glomeruli, thickening of the glomerular basement membrane, and tubular degeneration and necrosis in the kidney."

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by estradiol or progesterone.

Thomas C27,073/56; C15,187/56: In rabbits given i.v. injections of *E. coli* endotoxin, i.c. administration of ephedrine, vasopressin, histamine, 5-HT and ferritin (unlike epinephrine and norepinephrine) produce no hemorrhages at the dermal injection sites.

Byrom & Pratt C67,211/59: Following "sensitization" with estradiol s.c., synthetic oxytocin s.c. produces renal cortical necrosis with intense glomerular congestion in the rat.

Coriglione G28,855/64: The ocular SSP-L produced by local preparation and i.v. provocation with typhoid endotoxin in the rabbit can be prevented by STH, presumably because capillary permeability is diminished as judged by the fluorescein test. [The brief abstract does not permit accurate evaluation of the results (H.S.).]

Quattrocchi & de Gregorio E84,554/65: The SSP-L normally produced by two injections of typhoid endotoxin in the rabbit is aggravated by pretreatment with chorionic gonadotrophic hormone.

Tonutti B75,807/50: A single intracardiac injection of diphtheria toxin produces marked hemorrhagic necrosis in the uterus of castrate guinea pigs pretreated with estradiol. Progesterone prevents this effect. This is another example of hormonal conditioning for morbid reactions.

Byrom & Pratt C67,211/59: Following "sensitization" with estradiol s.c., synthetic oxytocin s.c. produces renal cortical necrosis with intense glomerular congestion in the rat.

Cooper & McKay C83,053/60: Combined treatment with progesterone, diethylstilbestrol and testosterone cannot substitute for pregnancy in preparing the rabbit for the production of an "SSP-G" by a single injection of bacterial endotoxin (kind not stated).

Waugh & Pearl C83,389/60: Contrary to earlier observations (performed on another strain of rats), progesterone produced no "eclampsia-like" changes in pregnant rats.

Stamler D4,281/61: Progesterone elicits a THP-G in the late-pregnant rat.

Moore D95,837/61; D34,394/62; D63,441/63; G28,594/65: Pregnant rats, fed an experimental diet and given progesterone during late pregnancy, develop intra-uterine hemorrhage with fetal death and, occasionally, renal cortical necrosis. The incidence of the renal lesions is not increased under these conditions if steroid hypertension is produced by desoxycorticosterone + unilateral nephrectomy + NaCl-supplements. Apparently, renal cortical necrosis is independent of hypertension.

McKay E4,788/65: Progesterone, given to late-pregnant rats, inhibits labor and thus pro-

longs gestation. "When the fetuses remain in utero beyond the usual period of gestation, there is an increasing incidence of intrauterine fetal death. The death of the fetus is followed by degeneration of the placental trophoblast. The trophoblast lines the maternal vascular spaces of the chorionic placenta and in this sense constitutes an 'endothelial' lining. With degeneration of this 'endothelium,' platelets agglutinate and undergo viscous metamorphosis, and release a clot-promoting agent into the maternal circulation which leads to local and disseminated clotting. In the animal 'prepared' by pregnancy, the intravascular clotting is manifested as the generalized Shwartzman reaction."

Other Hormones. There are only very few, scattered data in the literature concerning the influence of other hormones upon the production of THPs. Suffice it, therefore, to present succinct summaries of the few publications that deal with the influence of the male gonad thyroid, parathyroid, pancreas and kidney.

GONADAL HORMONES (MALE)

Pashaev B10,243/37: The SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit is not significantly influenced by removal of the testes.

Rossano et al. G18,406/61: An SSP-L induced in the classical manner by two injections of *E. coli* in the rabbit is partially inhibited by pretreatment with methandrostenolone (Dianabol).

THYROID HORMONES

Pashaev B10,243/37: The SSP-L, elicited by two injections of *E. coli* endotoxin in the rabbit, is not significantly affected by thyroidectomy.

Citarda B35,514/42: Thyroidectomy almost completely prevents the production of an SSP-L by two injections of *E. typhosa* endotoxin. Unilateral thyroidectomy is ineffective. Thyroxin restores the responsiveness of the thyroidecomized rabbit.

Fiorentino & Vegna G22,260/47: The SSP-L elicited in the rabbit by two injections of *S. typhosa* endotoxin is inhibited by pretreatment with methylthiouracil.

Becker B28,260/48: Thyroidectomy fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

PARATHYROID HORMONES

Hueper 98/27: In dogs given toxic doses of parathyroid extract, multiple hemorrhages and thromboses occur in various organs, particularly the liver, gastric mucosa, heart and brain.

Pashaev B10,243/37: The SSP-L, normally elicited by two injections of *E. coli* endotoxin in the rabbit, is not significantly influenced by parathyroidectomy.

PANCREATIC HORMONES

Pashaev B10,243/37: The SSP-L, normally elicited by two injections of *E. coli* endotoxin in the rabbit, is not significantly influenced by pancreatectomy.

Szildgyi et al. E23,139/63: The SSP-L elicited by two injections of *E. coli* endotoxin in rabbits, is markedly inhibited by alloxan and glucose but augmented by insulin. "A disturbance of carbohydrate metabolism is assumed to play a role in the mechanism of the Shwartzman reaction."

RENIN, HYPERTENSIN

Masson et al. B70,138/52: An "eclampsia-like syndrome" associated with widespread thrombohemorrhagic lesions in various organs is produced by renin in rats pretreated with desoxycorticosterone + unilateral nephrectomy + NaCl.

Kaley et al. G27,361/60: In rats rendered hypertensive by treatment with desoxycorticosterone + unilateral nephrectomy + dietary NaCl-supplements according to a previously described technique (*Selye et al. A58,748/43*), treatment with renin produces "an eclampsia-like syndrome accompanied by a degenerative glomerular lesion" while chronic treatment with *E. coli* endotoxin "produced a striking occlusive glomerular lesion associated with

fibrinoid degeneration of glomerular basement membranes in 18 of 24 animals. The histologic lesion seen in these kidneys had the salient features of human eclampsia and reproduces some of the changes seen in the generalized Shwartzman phenomenon."

Histamine, Antihistaminics, Histamine Dischargers, Histaminase. It has been claimed that both the SSP-L and the SSP-G can be reproduced by two properly spaced injections of *histamine* in the rabbit, but this work, though published 15 years ago, has never been confirmed.

Histamine pretreatment does not desensitize the guinea pig against the production of an SSP-L by endotoxins nor does it inhibit the classical SSP-L in the rabbit.

Histamine also fails to duplicate the local thrombohemorrhagic effect of epinephrine or norepinephrine, when given conjointly with an i.v. injection of endotoxin in rabbits. On the other hand, when histamine is injected into a dermal area prepared by endotoxin, it produces a local anemia surrounded by a corona of hemorrhages. This latter effect may be interpreted as a topical inhibition of the SSP-L in the center of the area of provocation.

Data on the effect of *antihistaminics* upon the SSP are contradictory, presumably because of differences in timing and in the kind of antihistaminic employed. However, it appears that at least certain antihistaminics can inhibit the SSP-L, especially if they are injected directly into the prepared area.

Histamine dischargers appear to exert no striking effect upon the classic SSP although they can markedly influence the course of certain pluricausal THPs (cf. p. 140).

Histaminase fails to influence the SSP-L, as judged by the scanty available data.

HISTAMINE

Gratia & Linz D6,544/32: Histamine does not desensitize the guinea pig against an SSP-L produced by two injections of *E. coli* filtrate, but the animals which exhibit the most pronounced SSP-L also manifest the most severe histamine shock.

Kielanowski & Selzer G23,077/34; D71,895/35: Histamine injected into a dermal area prepared by *E. coli* endotoxin, produces local anemia in the rabbit. Upon subsequent i.v. provocation, the SSP-L develops mainly around the anemic area.

Gangitano & Bondi B37,974/47: An "SSP-G" can allegedly be produced by two i.v. injections of histamine in the rabbit.

Bondi & Gangitano G22,706/50: In rabbits given 1 mg of histamine i.v., fractions of this amount will produce fatal shock when given 16-24 hrs. later. At autopsy, the animals exhibit serous and hemorrhagic exudates in the

Niesert & Schneider F32,779/65: Hypertensin II, given i.v. simultaneously with the second injection of *S. abortus* endotoxin, offers only questionable protection against the development of an SSP-G in the rabbit.

pleura, pericardium and peritoneum. Often, there were "coagula" (thrombi ?) in the large vessels and the heart and occasionally hemorrhagic foci in the lung and intestines. If histamine i.c. is followed by i.v. provocation with the same material, topical hemorrhagic-necrotic changes occur which resemble those of the SSP-L. "The clinical and pathologic-anatomic data appear to reproduce the Shwartzman-Sanarelli phenomenon exactly." Although treatment with an antihistaminic ("Dimetina") failed to prevent these changes, histamine is thought to play a decisive role in the production of the SSP.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by histamine.

Thomas C27,073/56: In rabbits given i.v. injections of *E. coli* endotoxin, i.c. administration of histamine (unlike epinephrine and norepinephrine) produces no hemorrhages at the dermal injection sites.

Gatling C83,022/60: Epinephrine or norepinephrine, given i.v. to hypersensitive rabbits in the presence of circulating specific antigen, produces topical hemorrhage with fibrinoid necrosis of arteries. Ephedrine, histamine and atropine i.c. are ineffective under the same conditions.

ANTIHISTAMINICS

Boquet G20, 920/43: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit is not inhibited either by vitamin K or by potent antihistaminics (929 F, Antergan). "The local hemorrhagic manifestations do not appear to be due exclusively to derangements in blood coagulability or the liberation of histamine by the provocative injection."

Bovet & Walthert G21,643/45: The SSP-L normally produced by two injections of *E. coli* endotoxin is largely inhibited, though not completely suppressed, by pyrilamine (2786 R.P.) and, to a lesser extent, by thymoxyethyl-diethylamine (929 F) and Antergan. These findings contradict earlier observations of Boquet (*G20,920/43*) who found the latter two antihistaminics ineffective in this respect.

Becker B28,260/48: Benadryl fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Maratka & Ivy B29,487/48: The SSP-L produced by two injections of *E. coli* endotoxin can be inhibited by Neo-Antergan and Benadryl.

Scuderi G22,360/48: Subconjunctival preparation with *B. proteus* endotoxin produces an ocular SSP-L in rabbits following i.v. injection of typhoid endotoxin. This response can be prevented by various pyrogens (vaccines, colloidal sulfur) but not by the antihistaminic Antistan.

Smith & Humphrey B59,532/49: The SSP-L, normally produced by two injections of *E. coli* endotoxin, can be prevented in the rabbit by pretreatment with sodium salicylate, while Anthisan is ineffective in this respect.

Pasteur Vallery-Radot et al. G22,703/50: The SSP-L normally elicited by two injections of *E. coli* endotoxin in the rabbit can be totally prevented by the antihistaminic promethazine (3277 R.P.) s.c. given 30 min. prior to the preparatory injections and during the 3 following days.

Reuse B76,139/50: Pretreatment with various antihistaminics (Histaphen, Neoantergan, Phenergan) does not prevent the production of an SSP-L by two injections of *E. coli* endotoxin in the rabbit. The earlier data are contradictory but "it is difficult to evaluate them on

a phenomenon which lends itself so badly to quantitative analysis."

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by tripelenamidine (Pyribenzamine).

Filipp & Kelenhegyi G23,257/51: An SSP-L is produced in the rabbit by two injections of a suspension of live *E. coli* organisms. Antistin given conjointly with the provocative bacterial i.v. injection greatly diminishes the intensity of the hemorrhagic inflammation at the prepared skin sites. This antihistaminic is ineffective, however, if given i.v. simultaneously with the first (preparatory) injection. If the prepared skin site itself is injected with Antistin just before i.v. provocation, topical inflammation is diminished.

Lawrence et al. G26,851/52: Suspensions of the transplantable *V₂* carcinoma given i.v. to rabbits cause thrombosis in the right side of the heart and in the pulmonary vessels owing to the thromboplastic property of the neoplasm. Benadryl does not protect against this effect.

Štork & Kováčiková C11,611/54: The SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit is inhibited by the topical administration of the antihistaminic Antistan although, in the same animals, control sites prepared by the endotoxin alone responded with hemorrhagic necrosis. On the other hand, given systemically, neither Antistin nor Phenergan offered protection.

Rall & Kelly C36,395/57: The antihistaminics diphenhydramine (Benadryl) and tripelenamidine (Pyribenzamine) given s.c., 5 minutes before to 3 hrs. after the provocative injection, failed to inhibit the SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit.

Hein & Günthner F28,509/65: A γ -globulin obtained from pooled human placenta blood ("Allerglobulin") inhibits the SSP produced by various bacterial endotoxins in the rabbit. Since the same globulin preparation also blocks several other histaminergic reactions, the effect is ascribed to some antihistaminic or histaminopexic action.

HISTAMINASE

Bosse A36,583/41: The SSP-L normally produced by two injections of *B. proteus* endotoxin in the rabbit cannot be prevented by histaminase p.o., s.c. or i.v. "Either histamine plays little part in the phenomenon or histaminase does not inactivate sufficiently the histamine released."

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by histaminase.

HISTAMINE DISCHARGERS

Rieder & Thomas C80,868/60: As little as 5 µg of *E. coli* lipopolysaccharide causes abortion in the mouse. This response is not blocked by 48/80 (which prevents endotoxin shock, the epinephrine THP and the SSP-G, though not the SSP-L).

Serotonin (5-HT), Antiserotonins. Unlike epinephrine, norepinephrine or vasoressin, 5-HT does not produce a local hemorrhagic necrosis in skin sites prepared by endotoxins, nor does it produce a THP-L when injected i.c. simultaneously with endotoxins i.v., or when given i.v. 24 hrs. after i.c. preparation of a skin with endotoxins.

If 5-HT inhibitors are administered before the provocative injection, the SSP-L can be prevented.

Rall & Gaskin C13,122/56: In rabbits prepared by *S. marcescens* endotoxin i.c., neither epinephrine nor norepinephrine, given i.v. 24 hrs. later, produces an SSP-L, but if these catecholamines are injected directly into the prepared skin sites, a local hemorrhagic necrosis results. Vasopressin (Pitressin) is also active locally, while 5-HT is not.

Thomas C15,187/56; C27,073/56: If *E. coli* or *E. typhosa* endotoxin is injected i.v. simultaneously with epinephrine or norepinephrine i.c. in the rabbit, hemorrhagic necrosis occurs at the site of catecholamine injection. Ephedrine, vasopressin and 5-HT have no such effect.

Rall & Kelly C36,395/57: In rabbits prepared by *S. marcescens* endotoxin i.c., the injection of 5-HT 24 hrs. later, either i.v. or directly into the prepared skin site, failed to produce an SSP-L.

Kaley et al. G27,361/60: In rats rendered hypertensive by treatment with desoxycorticosterone + unilateral nephrectomy + dietary NaCl supplements, renin produced "an eclampsia-like syndrome" while 5-HT produced no detectable lesions.

Waugh & Pearl C83,389/60: Various forms of

Niesert & Schneider F32,779/65: Rheomacrodex i.v. fails to prevent the SSP-G normally produced by two i.v. injections of *S. abortus equi* endotoxin.

Wilner G27,851/65: In pregnant rats, endotoxin (kind not stated) i.v. produces renal glomerular thrombosis and hepatic necrosis. Concurrent treatment with low molecular dextran increases the incidence of renal glomerular thrombosis, but decreases the frequency of hepatic necrosis.

renal cortical necrosis and acute nephrosis can be produced by different doses of 5-HT in the rat. The severity of these changes was not influenced by pregnancy, but widespread glomerular intercapillary thrombi and focal necrosis of the liver (which occurred rarely) were observed only in pregnant rats.

Antopol & Chryssanthou D18,742/64: The SSP-L, produced by two injections of *proteus vulgaris* endotoxin in the rabbit, is inhibited by antibradykinin and antiserotonin compounds such as aminopyrine (a bradykinin antagonist), PPBP and MAPTC (antiserotonins).

Antopol & Chryssanthou F5,788/64: The SSP-L produced by two injections of endotoxin (kind not stated) in rabbits is prevented if, prior to the provocative injections, cinnamamide (a 5-HT inhibitor) is given in combination with aminopyrine (an antibradykinin which also has some anti-5-HT activity). Given separately, these compounds are less effective.

Galton F53,009/65: The 5-HT antagonist UML 491, unlike SQ 10,643 afforded a high degree of protection against the "SSP-G" produced by colchicine in pregnant hamsters. No "SSP-G" could be produced in a hamster by combined treatment with EACA and 5-HT.

Bradykinin, Antib Bradykinins, Kallikrein. *Bradykinin* given i.v. simultaneously with the provocative injection, aggravates the SSP-L as well as the THP produced by endotoxins + epinephrine. On the other hand, *antibradykinins* (most of which are also anti-5-HTs) inhibit the SSP-L.

An impure *kallikrein* preparation from urine given i.v. produced a THP-L

following i.c. preparation with endotoxin. However, since pure kallikrein preparations were inactive, this effect must be ascribed to some contaminant. Yet, kallikrein mixed with endotoxin can produce a topical THP without provocation.

BRADYKININ, ANTIBRADYKININS

Antopol & Chryssanthou D56,730/63: The SSP-L, induced by two injections of *Proteus vulgaris* lipopolysaccharide in the rabbit, is aggravated by bradykinin when given i.v. simultaneously with the provocative injection. Similarly, bradykinin treatment also aggravated the "Thomas reaction" elicited by *Proteus vulgaris* lipopolysaccharide and epinephrine intradermally in the rabbit.

Antopol & Chryssanthou F5,788/64: The SSP-L produced by two injections of endotoxin (kind not stated) in rabbits is prevented if, prior to the provocative injection, cinnamanilide (a 5-HT inhibitor is given in combination with aminopyrine an antib Bradykinin which also has some anti-5-HT activity). Given separately, these compounds are less effective.

Antopol & Chryssanthou D18,742/64: The SSP-L, produced by two injections of *proteus vulgaris* endotoxin in the rabbit, is inhibited by antib Bradykinin and antiserotonin compounds such as: 1. Aminopyrine (Pyramidon, Merck), 2. PPBP, 1(N-methyl-piperidyl-4)-3-phenyl-4-benyl-4-pyrazolone-5 (KB-95, Sandoz) and 3. MAPTC, 2'-(3-dimethylamino-propylthio) cinnamanilide HCl (Squibb), administered s.c. at a distance from the site of preparation. Aminopyrine and MAPTC given i.c. into the prepared skin area cause no topical inhibition, while PPBP thus administered is effective. Aminopyrine is a bradykinin antagonist while PPBP and MAPTC are antiserotonins. Since the best inhibition of the SSP-L was obtained by systemic treatment with MAPTC and aminopyrine in combination, "it is postulated that the classical Shwartzman phenomenon involves several tissue responses mediated by multiple agents, including bradykinin and serotonin, which are sequentially or simultaneously re-

leased in a chain reaction initiated by endotoxin."

Chryssanthou & Antopol F3,858/64: In connection with the clotting defect during the SSP, it is of interest that endotoxin, 5-HT, and bradykinin, as well as certain 5-HT-blocking agents, inhibit plasmin fibrinolysis in vitro.

Galton F53,009/65: SQ 10,643, believed to possess antib Bradykinin activity, was ineffective in preventing the "SSP-G" normally produced by colchicine in the pregnant hamster.

KALLIKREIN

Christensen G24,144/52: If kallikrein is mixed with meningococcal endotoxin and injected i.v. into the clamped rabbit ear, the clamp being removed immediately after the injection, a hemorrhagic edematous local response occurs without any provocative i.v. injection. In rabbits given meningococcal endotoxin i.c., the i.v. injection of kallikrein 24 hrs. later produces a severe SSP-L at the site of preparation.

Werle & Backwinkel G23,258/54: In rabbits prepared by *E. coli* filtrate i.c., subsequent i.v. injection of various kallikrein preparations produces no SSP-L, with the exception of kallikrein prepared from human urine. Perhaps the active factor is not kallikrein itself but a urinary contaminant.

Halpern F2,441/64: An SSP-L can be elicited in the rabbit by preparation with *E. coli* endotoxin and provocation with isolated leukocyte granules, and this response can be inhibited by pretreatment with a potent kallikrein-inhibitor antiproteinase. "It is hypothesized that the tissue damage observed in the Shwartzman reaction is conditioned by release or activation of intracellular lysosomal enzymes contained in granulocytes."

Other Biologic Materials. Under this heading, we shall discuss the effects of various chemically, not fully characterized, animal- and plant-tissue extracts and fluids, e.g., blood, exudates, placental and tumor extracts, milk, bile, animal venoms, yeast, and plant pollens.

Blood. The fact that i.v. injection of blood foreign to a mammalian species produces multiple capillary thromboses, was first described by Landois in 1875 and subsequently confirmed by numerous investigators. It has also been noted that foreign blood may cause hemolysis and intravascular erythrocyte agglutination, even before fibrin thrombi develop. When heterologous serums are injected

s.c. into guinea pigs, topical necrosis tends to ensue at the site of injection. Indeed, in massive amounts, even the blood of a normal rabbit transferred to another rabbit by carotid jugular cross-transfusion can cause fibrinoid deposits within the cardiac valves, although other THP-manifestations are absent.

It is not possible to produce an SSP-L in the rabbit by two injections of horse serum or by horse serum i.c. followed by endotoxin i.v. Allegedly, eel serum i.c. can prepare the rabbit skin for the subsequent elicitation of an SSP-L by endotoxin i.v., but this claim has been challenged. While in rabbits, preparation with endotoxin i.c. followed by the i.v. injection of serums from various animals is inactive in producing an SSP-L, heterologous whole blood has occasionally been found to be efficacious.

If rabbit serum is injected i.c. together with normally ineffective doses of *E. coli* endotoxin, then i.v. provocation with the same material 24 hrs. later produces an SSP-L, apparently owing to the adjuvant effect of serum.

Unlike endotoxins, heterologous serums i.v. cannot sensitize the rabbit for the induction of a THP-L at the sites of i.c. injections of epinephrine or norepinephrine.

The hemorrhagic necrosis produced in transplantable tumors by endotoxins in mice can be prevented by some endotoxin-detoxifying component (EDC) present in the serums of different animal species.

(Experiments in which serum has been used as an allergen are discussed in the section "Immunity" on p. 47.)

Landois D18,258/1875: First description of the fact that i.v. injection of foreign blood causes multiple capillary thromboses.

Flexner E76,861/02: "Erythrocyte agglutination thrombi" can occur in various infectious diseases of man and animals, in eclampsia, and after i.v. injection of ricin, ether, or dog's serum into rabbits.

Loeb et al. D85,463/10: Dog serum i.v. produces hemolysis, erythrocyte agglutination, and fibrin thrombi, especially in the lungs and the heart of the dog. In the lungs, this is accompanied by periarterial hemorrhages. Hirudin i.v. prevents this response. Cattle serum produces only erythrocyte aggregation and its effect is not prevented by hirudin.

Aronson G23,549/28: Goat serum i.v. or i.p. produces hemolysis, retardation of blood coagulation and hemorrhages in the pleura and intestine of the guinea pig. This toxicity is abolished if the serum is heated at 56°C, or treated with kaolin, kieselguhr or charcoal. Earlier literature on the toxicity of heterologous blood transfusions is reviewed. Heterologous serums, injected s.c. into guinea pigs, produce topical necrosis and it is probable that the hemolytic, toxic and necrotizing actions of goat-serum are due to a single substance.

Shwartzman E53,222/30: It is not possible to produce an SSP-L in the rabbit by two injections of crystalline egg albumin or of horse serum given in the classical manner.

Sickles B78,436/31: An SSP-L may be elicited in the rabbit by meningococcal toxin i.c. followed by agar i.v. Local reactions did not occur at sites of agar i.c., followed by the endotoxin i.v. Galactose, gelatin, serum or India ink i.v., following meningococcal toxin i.c., failed to elicit the SSP-L.

Shwartzman G23,070/32: In rabbits prepared by *B. typhosus* endotoxin i.c., a subsequent i.v. injection, 24 hrs. later, of the following substances proved to be devoid of provocative potency: normal serum of man, rabbit, guinea pig, rat and chicken, antimeningococcus rabbit serum and antimeningococcus horse serum.

Michelazzi D92,869/33: Eel serum s.c., followed 24 hrs. later by *E. coli* endotoxin i.v., produces no THP-L in the rabbit.

Freund & Smith B78,144/34: Fresh eel serum i.c. is highly potent in preparing the skin for the elicitation of an SSP-L by the subsequent i.v. administration of *E. coli* or meningococcal endotoxins.

Barchi G28,646/35: In tuberculous rabbits, unlike in normal ones, i.v. injection of serum

from patients with malaria produces an SSP-G, while normal serum is ineffective. [Rather subjective description of observations on a very small number of animals (H.S.).]

Alechinsky G22,554/37: If the serum of a prepared or even that of a normal rabbit is injected i.c. together with a normally ineffective dose of *E. coli* endotoxin, then provocation by *E. coli* endotoxin i.v., 24 hrs. later, induces an SSP-L at the prepared site. Apparently, normal rabbit serum (and indeed even the serum of other species) can act as an adjuvant for endotoxin.

Shwartzman G18,862/37: In rabbits prepared by bacterial endotoxins i.c., the i.v. injection of human or guinea pig whole blood can act as a provocative agent, perhaps "due to some *in vivo* interaction between the blood and the natural antibodies of the rabbit."

Ogata & Akimoto G28,153/39: The SSP-L, normally elicited by two injections of *E. coli* endotoxin in the rabbit, can be prevented by the i.v. injection of cattle or pig serum simultaneously with the preparatory dose of endotoxin.

Moukhamediarov 81,331/40: In rabbits prepared by *E. coli* endotoxin i.c., subsequent i.v. injection of fresh human blood often elicits an SSP-L. The blood of syphilitic patients is most commonly effective but the response is by no means specific for this disease.

Samtsov G22,347/40: The i.v. injection of human, guinea pig, or canine blood produces an SSP-L in rabbits which 24 hrs. earlier received *E. coli* endotoxin i.c. Sheep, cat, rabbit, chicken, duck and turtle blood are ineffective.

Gamble & Brunson G21,645/55: When a normal rabbit is given the blood of another normal rabbit by carotid-jugular cross transfusion, fibrinoid deposits occur within the cardiac valves, although other manifestations of an SSP-G are absent. The material may be the "heparin-precipitable protein" which is greatly increased in rabbits given endotoxin i.v. but, allegedly, also occurs in 20% of normal rabbits. [The authors fail to explain why this precipitation occurs only on the cardiac valves, if it is due to the same material that normally produces an SSP-G (H.S.).]

McKay et al. G33,264/55: Pseudomembranous enterocolitis with intravascular clotting in the microcirculation of the bowel can be produced in dogs by the administration of incompatible blood into the aorta with concomitant surgical trauma in the abdomen.

Hardaway et al. G27,024/56: Rapid i.v. injection of human blood kills dogs almost immediately, with numerous small thrombi predominantly in the pulmonary, hepatic, pan-

creatic and gastrointestinal microcirculation. When the blood is injected slowly, the animals survive or die hours later with only a few residual thrombi in the lungs and gastrointestinal mucosa. "The information derived from the animal experiments may apply rather closely to human cases since there is considerable evidence from clinical observations (Hardaway et al. G26,830/54) and pathologic studies (Ratner E4,839/43) in man that incompatible blood transfusion produces intravascular coagulation in the human."

McKay et al. G9,469/56: In dogs, intra-aortic transfusion of human blood produced multiple thromboses and hemorrhages in the lung, liver, intestine and other organs. There was also hyaline thrombosis of the renal glomerular capillaries. When the transfusion was preceded by repeated renal biopsies and unilateral nephrectomy, capillary thromboses in the gastrointestinal tract were prominent, presumably because of topical sensitization through vasoconstriction.

Thomas C27,073/56: Extensive dermal hemorrhagic necrosis is produced in rabbits by the i.c. injection of as little as 5 µg of epinephrine or norepinephrine, followed within 4 hrs. by 1 µg of various endotoxins i.v. The response is apparently specific for endotoxins, since human or horse serum, ovalbumen, rabbit liver glycogen, and Fe-Os i.v. did not provoke hemorrhagic reactions at the sites of dermal epinephrine injections.

Ho & Kass E65,265/57; Rosen et al. G22,063/58: The lethality of crude endotoxins from *S. typhosa* and *E. coli* is attenuated when these preparations are incubated with normal human plasma fractions and injected intracardially into rats. The inactivation is thought to be probably enzymatic. "The data indicate a mechanism of resistance against a crude bacterial product such as may be found in natural infections."

Ravin et al. G27,057/58: The toxin that appears in the blood of dogs and rabbits during irreversible hemorrhagic shock resembles bacterial endotoxin in many of its pharmacologic and chemical properties. Concentrates of this toxin can act as the provocative factor of the "SSP-G" in rabbits prepared by *E. coli* endotoxin or Thorotrast i.v. It is concluded "that the circulating toxin in shock is similar to, or identical with, bacterial endotoxin."

Skarnes et al. G22,060/58: Using hemorrhagic tumor necrosis (produced by *S. marcescens* endotoxin in sarcoma-37 transplants in mice) as a test object, the "endotoxin-detoxifying component" (EDC) of the serum of different animal species was further characterized.

Antopol & Chryssanthou E30,599/59: *E. coli* endotoxin i.c. in itself rarely produces skin hemorrhages in mice but when human immune globulin is given i.p. 5 min. earlier, *E. coli* i.c. often produces intense local hemorrhagic reactions. γ -Globulin also increases the sensitivity of the mouse to an SSP-L elicited by an i.c. (preparatory) followed by an i.p. (provocative) *E. coli* endotoxin injection.

Hardaway & McKay D95,869/59: Acute hemorrhagic pancreatic necrosis is produced in dogs by the intra-aortic infusion of human blood. The reaction is associated with intravascular clotting in the pancreas and other organs. A review of the literature shows that hemorrhagic pancreatitis in man is also frequently associated with thrombosis in veins and capillaries, as well as lower nephron nephrosis.

Hardaway & McKay G33,251/59: A type of pseudomembranous enterocolitis with multiple thromboses in the microcirculation of the bowel can be produced in dogs by transfusion of incompatible blood. Heparin prevents this phenomenon.

Hardaway & McKay G26,516/59: In dogs, the picture of lower nephron nephrosis can be reproduced by the intra-aortic injection of human blood. Shock and death can be prevented if the bowel is protected against the formation of microthrombi by temporarily occluding the superior mesenteric arteries during the injection of the incompatible blood. When human blood is injected just above the origin of the renal arteries, thrombi develop predominantly in the renal glomerular and intertubular capillaries. This can be accompanied by renal cortical necrosis.

Hardaway et al. D9,396/61: Liberation of one kidney from its peritoneal attachments produces a Trueta shunt on both sides and predisposes the dog to the production of glomerular thromboses and renal cortical necrosis following intra-aortal injection of incompatible blood.

Komuro G24,699/61: Unlike the serum of normal pregnant women, that of patients with eclampsia or uterine cancer produces an "SSP-L" when given in two injections to rabbits.

Hardaway D12,907/62: Intra-aortic injection of incompatible blood resulted in intravascular clotting in dogs, as evidenced by the finding of capillary thrombi and hemorrhagic necrosis

throughout the bowel (most prominently in the duodenum and ileum), lung, liver and kidneys. Focal necrosis and hemorrhage occasionally also occurred in the pancreas.

Henry G33,285/62: Review on the production of thromboses with incompatible blood.

Hein & Günthner F28,509/65: A γ -globulin obtained from pooled human placenta blood ("Allerglobulin") inhibits the SSP produced by various bacterial endotoxins in the rabbit. Since the same globulin preparation also blocks several other histaminergic reactions, the effect is ascribed to some antihistaminic or histaminopexic action.

McKay E4,788/65: A review of the literature shows that incompatible blood transfusion in man causes afibrinogenemia with microscopic intravascular thrombi in various organs (including the renal capillary glomeruli), bilateral renal cortical necrosis, lower nephron nephrosis, pancreatic necrosis and hepatic infarcts. Essentially similar changes have been obtained in animals. For example, in dogs, the intra-aortic injection of human blood produced shock with hemorrhagic necrosis of the intestinal mucosa, pseudomembrane formation in the jejunum and ileum, with thrombosis of the capillaries of the intestinal mucosa, kidney, liver and lungs. However, necrosis of the intestinal tract was observed only in animals in which previously peritoneal interventions were performed. "The surgical trauma of this procedure apparently was responsible for localizing the thrombi in the intestinal mucosa. In terms of functional alterations, it is well known that surgical trauma causes 'compensated' shock, which is associated with arteriolar constriction and capillary dilation in the splanchnic bed. It seems likely that stasis of blood in the splanchnic capillaries is in part responsible for localizing the thrombi in the intestinal tract under the conditions of this experiment."

Waters & DeSuto-Nagy B64,578/49-50: Essentially identical arteriolar necroses with hemorrhages are produced in dogs by i.v. injections of large doses of epinephrine, N-amylamine, citrated compatible canine blood or epinephrine + large amounts of canine blood. Similar lesions are obtained by treatment of nephrectomized dogs with pressor renal extracts. The epinephrine-induced lesions can be prevented by dibenamine.

Exudates. As previously mentioned, various exudates share with whole blood and serum the capacity to act as adjuvants for endotoxins in the production of the SSP. Extracts prepared from skin lesions provoked by certain microorganisms, particularly streptococci, have been found to possess considerable SSP activity.

Gratia & Linz E68,985/31; E68,252/31: A sponge soaked with *E. coli* endotoxin is implanted s.c. in the rabbit and 24 hrs. later removed to recover the inflammatory exudate that has accumulated in it. If this exudate is injected i.c. in the rabbit, an SSP-L is produced following i.v. injection of *E. coli* endotoxin given 24 hrs. later. If the exudate is injected i.p., an SSP-G develops after the provocative i.v. injection. These findings are ascribed to the passive transfer of the SSP.

Capri G28,863/52: Following preparation of the skin with "leukotaxin" (extracted according to Menkin's technique from turpentine-induced pleural exudate of dogs), i.v. administration of *S. typhosa* filtrate, agar or pig serum induces an "SSP-L" in the rabbit.

Schwab et al. B33,779/53; Watson C29,780/54: Rabbits were given a small quantity of an extract prepared from the tissues of other rabbits infected with streptococci (group A, type 28) i.c.; 16 hrs. later they were injected with sublethal quantities of typhoid toxin i.v. These animals usually died within 24 hrs. while controls, receiving only typhoid toxin without preparation, survived. "This was the

first indication that a soluble product derived from group A streptococci could prepare rabbits for the generalized Shwartzman reaction. We were surprised, however, that the intradermal injection of lesion extract or 'preparative factor' did not prepare the animals for the local Shwartzman reaction." . . . "This failure, however, may be explained on the basis of the high content of hyaluronidase in the lesion extract which might permit a rapid diffusion of the factor into the circulation." The existence of an SSP-G was documented by the presence of hemorrhagic cardiac necrosis, but the characteristic renal lesions were absent. In rabbits prepared by the i.v. injection of streptococcal-lesion extract and challenged with streptolysin-O i.v., myocardial necrosis occurred in conjunction with bilateral renal cortical necrosis and hyaline thrombosis of the glomerular capillaries. The possibility of producing, with products derived entirely from group A streptococci, an SSP-G and cardiovascular lesions reminiscent of those seen in rheumatic fever, is taken as an indication that the SSP-G may play a part in the pathogenesis of rheumatic diseases.

Placental Extracts. A THP can be elicited in different animal species by the i.v. injection of aqueous placental extracts. In pregnant animals, such extracts may cause premature separation of the placenta. It is assumed that, here, the active factor is thromboplastin and that its exaggerated release may participate in the development of abruptio placentae and pregnancy toxicoses in women. However, amniotic fluid is poor in thromboplastin, yet, as we shall see later, amniotic fluid embolisms can produce THP manifestations in women (p. 210). Amniotic fluid is also highly potent in sensitizing the rat to the production of a THP by norepinephrine.

Obata 32,524/19: A thrombohemorrhagic syndrome can be produced in rabbits and Japanese dancing mice by the i.v. injection of an extract of human placenta. The changes are similar to those seen in eclampsia and this disease is attributed to intoxication with placental products.

Magara & Rin E83,072/40: An aqueous human placental extract, given i.v. to pregnant rabbits, produces premature detachment of the placenta with high mortality; nonpregnant animals tolerate such injections very well.

Magara et al. E83,073/41: A water soluble extract of human placenta, given i.v., causes abruptio placentae and retroplacental hemorrhages in the guinea pig and rabbit. The serum of patients with abruptio placentae, abortion and eclampsia exerts a similar effect: that of normal pregnant women is ineffective in this respect, except when taken during

labor. It is assumed that a placental factor may play a role not only in the development of pregnancy toxicosis and abruptio placentae but even in the induction of normal delivery.

Fulton & Page G20,921/48: Thromboplastin-containing human placental extracts i.v. normally produce an eclampsia-like condition with multiple necroses in the mouse. Following sublethal doses, the blood becomes incoagulable and the animals resistant to lethal doses of thrombin or thromboplastin i.v. Refractoriness is "abolished by restoring fibrinogen to the circulating blood, indicating that prothrombin is present."

Magara E83,075/50: An aqueous placental extract given i.v. to pregnant guinea pigs or rabbits produced retroplacental hemorrhage with abruptio placentae. The liver showed fibrin thrombi in the small portal veins with hemorrhage into the vessel wall and intense

capillary dilatation, resulting in necrosis. Eclampsia-like changes were also found in the kidney, heart and lungs. The active factor is thought to play a role in the pathogenesis of eclampsia.

Schneider B56,544/50; B58,008/50: In rabbits, thromboplastin-containing rabbit placenta extracts i.v. cause pulmonary thromboembolism, cerebral hemorrhages and liver necrosis, especially if the animals are pregnant. Similar results are obtained by trauma to the placenta. Perhaps "following placental damage, material from the placenta might gain access to the maternal blood circulation, and initiate clotting. Thromboplastin is considered to be the chief one of these activators." The changes thus produced may represent an experimental counterpart of obstetrical shock and eclampsia.

Takaoka G27,358/52: Human placenta extract was active either as the preparatory or the provocative agent when *E. coli* endotoxin was used as the other factor in the elicitation of an "SSP-L."

Kono G24,688/56: An SSP-L is produced in the rabbit, but not in the mouse or rat, by two injections of placental polysaccharides.

Magara G27,370/57; G27,946/58: A THP-G considered to be similar to pregnancy toxemia

can be produced in the rabbit by i.v. preparation with *E. coli* endotoxin followed by i.v. provocation with an aqueous placental extract.

Kuwayama G25,145/59: An "SSP-G," sometimes accompanied by renal cortical necrosis, can be produced in rabbits by i.v. injection of an aqueous placental polysaccharide extract given either as the preparatory or the provocative treatment in combination with *E. coli* endotoxin.

Stefanini & Turpini G24,241/59: In rabbits and dogs given i.v. injections of placental extracts or amniotic fluid, large infarcts were found in the major pulmonary vessels, causing multiple pulmonary infarcts. Placental thromboplastin and tissue fibrinokinase presumably cause this response.

Magara G25,146/61: A water-soluble, alcohol-insoluble substance prepared from the human placenta produces an "SSP-G" when given either as the preparatory or the provocative i.v. injection in combination with *E. coli* endotoxin i.v. to nonpregnant rabbits. Pregnant rabbits respond similarly to a single i.v. injection of the placental extract. Apparently, pregnancy induces a continuous state of "preparation."

Amniotic Fluid. Amniotic fluid exhibits THP-activity in various experimental arrangements. This is presumably due in part to its thromboplastin content and in part to the fact that it contains squamous cells which attract a large number of platelets.

Weiner et al. G26,133/49: Uncontaminated sterile amniotic fluid acts like thromboplastin on oxalated plasma in vitro. It also possesses antihemophilic properties.

Muirhead & Montgomery E83,590/51: Human amniotic fluid and autogenous blood clots injected i.v. in rabbits, produce widespread acute necrotizing pulmonary arteritis. Following multiple injections, subacute and chronic lesions characterized by fibrosis and hyalinization of the arterial wall result in the picture of endarteritis obliterans and pulmonary vascular sclerosis.

Stefanini & Turpini G24,241/59: In rabbits and dogs given i.v. injections of placental extracts or amniotic fluid, large infarcts were found in the major pulmonary vessels, causing multiple pulmonary infarcts. Placental throm-

boplastin and tissue fibrinokinase presumably cause this response.

Koutsuky et al. E52,939/61: I.v. injection of amniotic fluid causes rapid death in rats owing to the formation of platelet thrombi in the pulmonary arterioles. Filtered amniotic fluid is inactive and the effect is ascribed to the presence of epidermal squamous cells in the native amniotic fluid. Similar observations have been made in rabbits; here, it could also be shown that the formation of thrombi, which contain little fibrin and many platelets, is associated with hypofibrinogenemia and thrombocytopenia. Apparently, the thromboplastic activity of amniotic fluid is due to the fact that the squamous cells, suspended in it, attract large numbers of platelets which are then sequestered in the small vessels.

Tumor Extracts. Various tumor extracts, and particularly their polysaccharide fractions, have been found to possess THP-activity, but this may be due to endotoxins of microorganisms living in symbiosis with the neoplasms.

Shwartzman G24,102/35: Filtrates of Rous sarcoma tissue do not act either as preparatory or as provocative factors in rabbits in which typhoid endotoxin is used as the second factor in the elicitation of the "SSP-L."

Antopol G22,054/37: Extracts of various tumors of man proved to be active either as preparatory or as provocative factors in the production of an "SSP-L" when the other injection consisted of typhoid endotoxin.

Lawrence et al. G26,851/52: Suspensions of the transplantable V₂ rabbit carcinoma i.v.

cause thrombosis in the right side of the heart and in the pulmonary vessels owing to the thromboplastic property of the neoplasm. Heparin, dicoumarol, and a soybean inhibitor protect against this effect, while Benadryl is ineffective.

Perrault & Shear C4,405/55: Polysaccharides isolated from mouse Lymphoma 1 and Leukemia 1210 given i.c. or i.v. elicited the "SSP-L" in the rabbit. Rabbit skin polysaccharide was highly active as a preparatory, and moderately active as a provocative agent.

Leukocyte Extracts, "Leukotaxin." Both "leukotaxin" containing extracts and isolated leukocyte granules possess THP-activity. This is ascribed to the release of enzymes from the lysosomes of granulocytes.

Capri G28,863/52: Following preparation of the skin with "leukotaxin" (extracted according to Menkin's technique from turpentine-induced pleural exudate of dogs), i.v. administration of *S. typhosa* filtrate, agar or pig serum induces an "SSP-L" in the rabbit.

Halpern F2,441/64: An SSP-L can be elicited in the rabbit by preparation with *E. coli* endotoxin and provocation with isolated leukocyte granules. This response can be inhibited by pretreatment with a potent antiprotease. "It is hypothesized that the tissue damage observed in the Shwartzman reaction is con-

ditioned by release or activation of intracellular lysosomal enzymes contained in granulocytes."

Thomas F738/64: A THP-L can be elicited in the skin of the rabbit by i.c. injection of the granule fraction obtained from peritoneal granulocytes followed by i.v. provocation with *E. coli* endotoxin. "It is suggested that one or more of the acid hydrolases contained in granules may be implicated in the pathogenesis of vascular damage." Cortisol i.v. prevents this response, allegedly because of its stabilizing effect upon the lysosomes.

Extracts of Other Animal Tissues and Biologic Fluids. A number of biologic fluids have been found to possess no THP-L activity. Among these are spinal fluid, bile, milk, ascites fluid, and extracts of various organs. However, occasionally it was possible to obtain a certain degree of cutaneous preparation when local treatment with such materials was followed by the i.v. administration of potent endotoxins. In the interpretation of relevant results, special attention must be given to the possibility of contamination with endotoxin-producing micro-organisms.

von Oettingen & Schwoerer B16,158/26: A review of the literature reveals many observations showing that i.v. injection of various tissue extracts produces convulsions and disseminated thrombohemorrhagic lesions that resemble eclampsia. In this respect placental extracts are not much more potent than those of other tissues. A special placental poison does not exist.

Cope & Howell G23,093/31: No "SSP-L" could be obtained by two injections of egg white, dilute bile, ascites broth, spinal fluid and horse serum given in the usual way.

Gratia & Linz D6,544/32: No "SSP-L" could be elicited in rabbits by cow's milk i.c. followed by either milk or *E. coli* filtrate i.v.

Stolyhwo G21,662/35-36: In rabbits given a provocative i.v. injection of typhoid or para-

typhoid filtrate, preparation of skin sites with various nonbacterial proteins (horse serum, cow's milk, etc.) results in a typical "SSP-L," while topical trauma to the skin is ineffective.

Patania G19,702/36: An "SSP-L" can be obtained in the spleen of the rabbit by topical preparation followed by i.v. provocation with *S. typhosa*. Allegedly, an extract prepared from a spleen thus treated and mixed with *S. typhosa* endotoxin produces an "SSP-L" when given i.c. without the necessity of i.v. provocation.

Antopol & Glick D20,136/38: Fractions prepared from pancreas, testis, liver, kidney, brain, placenta, muscle, breast, and uterus tissue of man and various animals were shown to possess provocative potency for the "SSP-L" in rabbits prepared with *B. proteus* or *B.*

typhus endotoxin. Similarly prepared fractions from spleen gave negative results. Only pancreas, testis and liver extracts were tested for preparatory potency; these were active, at least in some rabbits.

Shwartzman et al. D71,760/50: The "SSP-L" produced by two injections of meningococcal endotoxin in the rabbit is not inhibited by milk nor by rat spleen extract or liver extract.

Good & Thomas B86,937/53: In rabbits prepared by meningococcal endotoxin i.c., the subsequent i.v. administration of glycogen, rabbit liver suspension, or human serum, suffices to elicit an "SSP-L."

Landy & Shear G21,289/57: A great variety of polysaccharides isolated from various animal and plant sources can substitute for bacterial endotoxins when given either as the preparatory or as the provocative injection in conjunction with *S. typhosa* or *S. marcescens* endotoxin in rabbits. Both the "SSP-L" and "SSP-G" can be elicited in this manner by combined treatment with a bacterial endotoxin and a polysaccharide of animal or plant origin. However, the plant polysaccharides do not provoke dermal hemorrhagic necrosis at the site of epinephrine.

Thiers et al. C98,136/60: Report on the extraction from urine of a mucoprotein capable of eliciting the "SSP-L" in the rabbit. [In this brief communication, no details are given (H.S.).]

Ferina & Buccheri E53,256/62: Rabbits received *E. coli* endotoxin alone or mixed with

synovial fluid i.c. at two sites. Following i.v. injection of the same toxin, the site treated with synovial fluid responded with a greatly lessened SSP-L in comparison with the control site. Possibly, the hyaluronic acid or similar compounds in the synovial fluid are responsible for the protection.

Henry G33,285/62: Review on the production of thromboses with various tissue extracts.

Hansson G35,342/65: In cats, perfusion of the kidney with cooled blood, homologous blood (ADP) or crushed connective tissue as well as transient mechanical interruption of the renal blood flow "induced a significant drop in thrombocyte counts and when a complete renal blood flow obstruction ensued, the small renal vessels were occluded by aggregated thrombocytes. This was especially easily demonstrated in the glomerular capillaries." Subsequently, the kidneys became edematous and studded with patchy hemorrhages. Apparently, "the renal vascular bed is especially vulnerable to thrombocyte aggregation in the blood, presumably due to the special characteristics of this vascular circuit."

Solum & Stormorken F56,817/65: In experiments on washed human blood platelets, it was found that thrombin and collagen, unlike ADP and epinephrine, require externally added fibrinogen for the induction of platelet aggregation. The participation of these phenomena in the production of thromboses is discussed.

Snake Venoms. Single i.v. injections of certain snake venoms can produce a THP, whereas pretreatment with such venoms offers a certain degree of immunity against the subsequent production of an SSP by the usual techniques. This protective effect is abolished if the venom is incubated with serum. Allegedly there is even a certain degree of "cross-protection" between the lethal effects of endotoxins and snake venoms. However, some investigators were unable to induce any resistance to the SSP-L or the SSP-G by pretreatment with snake venoms, and the possibility of a contamination of certain venom specimens with endotoxin cannot be easily excluded.

Flexner & Noguchi E76,724/02: If small amounts of rattlesnake venom are placed on the mesentery of the guinea pig or rabbit, the development of stasis and hemorrhage can readily be followed *in vivo*.

Miura & Sumikawa G22,370/02: The venom of *Trimere surus* Hilg. i.v. produces hemorrhagic necroses in various organs with severe hemorrhagic glomerulonephritis. After s.c. injection, this syndrome is associated with a pronounced hemorrhagic infiltration of the injection site.

Peck & Sobotka E75,167/31: Pretreatment

with moccasin venom (*Ancistrodon piscivorus*) induced (following an incubation period of about 14 days) a resistance to the development of an SSP-L by two injections of *E. coli* or *B. typhosus* endotoxin. The refractory state was still present 44 days after the first injection of the venom but no circulating antibodies could be demonstrated. Rattlesnake (*Crotalus atrox*) venom and antivenin had no effect on the course of the SSP-L.

Peck G21,648/33: Copperhead and moccasin venom pretreatment prevents the SSP-L normally produced by two injections of menin-

gococcal toxin in the rabbit. Bothrops and rattlesnake venom are ineffective under these same conditions.

Peck G23,100/34: The SSP-L normally produced by two injections of meningococcal endotoxin is inhibited in rabbits pretreated with moccasin venom. Incubation with normal horse serum abolishes this protective action, but no such inhibition is obtained by moccasin venom neutralized with the corresponding antivenin.

Taube & Essex G27,047/37: Multiple hemorrhages and necroses were observed in the internal organs of dogs given i.v. injections of rattlesnake venom (crotalins). The blood became incoagulable, but no mention is made of thromboses.

Azevedo & Castro Teixeira G26,897/38: In a patient who died 26 days after being bitten by a cobra (Bothrops jararaca), bilateral renal cortical necrosis developed as a consequence of diffuse glomerulonephritis with obliterative arteritis, affecting especially the interlobular, interlobar and arcuate arteries. Glomerular capillary thromboses were not found.

Boquet B18,397/40: On the basis of a very small number of experiments it is assumed that neither the venom of *Vipera aspis* nor the corresponding antivenin can prepare the rabbit skin for the production of an "SSP-L" by *E. coli* endotoxin i.v. These agents are also unable to provoke an SSP-L following cutaneous preparation by *E. coli* endotoxin. On the other hand, the precipitate obtained by mixing *V. aspis* venom with the corresponding antivenin, though ineffective as a preparatory substance, can provoke the response after cutaneous preparation with *E. coli* endotoxin.

Fidler et al. G26,853/40: Rattlesnake (*Crotalus atrox*) venom, given s.c. killed *Macaca mulatta* monkeys on the average after 36 hrs. There was marked hemorrhagic edema at the injection site and in the regional lymph nodes. Occasionally, petechial hemorrhages also occurred in the endocardium, pleura, hepatic capsule and cecum. Many of the vessels contained thrombi, and the exudate surrounding them was rich in erythrocytes. [No mention is made of renal glomerular capillary thrombosis (H.S.).]

Zahl & Hutmacher E41,878/44: Mice, immunized with moccasin (*Agkistrodon piscivorus*) venom, were protected against otherwise lethal doses of *S. typhimurium* endotoxin, and inversely salmonella-immunized mice were protected against the venom. "This cross-protection may be due to the presence in gram-negative organisms and moccasin venom of a common factor characterized by hemorrhagic action, antigenicity, and a lack of serological specificity."

Efrati & Reif G27,025/53: An analysis of sixty-five cases of viper bite in Israel. The prominent manifestations are hemorrhage and edema, not only at the bite site, but throughout the organism. In the acute stage, this is often accompanied by allergic signs (urticaria, Quincke's edema, eosinophilia).

Fulton et al. G26,198/56: Moccasin venom applied to the everted transilluminated cheek of the anesthetized golden hamster (*Mesocricetus auratus*) produces local petechiae whose development can be recorded cinematographically. There is first vasoconstriction with packing of erythrocytes, hemoconcentration, and stasis, whereupon the erythrocytes swell and are "seen spouting through the vessel wall 'one by one,' but without apparent rupture of the endothelium." The response is augmented by pretreatment with total body x-irradiation, diminished by carbazochrome salicylate (adrenosem) and uninfluenced by cortisone.

McCreary & Wurzel E38,554/59: In a man bitten by a rattlesnake (*Crotalus adamanteus*), edema and multiple ecchymoses developed topically within 30 min. The blood became incoagulable and there was afibrinogenemia as a result of the thrombin-like action of the venom. Gastrointestinal bleeding and serum sickness also developed but the patient recovered upon antivenin treatment.

Condie et al. D37,177/62: Snake venom (*Agkistrodon piscivorus*) failed to prepare for or to provoke an "SSP-L" or "SSP-G" in combination with a single injection of *E. coli* endotoxin in rabbits. Attempts to protect the rabbit by snake venom against the SSP-L or SSP-G, produced by two injections of *E. coli* endotoxin, were also unsuccessful.

Spies et al. G33,258/62: In a patient who died from South African treesnake (boomslang) bite "at postmortem examination evidence of haemorrhages could be found in practically every organ, including muscle and brain. Apart from this, the most interesting finding was the presence of fibrin thrombi in the capillaries and larger vessels of several organs, resembling the microscopical appearance of thrombotic thrombocytopenic purpura. Other important findings were an acute tubular necrosis of both kidneys and marked hepatic necrosis of centrilobular type."

Ghitis & Bonelli G33,273/63: Following snake bite (probably by *Bothrops atrox*), incoagulability of the blood with severe fibrinogenopenia developed in a 6-year-old girl in combination with multiple hemorrhages.

McKay E4,788/65: Most of the venomous snakes in North America are pit vipers or Crotalidae which include various rattlers, the

copperhead and the cottonmouth, or water moccasin. "The venom of most rattlesnakes acts as thrombin, converting fibrinogen to fibrin in the absence of other clotting factors. Others (e.g., *Vipera russelli*) have thrombo-plastic activity and convert prothrombin to thrombin. There is damage to vascular endothelium, and fibrinolysis is frequently observed. Hyaluronidase in the venoms facilitates the local spread of the toxins. The phosphatases are responsible for hemolysis. They also alter excitability and conduction in skeletal, smooth, and cardiac muscle. Lysolecithin

is formed from lecithin; it enhances hemolysis and produces hypotension via the release of histamine." Subcutaneous hemorrhages and necrosis may occur topically and the associated general signs include anaphylactoid shock, urticaria, Quincke's edema, hemolysis, a generalized hemorrhagic diathesis, afibrinogenemia, increased fibrinolytic activity, thrombocytopenia, hypothrombinemia and renal failure with disseminated fibrin thrombi in the renal capillary glomeruli. Sometimes, there is bilateral renal cortical necrosis.

Ascaris and Liver Fluke Extract. An "SSP-L" has been produced in the rabbit by two injections of ascaris or liver fluke extract given in the usual manner.

Mu E71,600/34-35: An extract of *Ascaris lumbricoides* given first i.c. and 24 hrs. later i.v., produces an "SSP-L" in the rabbit.

Vanni G22,353/38: If the filtered coelomic fluid of *Parascaris equorum* is injected i.c. and 24 hrs. later i.v. into rabbits, a typical "SSP-L" develops concurrently with visceral hemorrhages. It is assumed that certain symp-

toms of patients with ascaridiosis may be due to the same phenomenon.

Suzuki F35,186/64: An "SSP-L" can be obtained in rabbits by two injections of an extract made from the liver fluke *Clonorchis sinensis*. Detailed review of the Japanese literature on the production of similar lesions with extracts of other parasites.

Yeast Extracts. According to some investigators, yeast extract can act both as a preparatory and as a provocative injection in eliciting an "SSP-L" in the rabbit. Following i.p. injection of yeast extract in guinea pigs, *E. coli* endotoxin i.p. or i.v. produces a hemorrhagic peritonitis.

Zymosan (prepared from yeasts) is ineffective either as a preparatory or as a provocative factor in the production of an "SSP-L" in mice, when *E. coli* is administered as the other agent. Yet, in rats given endotoxin mixed with colloidal silver i.c., subsequent i.p. administration of zymosan induces an SSP-L.

Bock E72,616/32: Yeast extract can act both as the preparatory and as the provocative factor in the production of an "SSP-L" in rabbits which receive *E. coli* endotoxin as the second injection.

Ivánovics G27,772/34: Rabbits prepared by an aqueous yeast extract i.c. responded with a THP-L upon subsequent i.v. injection of Flexner bacillus filtrates.

Bordet B78,032/36: Topical inflammatory reactions obtained by i.p. administration of yeast (*Oidium albicans*) in guinea pigs become hemorrhagic upon i.p. or i.v. injection of *E. coli* cultures or filtrates. The same response is elicited if talcum is used for the production of peritonitis; hence, the sensitization is attributed to inflammation as such.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal

toxin in the rabbit is not inhibited by yeast extract.

Arndt et al. C82,082/59: In BSVS mice, zymosan is ineffective either as the preparatory or as the provoking agent when given in conjunction with a single dose of *E. coli* lipopolysaccharide under conditions on which two doses of the endotoxin are effective.

Kováts et al. D85,430/63: Unlike in guinea pigs, it was not possible to produce an SSP-L by two injections of endotoxin in rats, even after i.v. administration of colloidal silver. This failure was ascribed to the high properdin level of the rat. In support of this assumption, it was found that, if endotoxin mixed with colloidal silver is given i.c. to rats, subsequently receiving zymosan i.p., an "SSP-L" appeared. This was not enhanced by small doses of endotoxin i.v., given 24 hrs. later.

Plant Pollens. If rabbits or guinea pigs are sensitized to plant pollen, the same pollen given i.c. prepares for the production of an "SSP-L" by the subsequent in-

jection of *E. coli* endotoxin i.v. Conversely, *E. coli* endotoxin i.c. followed by the i.v. administration of pollen-antigen—pollen-antibody complex, produces an “SSP-L” at the site of preparation.

Albus & Fischer E63,720/38: In rabbits and guinea pigs sensitized by pretreatment with native plant pollen, the same plant pollen was injected i.c. at one site and *E. coli* endotoxin at another site. Subsequent i.v. provocation with *E. coli* endotoxin produced an “SSP-L” at both sites. In animals not sensitized with pollen but otherwise similarly treated, the pollen injection site did not respond, while the skin pretreated with endotoxin developed a typical SSP-L. Conversely,

E. coli endotoxin i.c. followed by the i.v. injection of pollen-antigen—pollen-antibody complex produced an “SSP-L” at the site of preparation in the guinea pig and rabbit. It is concluded that pollen-antigen—pollen-antibody complexes can act both as preparatory and as provocative stimuli in eliciting the “SSP-L” in conjunction with *E. coli* endotoxin.

Rasulov G28,489/63: An “SSP-L” has been produced in rabbits by two injections of cotton-dust extracts.

NERVOUS STIMULI

(Cf. ALSO NERVE DRUGS)

Several investigators have considered the possibility that some nervous factor may participate in the production of THPs in general, and the SSP in particular.

It will be recalled that the Reilly phenomenon (characterized by hemorrhagic lesions in the mesenteric lymph nodes, Peyer's plaques, and other tissues, often accompanied by renal lesions) has been elicited by the application of microbes, microbial toxins, metals, snake venoms and other irritants, to the splanchnic nerves and ganglia. It was assumed that sympathetic stimulation is largely responsible for these changes. However, the surprising and much quoted observations of Reilly and coworkers, though published 30 years ago, have not yet been adequately confirmed by other laboratories.

The production of an SSP-L in the rabbit kidney, by intrarenal “preparation” with endotoxin, followed 24 hrs. later by the i.v. administration of the same material, is not altered by complete denervation of the prepared kidney. One group of investigators challenged this claim, but they may have obtained protection owing to nonspecific, incidental trauma. The bulk of evidence argues against the assumption that the nerve supply of an organ must be intact in order to elicit a THP in it. Thus, if endotoxin is injected i.c. in both legs of a rabbit, one leg being completely denervated, the subsequent i.v. injection of endotoxin produces an equal SSP-L on both sides. Similar experiments in which both ears were prepared, after unilateral cervical sympathectomy, showed that i.v. provocation produces an even more pronounced SSP-L on the denervated than on the normal side.

If an SSP-G is elicited in a donor rabbit, and its blood is transfused into an unpretreated rabbit, SSP-G-like lesions develop in the latter. This observation likewise suggests that blood-borne humoral substances alone suffice to induce an “SSP-G.”

As outlined elsewhere, diverse forms of THPs can be decisively influenced by mediators and regulators of nervous activity (epinephrine, norepinephrine, adrenergic blocking agents, antihistaminics, antiserotoninins, tranquilizers, etc.); it remains to be seen, however, whether these compounds act on THPs through the nervous system, or through some direct effects of their own.

Loi & Cardia G23,201/34: The production of an SSP-L in the rabbit kidney by intrarenal preparation with typhoid endotoxin, followed 24 hrs. later by the i.v. administration of the same material, is not altered by complete denervation of the kidney (decapsulation and transection of the hilar nerves).

Reilly et al. G27,051/34; G21,897/35: Typhoid, paratyphoid and diphtheria bacilli or their endotoxins directly injected into the mesenteric lymph nodes or in the vicinity of sympathetic nerves (splanchnics, semilunar ganglion, adrenal medulla) in animals, produces changes similar to those of spontaneous typhoid fever in man. There is swelling and hemorrhage in the mesenteric lymph nodes and Peyer's plaques with exulceration of the latter in a great variety of species, including those that are quite insensitive to the same microbial products when administered through other routes. Even intracardiac injection of paratyphoid endotoxin causes intense perineuritis around the splanchnic nerves of the guinea pig owing to the neurotropic effect of this toxin. The response is largely nonspecific, since certain metals (cobalt, nickel, lead, arsenic, as well as nicotine, snake venoms, etc.) applied directly to the splanchnics of the guinea pig, produce similar gastrointestinal hemorrhagic responses. The same is true of mechanical trauma (by ligatures placed around the splanchnics) or prolonged faradic stimulation of these nerves. It is assumed that sympathetic stimulation is largely responsible for the gastrointestinal hemorrhagic syndrome characteristic of typhoid fever and that the close anatomical connections between the mesenteric lymph nodes and the splanchnic nerves accounts for the fact that application of the irritants to either of these structures is effective. [This form of hemorrhagic necrosis has become known as "Reilly's syndrome of neurovegetative irritation" (H.S.).]

Kolpakow E63,708/36: An SSP-L was produced by *E. coli* endotoxin i.v. in rabbits after i.c. preparation in both legs. The response was not inhibited when one leg was completely denervated by severing all structures except the femoral artery and vein. Since the SSP-L was of equal intensity in both legs, the author concludes that the peripheral nervous system is not necessary for its development.

Reilly G27,050/54: Faradic stimulation of the splanchnic nerves produces multiple hemorrhages and thromboses in the gastrointestinal tract, spleen, adrenals and kidneys of the guinea pig. In pregnant animals, retroplacental bleeding occurs. The rabbit, cat, dog and rat are decreasingly sensitive in the order listed. Various poisons, especially certain metals and alkaloids, applied to the sympathetic nervous system produce the same results. This "syn-

drome of neurovegetative irritation" presumably plays an important role in many diseases, especially in hemorrhagic pancreatitis, nephritis, intestinal intussusception, acute dilatation of the stomach, and the "malignant syndrome" that develops in acute hemorrhagic forms of typhoid, influenza, scarlet fever, rubeola, etc. The fact that chlorpromazine is particularly effective in preventing the syndrome of neurovegetative irritation further supports the view that nervous mechanisms play an important part in its pathogenesis.

Fowler C20,165/55: Unilateral cervical sympathectomy increases the intensity of an SSP-L if preparatory injections of *S. typhosa* endotoxin are given in both ears, followed by i.v. provocation with the same agent. Apparently, the SSP-L is subject to Cannon's "law of denervation."

Gamble & Brunson G21,645/55: In donor rabbits a THP-G was elicited by two injections of meningococcal endotoxin or by one injection of meningococcal endotoxin + Liquoid. When their blood was introduced (2-4 hrs. after the last injection) into unprepared recipients by carotid-jugular cross transfusion, a typical "SSP-G" developed in the recipients (except that the renal lesions were somewhat less pronounced than usual). Renal lesions characteristic of the SSP-G were produced with meningococcal endotoxin + Liquoid. Since normally endotoxin is rapidly cleared from the circulation, it is unlikely that residual endotoxin in the blood of the donors could be responsible for the observed changes. "The presence of fibrinoid following transfusion in unprepared recipient animals offers considerable evidence for its transfer by way of the blood stream."

Kesztyüs et al. C12,656/55: The SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit is not influenced by partial denervation (transection of the sciatic nerve with challenge in the corresponding leg skin, denervation of the challenged dorsal skin region).

Vrubel G26,197/58: Rabbits were given i.c. injections of *E. coli* into both hind limbs followed by i.v. injection of the same material. The resulting SSP-L was diminished by unilateral sympathectomy and augmented by transection of the sciatic nerve, as compared with the response on the contralateral limb in which the nerves were left intact.

Palmerio et al. D20,609/62: Unilateral denervation of the renal pedicle partially or completely protected the corresponding kidney against the induction of SSP-G changes by two i.v. injections of *E. coli* endotoxin. It is concluded "that an intact sympathetic nervous system as well as endotoxin from the intestine, are necessary for the production of the generalized Shwartzman reaction."

DRUGS

The following pages summarize the literature on the effect of various drugs upon THPs. In general, the chemicals are listed in alphabetic order, although in some cases compounds with essentially similar actions are grouped together under a class title (e.g., antibiotics, enzymes, nitrogen mustard, nerve drugs, sulfonamides, vitamins). Certain compounds which act through biologic mechanisms that play a particularly important role in regulating the development of THPs are discussed separately in other sections such as *Immune Reactions* (p. 47), the *RES* (p. 58), *Factors Influencing Blood Coagulation* (p. 62), *Hormones and Hormone-like Substances* (p. 71), *Stressors and Physical Agents* (p. 119). Here, in these introductory remarks, we shall comment only on compounds exhibiting particularly noteworthy actions; for additional details the reader is referred to the abstracts that follow.

Agar, which has been widely used recently as an ingredient of pathogenic situations conducive to pluricausal THPs (p. 139), received scant attention in the early literature. Anaphylatoxin, prepared by incubating agar with blood serum, produces a transitory thrombocytopenia but, allegedly, "on no occasion was this accompanied by the production of hemorrhages" in rabbits. After endotoxin i.c., agar i.v. can produce an "SSP-L" while agar i.c. followed by endotoxin i.v. is ineffective. Apparently, agar possesses provocative but no preparatory potency.

Amidopyrine, an antipyretic and antibradykinin agent, is a potent inhibitor of the SSP-L. Here, as in the case of many other "antenergetics" (drugs which inhibit several mechanisms regulating tissue responses to injury) it is difficult to identify the particular action(s) responsible for the protection against the SSP-L.

Several *antibiotics* have been found to be inactive in producing an SSP-L when given either as the preparatory or the provocative agents in combination with an active endotoxin, or when used both for preparation and provocation, without endotoxins. However, in patients suffering from various infections, treatment with antibiotics has repeatedly been observed to produce a THP. Here, sudden liberation of endotoxins from bacteria damaged by the antibiotic may have acted as the provocative agent. We shall have more to say about this in the chapter *Clinical Implications*.

The "SSP-L" which can occasionally be produced in certain strains of mice by a single i.c. injection of endotoxin is largely prevented by terramycin. Allegedly, such responses to single injections may depend on provocation by the natural flora of the intestine which would be eliminated by the antibiotic. The prevention by neomycin p.o. of the THP otherwise produced by repeated Thorotrast injections in the rabbit, and the protection offered by various antibiotics against the THP elicited in pregnant rats by a vitamin-E-deficient diet containing oxidized lipids, has been ascribed to the elimination of endotoxin-producing bacteria.

A single i.p. injection of *colchicine* produces a THP in pregnant but not in nonpregnant hamsters. This effect was attributed to the action of intestinal endotoxin which is allowed parenteral access as a result of colchicine-induced injury to the intestinal mucosa.

A single injection of *cysteine* i.c., given 1 hr. after meningococcal endotoxin i.v. produces a THP-L in the rabbit.

Large molecular *dextrans*, and particularly dextran sulfates, can produce THP-like manifestations in various species (especially when given in combination with endotoxins), perhaps owing to the formation of insoluble complexes with fibrinogen.

Several enzymes appear to play a role in the production of a THP. Hyaluronidase given together with the preparatory injection of endotoxin i.c., increases the diameter of the SSP-L induced by the subsequent i.v. injection of endotoxins. This form of adjuvation has been attributed to the spreading effect of the hyaluronidase which would permit the diffusion of the endotoxin through large areas of skin. Streptokinase, on the other hand, tends to prevent the SSP-G as a consequence of its fibrinolytic action which interferes with persistent fibrin-clot formation.

Various diets rich in *lipids* facilitate the production of thromboses and, under certain circumstances, even of thrombohemorrhagic lesions, especially in pregnant animals and in those kept on vitamin-E-deficient diets. The mechanism of this action has not yet been clarified, but it has been tentatively ascribed to an acceleration of intravascular clotting and also to a blockade of the RES, which would prevent effective fibrin removal from the blood.

Under the general caption of "Nerve Drugs," we shall discuss the literature on the effects of autonomic blocking agents, acetylcholine, atropine, general and local anesthetics, tranquilizers, curare, etc., whose predominant actions are related to the function of the nervous system. The classical SSP-L or SSP-G produced by two injections of endotoxin, is not significantly affected by acetylcholine, cocaine, curare, ether anesthesia, mecholyl, morphine, pendiomid, physostigmine, pilocarpine or procaine; the data concerning the possible inhibitory effect of urethane anesthesia and atropine intoxication are contradictory.

On the other hand, some nerve drugs can decisively influence at least certain types of THPs. Thus, chlorpromazine inhibits the THP-L produced by epinephrine i.c. + endotoxin i.v. Dibenamine blocks the hemorrhagic necrosis produced in murine sarcoma transplants by endotoxin. If given at the proper time it also prevents the classical SSP-L elicited by two injections of endotoxin and the THP-G induced by Thorotrast alone or in combination with hemorrhage. The THP-L produced by epinephrine i.c. and endotoxin i.v. is diminished when dibenamine is added to the epinephrine for topical application. A similar inhibition can be obtained by adding dibenamine to the preparatory i.c. dose of endotoxin in the case of the classic SSP-L. Following pretreatment with ergotamine, the sensitivity of the rabbit to the production of a typical SSP-L is allegedly increased; hence, it was concluded that the adrenergic action of endotoxins cannot play an important role in the production of this phenomenon. On the other hand, such ganglionic blocking agents as hexamethonium, TEAB, and compound SY-28, inhibit the classic SSP-L. Several anesthesia applied both before the preparatory and the provocative injections is equally effective in this respect.

Intradermal injection of in themselves well tolerated doses of epinephrine, nor-epinephrine or *E. coli* endotoxin produce topical necrosis without hemorrhage in rabbits exposed to "rotational shock" in the Noble-Collip drum. This response is diminished by pretreatment with phenothiazine derivatives such as promethazine and promazine.

It remains to be shown whether the nerve drugs which inhibit the THP do so by virtue of their effects upon the nervous system. However, the fact that several of these drugs protect only against THPs produced by certain agents, suggests fundamental differences in the mechanisms through which diverse pathogens produce structurally quite similar thrombohemorrhagic lesions.

The fact that pretreatment with *nitrogen mustard* prevents the classical SSP-L in the rabbit has been well documented. Protection of the prepared skin area by temporary occlusion of its vessels fails to influence this inhibition, but when the lower limbs are similarly protected against nitrogen mustard, the prophylactic effect of the latter is blocked. It has, therefore, been concluded that inhibition of the SSP-L by nitrogen mustard depends upon the bone-marrow damaging action of this drug and, perhaps more particularly, upon the resulting leukopenia. This view appears to have received confirmation from the observation that benzene (which also causes leukopenia) likewise inhibits the SSP-L and that sulfapyridine (which prevents the benzene-induced leukopenia) tends to prevent this protection. Cysteine and inflammation produced by various irritants also inhibit both the leukopenia and the SSP-L-blocking action of nitrogen mustard.

An "SSP-L" is elicited in rabbits sensitized to human serum by endotoxin i.c. followed by i.v. challenge with the same antigen. This THP is likewise inhibited by nitrogen mustard. The same is true of the cutaneous and renal lesions elicited by endotoxins i.v. + Thorotrust i.v., the renal cortical necrosis produced by endotoxin i.v. in cortisone-pretreated rabbits, and several other reactions related to the THP.

On the other hand, the THP-G produced by Liquoid i.v. plus endotoxin i.v., though preventable by heparin, is not inhibited by nitrogen mustard. The hemorrhagic skin necrosis produced in rabbits by mixtures of bacterial toxins and epinephrine, is inhibited by chlorpromazine or cortisone, but not by nitrogen mustard, or heparin. The topical necrosis produced by i.c. injections of epinephrine, norepinephrine or endotoxin in rabbits exposed to "rotational shock" could not be prevented by nitrogen mustard or heparin, although—as just stated—they were at least attenuated by mixtures of promethazine and promazine. All these observations suggest fundamental differences in the mechanisms through which various agents produce THPs.

Ricin has long been known to produce "erythrocyte agglutination thrombi." The compound elicits no THP-L when given first i.c. and then i.v., but if ricin is administered i.c. and then *E. coli* endotoxin is injected i.v., a mild THP-L may develop.

It is generally agreed that sodium *salicylate* can prevent the SSP-L, although this inhibitory effect is not always very obvious.

Silver nitrate s.c. prepares the skin of the guinea pig so that it responds with hemorrhagic necrosis to the subsequent i.c. injection of typhoid endotoxin.

In rabbits prepared by endotoxin i.c., subsequent i.v. injection of *starch* elicits a THP-L, but starch is ineffective as a preparatory agent.

Sulpha drugs, which inhibit the growth of meningococci in vitro, can also prevent the SSP-L elicited by two injections of live meningococci in the rabbit. However, sulpha drugs have no obvious effect upon the SSP-L elicited by endo-

toxins. Curiously, the endotoxin induced hemorrhagic necrosis of transplantable murine sarcomas can be prevented by sulphanilamide p.o.

Following i.p. injection of *talcum*, the i.p. or i.v. administration of *E. coli*, cultures or filtrates, produces hemorrhagic peritonitis in the rabbit. Here, apparently, a nonspecific inflammatory reaction has localized the hemorrhagic effect of the endotoxin.

Theophylline i.v. just prior to the provocative injection prevents the SSP-L in the rabbit, perhaps owing to the vasodilator and antiallergic action of the drug.

Whether *turpentine* can prepare the skin for the subsequent production of a THP-L by the i.v. administration of endotoxin, is debatable.

Uranium salts produce renal glomerular capillary thromboses in rabbits. This change has been considered to be characteristic of the SSP-G, but under the influence of uranium it occurs unassociated with generalized thrombohemorrhagic lesions.

There is no clear-cut evidence that the SSP-L can be inhibited by pretreatment with any of the members of the *vitamin-B* complex. Thiamine, folic acid, para-aminobenzoic acid, biotin, choline, riboflavin, nicotinic acid, pantothenic acid and inositol were all found to be inert in this respect.

Vitamin C likewise fails to prevent the classic SSP-L. However, allegedly, the hemorrhagic necrosis normally produced by endotoxins in transplantable murine neoplasms is prevented by ascorbic acid pretreatment and, when given in combination with desoxycorticosterone, this vitamin is said also to inhibit the classic SSP-L. But both these claims require confirmation.

Vitamin E also fails to prevent the classic SSP-L. However, in pregnant rats the production of an eclampsia-like thrombohemorrhagic syndrome by diets rich in oxidized lipids, is greatly enhanced by concurrent vitamin-E deficiency and can be prevented by vitamin-E supplements (cf. also *Pregnancy*, p. 43).

Vitamin K does not protect against the classic SSP-L, but allegedly, pretreatment with repeated i.v. injections of vitamin K_3 accelerates the healing of SSP-L lesions.

Data concerning the effect of the *vitamin-P* complex are somewhat contradictory, especially regarding hesperidin. Rutin and citrin are ineffective.

Neither distilled water nor hypertonic NaCl i.c. can prepare the skin of the rabbit for the subsequent elicitation of a THP-L by endotoxins i.v. Distilled water also fails to protect against a classic SSP-L.

Acetylcholine. cf. *Nerve-drugs, Choline.*

Acrolein. Soriano G22,363/64: Acrolein i.v. produces hemorrhages in various internal organs of the dog associated with hyaline deposition on the cardiac valves and in the renal glomeruli. The changes are compared to those of the collagenoses.

ADP. Solum & Stormorken F56,817/65: In experiments on washed human blood platelets, it was found that thrombin and collagen, unlike ADP and epinephrine, require externally added fibrinogen for the induction of platelet aggregation. The participation of

these phenomena in the production of thromboses is discussed.

Hansson G35,342/65: In cats, perfusion of the kidney with cooled blood, homologous blood (ADP) or crushed connective tissue as well as transient mechanical interruption of the renal blood flow "induced a significant drop in thrombocyte counts and when a complete renal blood flow obstruction ensued, the small renal vessels were occluded by aggregated thrombocytes. This was especially easily demonstrated in the glomerular capillaries." Subsequently, the kidneys became edematous

and studded with patchy hemorrhages. Apparently, "the renal vascular bed is especially vulnerable to thrombocyte aggregation in the blood, presumably due to the special characteristics of this vascular circuit."

Nordøy & Rørvik F56,815/65: After a review of the literature on the probable role of stress and epinephrine in the production of thrombo-embolic disorders, the authors describe observations showing that in heparinized platelet-rich plasma aggregation, adhesion of platelets occurs upon incubation with epinephrine. "In plasma from rats given adrenaline in oil to induce a state of 'adrenaline stress,' a higher total platelet count was found than in control animals." Intravenous injection of an LD₅₀ of ADP elicits pulmonary platelet thrombi in control rats while in "adrenaline-stressed" animals, the mortality is reduced and platelet thrombi are absent.

Adenosine-5-phosphoric Acid. *Shwartzman et al. D71,760/50:* The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by adenosine-5-phosphoric acid.

Agar. *Bedson G21,641/22:* The anaphylatoxin of "agar-serum" (agar incubated with serum) i.v., causes a transitory fall in blood platelets in the rabbit, but "on no occasion was this accompanied by the production of haemorrhages."

Sickles B78,436/31: "SSP-L" may be elicited in the rabbit by meningococcal toxin i.c. followed by agar i.v. Local reactions did not occur at the site of i.c. agar injections followed by the bacterial toxin i.v. Galactose, gelatin, serum or India ink i.v., following meningococcal toxin i.c., failed to elicit the SSP-L.

Shwartzman G23,070/32: In rabbits prepared by *B. typhosus* endotoxin i.c., agar suspensions i.v. produce an "SSP-L." However, agar has no skin-preparatory potency demonstrable in rabbits subsequently challenged by *B. typhosus* endotoxin i.v.

Sickles D36,865/33: An SSP-L can be elicited in the rabbit by meningococcal endotoxin i.c. followed 18 hrs. later by 0.2% agar i.v.

Gentile G26,188/34: After preparation with typhoid endotoxin i.c., agar i.v. suffices to produce an SSP-L in the rabbit, presumably because "the colloidal equilibrium of the blood" is disturbed.

Capri G28,863/52: Following preparation of the skin with "leukotaxin" (extracted according to Menkin's technique from turpentine-induced pleural exudate of dogs), agar i.v. induces an SSP-L in the rabbit.

Alypin. *Shwartzman et al. D71,760/50:* The SSP-L produced by two injections of menin-

goccal toxin in the rabbit is not inhibited by alypin.

Amidopyrine. *Antopol & Chryssanthou D56,730/63:* Amidopyrine inhibits the SSP-L produced in the usual manner by two injections of *Proteus vulgaris* lipopolysaccharide. At the same time, the potentiation of the Thomas reaction by bradykinin is inhibited by amidopyrine. Curiously, acetylsalicylic acid and salicyl are ineffective in these respects.

Antopol & Chryssanthou D18,742/64: The SSP-L produced by two injections of *proteus vulgaris* endotoxin in the rabbit is inhibited by antibradykinin and antiserotonin compounds such as: 1. amidopyrine (Pyramidon, Merck), 2. PPBP 1-(N-methyl-piperidyl-4)-3-phenyl-4-benzyl-4-pyrazolone-5 (KB-95, Sandoz) and 3. MAPTC 2'-(3-dimethylamino-propylthio)cinnamanilide HCl (Squibb), injected s.c. at a distance from the site of preparation. Amidopyrine and MAPTC given i.c. into the prepared skin area causes no topical inhibition, while PPBP, thus administered, is effective. Amidopyrine is a bradykinin antagonist while PPBP and MAPTC are antiserotonins. Since the best inhibition of the SSP-L was obtained by systemic treatment with MAPTC and amidopyrine in combination "it is postulated that the classical Shwartzman phenomenon involves several tissue responses mediated by multiple agents, including bradykinin and serotonin, which are sequentially or simultaneously released in a chain reaction initiated by endotoxin."

Amino Acids. *Shwartzman et al. D71,760/50:* The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by various amino acids.

N-Amylamine. *Waters & DeSuto-Nagy B64,578/49-50:* Essentially identical arteriolar necroses with hemorrhages are produced in dogs by i.v. injections of large doses of epinephrine, N-amylamine, citrated compatible canine blood or epinephrine + large amounts of canine blood. Similar lesions are obtained by treatment of nephrectomized dogs with pressor renal extracts. The epinephrine-induced lesions can be prevented by dibenamine.

Antibiotics. *Becker B28,260/48:* Crude penicillin extract, penicillin G and streptomycin fail to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Boelter & Hatoff G23,052/49: A 10-year-old girl was given several injections of penicillin in oil into the buttocks. The subsequent administration of regular penicillin i.m. at another site elicited urticarial wheals surrounding the puncture sites of previous penicillin-

in-oil injections. The phenomenon was ascribed to an SSP-L.

Kerby & Muller G21,649/50: No SSP-L could be elicited in rabbits given a single injection of meningococcal endotoxin either for preparation or for provocation when various antibiotics (penicillin, dihydrostreptomycin, aureomycin, chloramphenicol, or terramycin) were employed for the other injection. Two injections of the same antibiotic, given in the usual manner, likewise failed to elicit the SSP-L. It is concluded that antibiotics contain no "Shwartzman activity," although SSP-like phenomena have been observed in patients suffering from infectious diseases as a consequence of antibiotic therapy. [The authors fail to consider the possibility that, in patients, antibiotics may have acted by liberating bacterial endotoxins from destroyed bacteria (H.S.).]

Rubens G23,062/51: In a baby who had received procaine penicillin into the buttocks 6 weeks earlier for an upper respiratory infection, reinjection with the same preparation into the right buttock produced a large local hemorrhagic necrosis. "Arthus phenomenon, Shwartzman phenomenon, and embolia cutis medicamentosa are discussed as possible diagnoses."

Nelson & Braslow G21,650/53: In a 5½-month-old child who received chloramphenicol treatment for rubeola, fatal thrombohemorrhagic cutaneous and internal lesions developed which were interpreted as an SSP.

Arndt & Schneider D9,369/58: The "SSP-L," which can occasionally be elicited in certain strains of mice by a single i.c. injection of *E. coli* endotoxin, is largely prevented by terramycin. This finding appears to confirm "the hypothesis that the 'natural' flora in the animals was related, in some way, to the observed variability." The effect of terramycin diminished on continued therapy, suggesting that the endogenous microbial agent develops some resistance on continued exposure to the antibiotic.

Fine et al. D98,173/59: The "SSP-G" produced by two doses of Thorotrast in the rabbit can be prevented by 4 days' pretreatment with neomycin p.o. Polymyxin exerts a similar effect. Since the latter "given by gavage is nonabsorbable, it can only elicit the lesions described in the Thorotrast-pretreated animal when so given in virtue of its bactericidal effect on the Gram-negative organisms within the gastrointestinal tract."

McKay D15,443/62: In pregnant rats, feeding of a vitamin-E-deficient diet containing oxidized lipids induces the "SSP-G" in association with fibrin thrombi in the placenta, placatitis and fetal death. Oral administra-

tion of antibiotics reduces the incidence of this disease.

Marie et al. G20,767/64: Intraligual injection of benzathine-penicillin produced intense local hemorrhagic necrosis "accounted for either by a sensitization phenomenon related to Arthus' or Shwartzman's phenomenon or by a mechanical accident of intra-arterial injection."

Antibradykinin, Antihistamine, anti-5-HT. cf. Hormones and hormone-like substances.

Arsenic. **Miessner G26,891/11:** Acid solutions of Salvarsan can produce hemorrhagic lung edema with multiple thromboses in the pulmonary arteries of cattle and man. The thrombi consist of protein and Salvarsan.

Amantea 43,781/33: In rabbits deprived of their complement by hirudin or arsenobenzol, an SSP-L can still be produced by bacterial endotoxins; hence, the response differs from anaphylaxis.

Sézary et al. G28,163/35: In guinea pigs given novarsenobenzol i.c., a second injection of the same material i.v. 12 days later, elicits a hemorrhagic response at the prepared skin site which is considered to be "a Shwartzman reaction."

Renaux & Alechinsky G18,585/36: If a preparatory i.v. injection of *E. coli* endotoxin is followed by daily i.v. injections of neosalvarsan, a provocative i.v. injection of *E. coli* endotoxin, given on the fourth day, produces cutaneous purpura and internal lesions characteristic of the SSP-G. It is concluded that neosalvarsan prolongs the critical period and so alters the response that both cutaneous and internal hemorrhages occur.

Pierret G23,060/42: The SSP-L normally elicited by two injections of *E. coli* endotoxin is inhibited by the i.p. administration of 100 ml of 2 arsenical mineral waters (Choussy-Perrière and Croizat). [It is not evident why the author chose the i.p. route for the testing of mineral waters; in any event, the number of experiments performed was hardly sufficient to give statistically significant results (H.S.).]

Atropine. cf. Nerve-drugs.

BAL. **Becker B28,260/48:** BAL fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Thomas & Stetson D70,785/49: An "SSP-L" can be produced in the rabbit by papain, cysteine or BAL i.c., given 1 hr. after meningococcal toxin i.v.

Hasselmann et al. G22,335/51: In guinea pigs given repeated i.m. injections of BAL, subsequent infections with various bacteria produce thrombohemorrhagic necroses at the BAL injection sites. Similar observations have been

made in pigs and man treated with BAL for various infections. The phenomenon is ascribed to the SSP. Repeated daily i.m. injections of BAL followed by mild crushing of the testis produce topical necroses at the injection sites and extensive testicular hemorrhages which are ascribed to the SSP.

Benadryl. cf. Nerve-drugs.

Benzene. Becker B28,260/48: Benzene prevents the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Thomas & Stetson B28,612/48: The production of an SSP-L by two injections of *E. coli*, *S. marcescens* or meningococcal toxin in the rabbit can be prevented by a single application of bromobenzene to the surface of the prepared skin areas at any time during the 20 hrs. after the i.c. injection of endotoxin. Similar results were obtained with chlorobenzene, iodobenzene and benzene. Chloroform and methyl salicylate gave less constant results. Possibly, increased capillary permeability may have resulted either in the entrance of an inhibitory substance from the blood into the prepared area or the exit of a damaging substance from the prepared skin. However, Evans Blue i.v. was shown to appear at the site of a single application of bromobenzene to normal skin but not at that prepared by endotoxin.

Stetson & Good C69,100/51: Pretreatment with either nitrogen mustard or benzene causes leukopenia and inhibits the SSP-L normally produced by two injections of meningococcal toxin. Sulfapyridine, which prevents the benzene-induced leukopenia, also tends to prevent its protective effect against the SSP-L. Leukocytic infiltration of the injection site is the most evident morphologic expression of local "preparation." It is assumed "that polymorphonuclear leucocytes play an essential role in the preparation of the skin for the Shwartzman phenomenon."

Bradykinin. cf. Hormones and hormone-like substances.

Caffeine. Štork & Kovaříková C11,611/54: Caffeine failed to prevent the SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit.

Calcium. Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by calcium chloride or gluconate.

Carageenin. Morard et al. F9,622/64: Carageenin i.v. produces renal cortical necrosis with fibrin thrombi in the glomerular capillaries of rabbits, rats and guinea pigs. At the same time, there is hemoglobinuria and a decrease in serum complement.

Casein. Shwartzman et al. D71,760/50: The

SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by casein hydrolysate.

Cevanol, Chloral Hydrate, Chlorpromazine. cf. Nerve-drugs.

Choline. cf. also Acetylcholine. Moore D34, 394/62: Renal cortical necrosis with thrombosis in the glomerular capillaries and intrauterine hemorrhage with fetal death were observed in late-pregnant rats given progesterone and kept on a certain choline-deficient diet. However, choline itself does not appear to be the decisive factor since supplements of it did not prevent these changes. Still, some dietary factor was important as no such lesions were observed in similarly treated pregnant rats kept on ordinary rat meal.

Citrin. Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by citrin.

Cocaine. cf. Nerve-drugs (Procain).

Colchicine. Galton D58,259/63; F53,009/65: A single i.p. injection of colchicine or *E. coli* endotoxin regularly elicits the "SSP-G" in the pregnant, but not in the nonpregnant hamster. "The superiority of colchicine, as opposed to foreign endotoxin, in the pregnant subject, may be attributed to the action of native endotoxin which is allowed parenteral access as a result of colchicine-induced injury to the intestinal mucosa."

Galton G9,002/64: In pregnant hamsters, colchicine produces a typical THP-G with characteristic renal glomerular lesions, while vincleukoblastine (another stathmokinetic drug) and *E. coli* endotoxin are inactive in this respect. Devitalization of intestinal segments is efficacious perhaps owing to the absorption of some special endotoxin from the intestinal flora. [Other stressors have not been tested (H.S.).]

Innerfield et al. G27,038/64: A single i.p. injection of colchicine produces a THP-G with renal capillary thromboses in the pregnant golden hamster. This response is inhibited by the oral administration of streptokinase.

McKay E4,788/65: Earlier observations showed that colchicine can produce an "SSP-G" in pregnant, but not in nonpregnant, golden hamsters. "In all the experiments on pregnant animals, whether the reaction is induced by endotoxin, dietary oxidized lipid, progesterone, or colchicine, the systemic thrombosis is a consequence of damage to the placental trophoblast. Placental damage is analogous to the 'provoking' injection of endotoxin in the classic Shwartzman reaction."

Galton F51,263/65: During the THP-G elic-

ited by colchicine in the pregnant hamster, India ink i.v. is trapped by some amorphous deposit in the glomerular capillaries.

Copper. *Marginesu G21,460/34:* Preparation of the skin with copper acetate followed by *E. coli* endotoxin i.v. results in no "SSP-L" in the rabbit.

Curare. cf. Nerve-drugs.

Cysteine. *Thomas & Stetson D70,785/49:* An "SSP-L" can be produced in the rabbit by papain, cysteine or BAL i.c., given 1 hr. after meningococcal toxin i.v.

Bennett & Cluff B90,942/52: Nitrogen mustard inhibits the SSP-L produced by two injections of *S. marcescens* endotoxin in the rabbit and concurrently produces leukopenia. This protective effect is abolished by cysteine, which also prevents the leukopenia, but not by Thorotrust.

Jókay et al. G28,485/64: Earlier experiments had shown that in vitro cysteine prevents platelet aggregation as well as the release of histamine and 5-HT which normally occur under the influence of endotoxin in rabbit blood. It is now found that, in rabbits prepared for the SSP-L, simultaneous administration of the provoking dose of *E. coli* endotoxin and cysteine i.v. inhibits thrombopenia and enhances leukopenia. At the same time, the resulting SSP-L is aggravated. It is concluded that, in the production of an SSP, platelet aggregation is less important than leukopenia.

Dextran. *Bennett G21,297/52:* Following *S. marcescens* endotoxin i.c., the i.v. administration of very high molecular native dextran produces an "SSP-L" in the rabbit while clinically used dextrans (molecular weight about 75,000) are ineffective. Native dextran is not effective as a skin preparatory treatment when followed by the i.v. injection of bacterial toxin. The skin reaction elicited by provocation with native dextran resembles that seen after injection of starch or glycogen in its early appearance and in the lack of systemic manifestations of intoxication.

Walton G21,527/54: Large molecular dextran sulfates produce a THP in the mouse, rat, and rabbit, especially when given i.v., although, to a lesser extent, s.c., i.m., and i.p. administration is also effective. The phenomenon is ascribed to the formation of insoluble complexes with fibrinogen and the subsequent agglutination of formed blood elements. Thus thrombi arise which eventually assume a hyaline appearance. Earlier publications are quoted which show that other macromolecular materials have a similar effect. Small molecular dextran sulfates are ineffective.

Brunson et al. C14,440/55: An "SSP-G" can

be elicited in the rabbit by polyvinyl alcohol polysulfonic acid ester (PVAS) or dextran sulfate followed by meningococcal endotoxin i.v. Less pronounced changes are obtained by PVAS or dextran given alone.

Hestrin & Davies C23,684/56: The native levan of *Aerobacter levanicum*, given i.c. and then i.v., produces a typical SSP-L in the rabbit. The response is inhibited if native levan or native dextran is given i.v. just before the preparatory i.c. dose of toxin. Since i.v. injection of the levan or dextran produced leukopenia "the leucopenogenic activities of polymers and their ability to depress diapedesis and block skin preparation in the Shwartzman reaction are seen to be correlated properties. The findings support the view that induction of skin reactivity in the Shwartzman phenomenon requires infiltration of the prospective site by leucocytes during the phase of skin preparation."

Graber et al. C85,671/60: *S. marcescens* endotoxin i.v., followed by dextran i.v., produced an SSP-G in one rabbit.

Patterson et al. F50,894/65: In an eleven-year-old boy with Purpura fulminans (thought to be possibly related to the SSP-G), dextran i.v. resulted in a remarkable recovery, after antibiotics, corticoids and heparin were shown to be ineffective.

Dibenamine. cf. Nerve-drugs.

Egg albumen. *Shwartzman E53,222/30:* It is not possible to produce an SSP-L in the rabbit by two injections of crystalline egg albumen or of horse serum given in the classical manner.

Thomas C27,073/56: Extensive dermal hemorrhagic necrosis is produced in rabbits by the i.c. injection of as little as 5 µg of epinephrine or norepinephrine, followed within 4 hrs. by 1 µg of various endotoxins. The response is apparently specific for endotoxins, since many agents including ovalbumen i.v. did not provoke hemorrhagic reactions at the sites of dermal epinephrine injections.

Ellagic acid. *Botti & Ratnoff G8,815/64:* In dogs, ellagic acid (4,4',5,5',6,6'-hexahydroxydiphenic-2,6,2',6'-dilactone) i.v., produces a striking decrease in clotting time, presumably due to activation of the Hageman-factor. However, thrombosis only occurs when complete stasis of the circulation is induced (e.g., by clamping off a segment of the jugular vein). "That an alteration in coagulability can create a predisposition to thrombosis cannot as yet be substantiated in clinical conditions." In any event, ellagic acid produced no hemorrhage, and hence, here we cannot speak of a THP.

HYALURONIDASE

Enzymes. *Bier G26,883/32; G23,084/33:* Addition of testicular hyaluronidase to the i.c. dose of typhoid endotoxin accelerates and enlarges the SSP-L resulting from the subsequent i.v. provocation with typhoid endotoxin in the rabbit.

Cassuto G27,041/33: Pretreatment of a skin area with testicular hyaluronidase can prevent the subsequent production of an SSP-L by typhoid endotoxin in the rabbit. This may be due to excessive dilution by diffusion of the endotoxin.

Duran-Reynals 15,445/33: The cutaneous lesions of an SSP-L produced by two injections of *E. coli* endotoxin are greatly spread, but decreased in intensity, when a hyaluronidase containing testicular extract is mixed with the toxin used for cutaneous preparation.

STREPTOKINASE

Condie et al. G21,646/57: The production of an SSP-L or SSP-G by two injections of endotoxin (kind not stated) in rabbits is reversed when streptokinase is given i.v. 4 hrs. following the second i.v. injection at a time when fibrin deposition has already begun. Streptokinase produces immediate fibrinolysis and presumably reverses fibrinoid formation as a consequence of this action, thereby also preventing hemorrhagic necrosis.

Kliman & McKay E53,773/58; G21,280/58: The bilateral renal cortical necrosis and glomerular thrombosis, normally elicited by two i.v. injections of Shear's polysaccharide, were prevented by streptokinase given 30 min. after the second endotoxin injection. However, there was no reduction in the number of thrombi in the lungs, liver and spleen. In the latter organs, however, thrombi appeared after a single injection of endotoxin, and when streptokinase was given 30 min. after the preparatory injection, thrombosis was prevented in the extrarenal tissues as well. "These findings suggest that 1) fibrinolysis prevents the glomerular thrombosis and bilateral renal cortical necrosis of the Shwartzman reaction; 2) fibrinolytic activity greatly reduces the number of thrombi in liver and lungs when streptokinase is given with the first injection; 3) fibrinolysis does not destroy thrombi when they have been present for 24 hrs.; and 4) in order for fibrinolysis to destroy these thrombi, it must be present when they are forming."

Lasch et al. E64,434/61: If, in the course of an SSP-G produced by two i.v. injections of bacterial toxin (kind not stated) in the rabbit, streptokinase is administered, the animals survive a normally fatal response, presumably be-

cause of the lysis of microthrombi. However, the mean values for prothrombin factor V, factor VII and blood platelets are not altered by the streptokinase-induced fibrinolysis.

Innerfield et al. G27,038/64: A single i.p. injection of colchicine produces a THP-G with renal capillary thromboses in the pregnant golden hamster. This response is inhibited by the oral administration of streptokinase.

Rodriguez-Erdmann G31,454/64: Streptokinase i.v. given 4 hrs. after the provocative injection of *E. coli* endotoxin to rabbits, prevents the usual renal cortical necrosis of the SSP-G, presumably as a result of induced fibrinolysis; yet the factor V level of the plasma decreases abruptly. By inference "the presence of intravascular thrombin 4 hours after the second endotoxin injection" is postulated.

TRYPSIN, FIBRINOLYSIN

Fulton & Page E87,006/48: Soybean trypsin inhibitor i.v. or i.m. protects the mouse against the lethal effect of human placental thromboplastin i.v.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by trypsin.

Lawrence et al. G26,851/52: A suspension of the transplantable V_2 rabbit carcinoma i.v. causes thrombosis in the right side of the heart and in the pulmonary vessels owing to the thromboplastic property of the neoplasm. Heparin, dicoumarol, and soybean trypsin inhibitor protect against this effect, while Benadryl is ineffective.

Antopol & Chryssanthou E43,251/60: The addition of trypsin to the preparatory i.c. inoculum augments the SSP-L produced by two injections of *E. coli* or *P. vulgaris* endotoxin in the rabbit. Trypsin is used in the preparation of many plant and bacterial products employed for the production of the SSP-L; hence the augmenting effect of the enzyme must be taken into consideration since the final products could contain residual trypsin.

Chryssanthou & Antopol E43,280/61: The SSP-L normally produced by two injections of *E. coli* endotoxin in the rabbit is diminished or prevented by various trypsin inhibitors (pancreatic, soybean) given i.v. at the time of the provocative endotoxin injection. The inhibitors are not effective when given i.c. mixed with the endotoxin or i.v. at the time of preparation. The SSP-G can also be prevented by trypsin inhibitors i.v. at the time of provocation.

D'Amico G27,449/64: The SSP-L normally elicited by two injections of paratyphoid-B

endotoxin in the rabbit can be prevented by combined administration of trypsin and chymotrypsin i.m. This inhibition is manifest if treatment with high doses is begun three days prior to the preparatory endotoxin injection, but not if given 1 hr. before the provocative injection.

Beller & Mitchell G27,060/65: An "SSP-G" is produced in rabbits by the simultaneous i.v. infusion of thrombin and EACA or other protease inhibitors (e.g., Trasylol, soya bean trypsin inhibitor, lima bean trypsin inhibitor and ovomucoid). The response disappears after the injection of streptokinase, suggesting that the intravascular deposits are fibrin which can undergo lysis.

McKay E4,788/65: A review of the literature shows that several authors have succeeded in producing disseminated intravascular coagulation, hemorrhage and alterations in blood coagulation factors by the i.v. administration of trypsin in experimental animals. Whether minute coagula will form in the microcirculation or large clots in the heart, depends largely on the speed of injection. Crystalline trypsin has been given i.v. in man to rid large veins of occlusive thrombi. Occasionally, it has produced thrombosis in the vein into which it was injected and secondary embolism. Trypsin converts prothrombin to thrombin and the latter causes agglutination of platelets with a release of their contents into the plasma.

Niesert & Schneider F32,779/65: Trasylol (Bayer 3380-RK), a trypsin and kallikrein inhibitor, partially inhibits the SSP-G normally produced by two i.v. injections of *S. abortus equi* endotoxin.

Cavanagh & Albores G31,619/65: Even single i.v. injections of *E. coli* endotoxin can produce hyaline thromboses of the renal glomerular capillaries in the rabbit. Fibrinolysin largely protects against such changes.

Haustein & Markwardt G33,841/65: The THP-L elicited by two injections of *E. coli* endotoxin in the rabbit can be prevented by the thrombin inhibitor hirudin, but not by p-aminomethylbenzoic acid (PAMBA) nor by the trypsin, kallikrein and plasmin inhibitor Contrykal.

Ergot, Ether. cf. Nerve-drugs.

Ferric Oxsaccharate (Fe-OS). *Thomas C27,073/56:* Extensive dermal hemorrhagic necrosis is produced in rabbits by the i.c. injection of as little as 5 µg of epinephrine or norepinephrine, followed within 4 hrs. by 1 µg of various endotoxins. The response is apparently specific for endotoxins, since various agents including ferric oxsaccharide i.v. did not pro-

voke hemorrhagic reactions at the sites of dermal epinephrine injections.

Ferritin. *Thomas C27,073/56:* In rabbits given i.v. injections of *E. coli* endotoxin, administration of epinephrine, vasopressin, histamine, 5-HT and ferritin (unlike epinephrine, and norepinephrine) i.c. produces no hemorrhages at the dermal injection sites.

Formic Acid. *Gentile G26,188/34:* Preparation of the skin with simple inflammatory irritants such as formic acid or turpentine, does not permit the production of an "SSP-L" in rabbits subsequently treated with typhoid filtrate i.v.

Galactose. *Sickles B78,436/31:* Galactose i.v., following meningococcal toxin i.c., failed to elicit the "SSP-L" in the rabbit.

Gelatin. *Sickles B78,436/31:* SSP-L may be elicited in the rabbit by intracutaneous injection of meningococcal toxin followed by agar i.v. Local reactions did not occur at the site of intracutaneous agar injections followed by the bacterial toxin i.v. Gelatin i.v., following meningococcal toxin i.c., failed to elicit the "SSP-L" in rabbits.

Glucose. *Shwartzman et al. D71,760/50:* The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by glucose.

Szilágyi et al. E23,139/63: The SSP-L elicited by two injections of *E. coli* endotoxin in rabbits, is markedly inhibited by alloxan and glucose but augmented by insulin. "A disturbance of carbohydrate metabolism is assumed to play a role in the mechanism of the Shwartzman reaction."

Glutathione. *Nitta F47,755/65:* After an SSP-L (produced by two injections of *Pseudomonas aeruginosa*) begins to heal in the rabbit, the topical injection of reduced glutathione reactivates the lesions. Other inflammatory responses can be similarly reactivated presumably because of the action of reduced glutathione upon proteolytic enzymes.

Glycogen. *Glick & Antopol G22,256/39:* "Glycogen and kerasin were found to have no ability to prepare skin sites, though they could elicit reactions when used intravenously in rabbits prepared with active *B. proteus* extracts."

Bier & Amaral G22,098/44-45: An "SSP-L" is produced in the rabbit by meningococcus endotoxin i.c. and glycogen i.v. The provocative potency of glycogen is tentatively ascribed to its thrombocytopenic action.

Glycyrrhizin. *Fukui et al. G33,120/64:* The "reversed Shwartzman phenomenon" obtained in rabbits by i.v. preparation followed by i.c.

provocation with *E. coli* endotoxin can be inhibited by glycyrrhizin.

Guaiacol. Benoit G19,676/28: Single s.c. injections of guaiacol produce severe renal tubular lesions with hyalinization of glomerular capillaries in the rabbit.

Guanethidine. Stamler D4,281/61: The eclampsia-like THP-G elicited by progesterone overdosage in late pregnant rats is not inhibited by guanethidine.

Hematin. Anderson et al. E83,338/42: In dogs, hematin (ferrihemate) i.v. causes vascular congestion, hemorrhages and thromboses in the heart, liver, kidney, meninges, brain and other organs. The renal glomerular capillaries are engorged and often contain hyaline thrombi. The RES stores hematin, which is apparently difficult to metabolize. The changes resemble those of malaria and blackwater fever.

McKay E4,788/65: A review of the literature suggests that the intravascular coagulation seen in malaria may be due to the formation of malarial pigment which is similar to hematin, since hematin i.v. elicits similar changes in rabbits.

Hexamethonium. cf. Nerve-drugs.

Hydralazin. Stamler D4,281/61: The eclampsia-like THP-G elicited by progesterone overdosage in late-pregnant rats is not inhibited by hydralazin.

5-HT, Histamine. cf. Hormones and hormone-like substances.

Kerasin. Glick & Antopol G22,256/39: Glycogen and kerasin were found to have no ability to prepare skin sites, though they could elicit reactions when used intravenously in rabbits prepared with active *B. proteus* extracts."

Laminarin. Adams & Thorpe D70,175/57: Laminarin is a polysaccharide obtained from *Laminaria cloustoni* frond. Laminarin sulfate i.v., given repeatedly to rabbits, produces fibrin thrombi in the renal glomerular capillaries, the pulmonary arteries and, occasionally, the portal veins.

Levan. Hestrin & Davies C23,684/56: The native levan of *Aerobacter levanicum*, given i.c. and then i.v., produces a typical "SSP-L" in the rabbit. The response is inhibited if native levan or native dextran is given i.v. just before the preparatory i.c. dose of toxin. Since i.v. injection of the levan or dextran produces leukopenia "the leucopenogenic activities of polymers and their ability to depress diapedesis and block skin preparation in the Shwartzman reaction are seen to be correlated properties. The findings support the view that induction of skin reactivity in the Shwartz-

man phenomenon requires infiltration of the prospective site by leucocytes during the phase of skin preparation."

Lipids. cf. also Pregnancy, vitamin-E deficiency and choline (a lipotropic factor). Moore G28,864/57: In male weanling rats maintained on a choline-deficient diet, severe renal lesions develop which include cortical necrosis, hemorrhages and fibrin thrombi in arterioles and glomerular capillaries. [Although such capillary thrombi are allegedly pathognomonic of the SSP, the author does not mention the possibility of a relationship to the latter (H.S.).]

Hartroft et al. G24,616/59: Coronary arterial thrombosis with infarct formation has been obtained in rats by various diets containing supplements of fats, cholesterol and thiouracil. [In this case we cannot speak of a THP since the thromboses were not associated with noteworthy hemorrhages (H.S.).]

Berken & Wolman D85,445/62: After pre-treatment with ethyl stearate i.v., a single dose of *E. coli* endotoxin suffices to produce an "SSP-G" in the rabbit.

Connor D28,719/62: Long-chain, saturated fatty acids greatly accelerate thrombus formation in an *in vitro* system "that perhaps the negatively charged micelle found in sodium salt solutions of long-chain, saturated fatty acids activated the Hageman factor."

Connor et al. G6,603/62: Infusion of long-chain, saturated fatty acids i.v. in dogs, followed by clamping of a jugular-vein segment produces massive jugular-vein thrombosis. Since these were unaccompanied by hemorrhages, their possible relationship to the THP cannot be ascertained.

Connor et al. D68,280/63: "Long-chain, saturated fatty acids produced extensive thrombosis and death when given intravenously to dogs. Thrombi were found in the veins and chambers of the heart and occasionally in the peripheral arteries." This form of thrombosis is tentatively ascribed to an activation of the Hageman factor. Similar infusion of unsaturated fatty acids and of saturated fatty acids, having a chain length of Cl2 or less, caused no massive thrombosis but did induce some hypercoagulability as indicated by the formation of thrombi in isolated jugular vein segments.

Renaud & Allard D35,261/62: In rats kept for one year on diets rich in butter, cholesterol and cholic acid, there developed a syndrome characterized by multiple thrombi (presumed to consist of platelets) which were located mainly in the arterioles and capillaries of the heart, but occasionally also in other organs. They "presented a histological picture that

resembled thrombotic thrombocytopenic purpura rather than coronary disease." Just before death, there developed anemia and thrombocytopenia; however, "ecchymoses were not seen in the thrombotic animals."

Renaud G23,270/62: Rats kept for several months on a high-fat diet containing supplements of cholic acid, develop multiple platelet and fibrin thrombi often located in aneurysmic dilatations in the heart, kidneys, lungs and adrenals. Only small vessels are affected but, occasionally, minute cardiac infarcts occur. The syndrome is associated with icterus, hemolytic anemia and thrombocytopenia. Although only minute petechiae are seen in the lungs and heart, the condition is thought to resemble thrombotic thrombocytopenic purpura.

Renaud G31,776/63; G31,557/65: In rats kept on a high-fat diet containing 2% cholic acid and 11% casein as the sole source of protein, a high incidence of massive red infarcts with platelet thrombi in the hepatic veins can be obtained by single i.v. injections of *Proteus mirabilis* or *E. coli* endotoxins. Occasionally, similar thrombi were also found in the lungs, kidneys, spleen, pancreas and cardiac cavities. However, renal glomerular thromboses were not observed.

Day & Soloff G117/63: The sodium salts of oleic, linolenic, palmitic and stearic acids were infused into the femoral veins of dogs. "The saturated fatty acids were associated with a mortality of 33% with thrombosis in almost all cases. Associated was shortening of the recalcification time, SPT, stypven, and silicone clotting times."

Hoak F19,284/64: I.v. injection of sodium stearate produced massive general thrombosis and death in mice. Electron-microscope showed that the thrombi contain large aggregates of platelets, many of which have lost their granules. Hemorrhagic lung edema and congestion of the liver and kidneys were common.

Huth et al. G33,036/64: Even the first i.v. injection of endotoxin (kind not stated) produces a pronounced increase in the blood level of total fats, blood lipoproteins, cholesterol and, to a lesser extent, phospholipids. The simultaneous decrease in α -lipoproteins results in a considerable augmentation of the β - α -lipoprotein quotient which exhibits a further pronounced increase following the provocative i.v. injection. Administration of essential phospholipids (EPL) increases the survival rate and prevents the accentuated response of the blood-clotting factors to the second i.v. injection of endotoxin. An important causal role in the development of the coagulation defect

of the SSP-G is ascribed to changes in blood lipids.

Müller-Berghaus et al. D13,794/64: An SSP-G elicited by two i.v. injections of *E. coli* lipopolysaccharide in the rabbit results in a rise in blood lipids, particularly cholesterol, β -lipoproteins and cholesterol/phospholipid ratio. Administration of "essential" phospholipids at the proper time restores the cholesterol/phospholipid ratio to normal and renders the second dose of endotoxin ineffective in eliciting the SSP-G. The authors believe that the increased blood lipids not only accelerate intravascular coagulation but also block the RES and thus prevent the effective removal of fibrin and fibrin polymers.

McKay E4,788/65: Review of the literature on the production of disseminated intravascular coagulation by diets rich in lipids. Phospholipids are especially important participants in the blood coagulation mechanism. The clotting time is prolonged when chylomicra are removed from the plasma by high speed centrifugation, while the addition of a suspension of chylomicra restores blood-clotting time to normal. Phosphatidyl ethanolamine is presumably the active fraction of chylomicra, but phosphatidyl serine (extracted from platelets and erythrocytes) is even more active in forming thromboplastin than phosphatidyl ethanolamine.

Renaud & Allard F38,582/65; Renaud F40,451/65: In rats kept on lipid-rich, low-protein diets containing sodium cholate, a high incidence of thrombosis in the large hepatic veins could be produced by the i.v. administration of *E. coli* or *S. typhosa* lipopolysaccharides.

Renaud G31,668/65: In rats made hyperlipemic by prolonged maintenance on a special diet, *S. typhosa* or *E. coli* endotoxin i.v. consistently produce thromboses in the large hepatic veins with consequent red infarcts of the liver. Heparin, hirudin or acenocoumarin given just before the endotoxin considerably lowered the incidence of thrombosis and the mortality rate.

Rodriguez-Erdmann G34,859/65: In rabbits pretreated with Thorotrast, i.v. injection of phospholipids, containing platelet factor 3 or Inosithin (soya bean phospholipid) there developed an SSP-G associated with the typical alterations of the clotting mechanism.

Luviskol. cf. PVP.

Mapharsen. Becker B28,260/48: Mapharsen fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Mecholil, Morphine. cf. Nerve-drugs.

Mercury. Pierson *et al.* G29,948/65: A six-year-old girl developed severe acrodynia with trophic disturbances in hands and feet after prolonged use of calomel. Urinary catecholamine is increased and the derangement in catecholamine metabolism is supposed to play a role in the pathogenesis of acrodynia.

Neodymium. Vincke B24,876/47: According to the method of Dietrich (E55,223/41), jugular vein thrombosis is produced in rabbits by partially constricting the vessel and then giving *E. coli* bacilli into the ipsilateral ear vein followed 24-48 hrs. later by the i.v. administration of *E. coli* filtrate into the contralateral ear vein. This thrombosis is inhibited by pre-treatment with heparin or neodymium nicotinate.

Beller D78,036/60: Various rare-earth elements, especially salts of neodymium and praseodymium, have long been used as anti-coagulants in clinical medicine. Thrombocyte agglutination and fibrin precipitation are mentioned as occasional side effects.

Neosalvarsan. cf. Arsenic.

Nialamide. Shimamoto & Ishioka D57,197/63: In preparations of the rabbit aorta perfused in vitro, addition of small doses of epinephrine to the perfusion fluid causes a release of thromboplastic activity from the vessel wall. Norepinephrine and large doses of epinephrine are ineffective. The release of thromboplastic activity by epinephrine can be blocked by a MAO inhibitor such as nialamide.

Nerve Drugs

ACETYLCHOLINE

Shwartzman *et al.* D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by acetylcholine.

ATROPOINE

Shwartzman *et al.* D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by atropine.

Rall & Gaskin C13,122/56: In rabbits given *S. marcescens* endotoxin i.c., the subsequent injection of epinephrine or norepinephrine into the prepared skin sites produces a local hemorrhagic necrosis. This response is prevented by the adrenergic blocking agent SY-28. However, atropine and heparin, both of which inhibit the classic SSP-L, are ineffective. "These data support the hypothesis that sympathetic nerve-mediated vasoconstriction is an

important factor in the local Shwartzman reaction."

Gatling C83,022/60: Epinephrine or norepinephrine, given i.v. to hypersensitive rabbits in the presence of circulating specific antigen, produces topical hemorrhage with fibrinoid necrosis of arteries. Ephedrine, histamine and atropine i.c. are ineffective under the same conditions.

Kováts *et al.* D9,550/64: The "Thomas reaction" is induced by giving epinephrine i.c. and typhoid endotoxin i.v., in rabbits. If epinephrine was mixed with the same amount of dibenamine, the reaction was diminished or disappeared, while atropine had an opposite effect. When a true SSP-L is produced by two injections of typhoid endotoxin, dibenamine applied at the site of i.c. preparation simultaneously with the i.v. dose of endotoxin, diminished the skin hemorrhage, but epinephrine given in the same manner did not aggravate it, indeed it delayed its appearance. Atropine failed to influence this classic SSP-L. In all these respects, the effect of the drugs upon the SSP-L differs from their influence upon the "Thomas reaction."

BENADRYL

cf. Antihistaminics.

CHLORAL HYDRATE

Gaiginschi *et al.* G22,148/64: Chloral hydrate anesthesia inhibited the development of an SSP-L following two injections of *E. coli* endotoxin in the guinea pig.

CHLORPROMAZINE

Reilly G27,050/54: The fact that chlorpromazine is particularly effective in preventing the "syndrome of neurovegetative irritation" further supports the view that nervous mechanisms play an important part in its pathogenesis.

Thomas C27,073/56; C15,187/56; Thomas & Zweifach C13,961/56: Epinephrine i.c. produces extensive skin hemorrhages in rabbits when given one hr. after *E. coli*, *E. typhosa*, or *S. marcescens* endotoxin i.v., presumably because the hormone produces an unusually prolonged local ischemia. This response is prevented by chlorpromazine or cortisone, but not affected by heparin or nitrogen mustard.

Gatling C58,378/58: Epinephrine or norepinephrine injected i.c. in hypersensitized rabbits immediately after a challenge dose of horse serum i.v., cause a THP-L which is prevented by heparin but not by chlorpromazine.

Kesztyüs et al. G22,097/58: Pretreatment with chlorpromazine allegedly not only fails to diminish but actually increases the sensitivity of the rabbit to the production of an SSP-L by two injections of *E. coli* endotoxin.

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, and rises in hematocrit and plasma hemoglobin. These changes "apparently result from a sympathomimetic action of endotoxin on the bowel," and are inhibited by adrenergic blocking agents such as chlorpromazine and dibenzyline.

Gatling C83,022/60: The topical hemorrhage and fibrinoid necrosis of arteries, produced by epinephrine or norepinephrine i.c. in hypersensitive rabbits, is inhibited by heparin and cortisone but not by nitrogen mustard, chlorpromazine or sodium salicylate.

Rieder & Thomas C80,868/60: As little as 5 µg of *E. coli* lipopolysaccharide causes abortion in the mouse. This response is not blocked by chlorpromazine, which inhibits endotoxin shock and the epinephrine THP, but not the SSP-G.

COCAINE

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by cocaine.

CURARE

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by curare.

DIBENAMINE

Waters & DeSuto-Nagy B64,578/49-50: Essentially identical arteriolar necroses with hemorrhages are produced in dogs by i.v. injections of large doses of epinephrine, N-amylamine, citrated compatible canine blood or epinephrine + large amounts of canine blood. Similar lesions are obtained by treatment of nephrectomized dogs with pressor renal extracts. The epinephrine-induced lesions can be prevented by dibenamine.

Pradhan et al. E73,059/56: The hemorrhagic necrosis of murine sarcoma-37 transplants produced by podophyllotoxin is not modified by dibenamine and related compounds, while that of *S. marcescens* endotoxin is diminished.

Rall & Kelly C36,395/57: Dibenamine, i.p. 1 hr. prior to the provocative injection inhibits the SSP-L normally elicited by two in-

jections of *S. marcescens* endotoxin in the rabbit.

Fine et al. D98,173/59: Dibenamine prevents the "SSP-G" normally produced by one large or two smaller i.v. doses of Thorotrast or by a small dose of Thorotrast combined with hemorrhagic shock. "It appears that the hemorrhages and the peripheral vascular collapse require the participation of the adrenergic system."

Kováts et al. D9,550/64: The "Thomas reaction" is induced by giving epinephrine i.c. and typhoid endotoxin i.v., in rabbits. If epinephrine is mixed with the same amount of dibenamine, the reaction diminishes or disappears; atropine has an opposite effect. When a true SSP-L is produced by two injections of typhoid endotoxin, dibenamine applied at the site of i.c. preparation simultaneously with the i.v. dose of endotoxin, diminishes the skin hemorrhage, but epinephrine given in the same manner does not aggravate it, indeed it delays its appearance. Atropine failed to influence the SSP-L. In all these respects, the effect of the drugs upon the SSP-L differs from their influence upon the "Thomas reaction."

DIBENZYLIN

Thomas C27,073/56: The skin necroses produced by epinephrine i.c. in rabbits given *E. coli* endotoxin i.v., are prevented by pretreatment with cortisone, dibenzyline (phenoxybenzamine hydrochloride) and chlorpromazine, while heparin and nitrogen mustard offers no protection.

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, and rises in hematocrit and plasma hemoglobin. These changes "apparently result from a sympathomimetic action of endotoxin on the bowel." The syndrome is inhibited by adrenergic blocking agents (chlorpromazine, dibenzyline), artificial hypothermia and, to a lesser extent, by cortisol.

Neter et al. C85,418/60: Purified polysaccharide-free "lipoid A component of *E. coli* O111:B4 endotoxin" i.v., in an amount as small as two µg per kg so alters the reactivity of the animal that epinephrine (100 µg) i.c. causes topical hemorrhagic necrosis. This reaction is inhibited by dibenzyline.

Neter et al. C97,516/60: Following i.v. injection of living *S. aureus* organisms or their endotoxins, epinephrine i.c. produces hemorrhagic lesions in the abdomen or back, but

not in the ear of the rabbit. The changes can be prevented by dibenzyline.

Rieder & Thomas C80,868/60: As little as 5 µg of *E. coli* lipopolysaccharide causes abortion in the mouse. This response is not blocked by dibenzyline, which inhibits endotoxin shock and the epinephrine THP, though not the SSP.

Levin & Cluff G25,181/65: In the rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, unlike the SSP this response is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment. The adrenal hemorrhages are also prevented by certain adrenergic blocking agents such as dibenzyline alderlin, or 1(3',4'-dichlorophenyl)-2-(isopropylamino) ethanol.

ERGOT

Ivánovics G27,772/34: Ergot extract i.c. prepares the rabbit for the production of a THP-L following subsequent i.v. administration of paratyphoid filtrate.

Rall & Kelly C36,395/57: Dihydroergotamine given 5-10 min. prior to the provocative injection does not inhibit the SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit.

Kesztyüs et al. G22,097/58: Following pretreatment with sympatholytic agents such as ergotamine (and to a lesser extent chlorpromazine), the sensitivity of the rabbit to the production of an SSP-L by two injections of *E. coli* endotoxin, far from being blocked, actually rises. This observation makes it unlikely that the adrenergic action of endotoxins is of primary importance in the production of an SSP.

McKay E4,788/65: Thrombosis in small vessels, with consequent necrosis, frequently occurs in ergot poisoning. In roosters, the comb and wattles may become gangrenous and drop off as a consequence of thromboses in small arteries.

ETHER

Flexner E76,861/02: Erythrocyte agglutination thrombi can occur in various infectious diseases of man and animals, in eclampsia, and after i.v. injection of ricin, ether, or dog's serum into rabbits.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by ether anesthesia.

HEXAMETHONIUM

Szildgyi & Damjanovich D18,970/64: Ganglionic blocking agents such as hexamethonium and TEAB inhibit the SSP-L produced by two injections of *E. coli* endotoxin in the rabbit.

MECHOLYL

Patterson et al. D58,647/63: Mecholyl failed to influence the SSP-L elicited by two injections of *E. coli* toxin.

MORPHINE

Stork & Kovaříková C11,611/54: Morphine failed to prevent the SSP-L produced by two injections of *E. coli* endotoxin in the rabbit.

PENDIOMID

Mignani & Graev C16,652/55: An SSP-L produced by two injections of *E. coli* endotoxin is not inhibited by pretreatment with a ganglionic blocking agent Pendiomid, but the structure of the cutaneous lesions is changed. It is concluded that the autonomic nervous system plays a part in this response. [In view of the small number of animals used and the comparatively moderate change in response, the interpretation of these findings is difficult (H.S.).]

PHENOTHIAZINE DERIVATIVES

Evers & Brunson C97,146/60: In themselves well tolerated i.c. doses of epinephrine, norepinephrine or *E. coli* endotoxin produce topical necrosis without hemorrhage, in rabbits exposed to "rotational shock" in the Noble-Collip drum. The response was more constant when the rotation preceded, than when it followed, the i.c. injections. Similar changes were obtained by phenylephrine, ephedrine and isopropylarterenol administered during rotational shock. These lesions could not be prevented by nitrogen mustard or heparin. They were prevented or attenuated, however, by pretreatment with mixtures of promethazine and promazine.

PHYSOSTIGMINE

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by physostigmine.

PILOCARPINE

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by pilocarpine.

PROCAINE

Štork & Kovaříková C11,611/54: Procaine, given either systemically or at the site of cutaneous preparation, failed to influence the SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit.

RESERPINE

Stamler D4,281/61: The eclampsia-like THP-G elicited by progesterone overdosage in late-pregnant rats is not inhibited by reserpine.

SCLEROSING AGENTS

Henry G33,285/62: Review on the production of thromboses with various sclerosing agents.

SEVENAL

Kesztyüs & Csernyánszky C10,849/54: The SSP-L produced in rabbits by two injections of *E. coli* endotoxin is partially inhibited if the animals are anesthetized with Sevenal, both during the preparatory and the provocative injection.

Kesztyüs et al. C12,656/55: The SSP-L, elicited by two injections of *E. coli* endotoxin in the rabbit, is prevented by Sevenal anesthesia applied both before the preparatory and the provocative injection. Sevenal anesthesia given only before the preparatory injection results in partial inhibition, while similar anesthesia, given only before the provocative injection, is inactive.

SY-28

Rall & Gaskin C13,122/56: In rabbits given *S. marcescens* endotoxin i.c., the subsequent injection of epinephrine or norepinephrine into the prepared skin sites produces a local hemorrhagic necrosis. This response is prevented by SY-28 (*N*-ethyl-*N*-[2-bromoethyl]-1-naphthalenemethylamine) an autonomic blocking agent. However, atropine and heparin, both of which inhibit the classic SSP-L, are ineffective. "These data support the hypothesis that sympathetic nerve-mediated vasoconstriction is an important factor in the local Schwartzman reaction."

Kelly et al. D3,776/57: The SSP-L produced by various bacterial endotoxins in susceptible strains of mice can be prevented by the SY-28.

Rall & Kelly C36,395/57: SY-28 given i.p. 1 hr. prior to the provocative injection, inhibits the SSP-L normally elicited in the rabbit by two injections of *S. marcescens* endotoxin. This SSP-L is aggravated by the injection of epinephrine into the prepared skin

site and the enhanced reaction is also inhibited by giving SY-28 i.p. 1 hr. before epinephrine.

TEAB

Szilágyi & Damjanovich D18,970/64: Ganglionic blocking agents such as hexamethonium and TEAB inhibit the SSP-L produced by two injections of *E. coli* endotoxin in the rabbit.

URETHANE

Becker B28,260/48: Urethane fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Schwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by urethane.

Štork & Kovaříková C11,611/54: The SSP-L elicited by two injections of *E. coli* endotoxin is inhibited in the rabbit by induced urethane or dial anesthesia. Presumably, the central nervous system plays an important part in the development of this response.

Pradhan et al. E73,059/56: Urethane anesthesia diminishes the ability of *S. marcescens* endotoxin to produce hemorrhagic necrosis in murine sarcoma-37 transplant, while barbiturates are ineffective in this respect.

Nitrogen Mustard. *Becker B28,260/48:* Nitrogen mustard prevents the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Hausner G19,190/49; Richter & Johne G23,888/50: In a 44-year-old woman with chronic generalized lymphogranulomatosis and scabies with pyoderma, nitrogen-mustard (HN_2) therapy elicited multiple thrombophlebitic lesions in the skin. Immediately after a new attack of thrombophlebitis, there developed a generalized herpes zoster with hemorrhagic vesicles, and 6 days later the patient died. Apart from the lymphogranulomatosis, autopsy revealed hemorrhagic necrosis of the small intestine, pleura and lungs. The authors assume that a decrease in the antibody titer, induced by lymphogranulomatosis and nitrogen mustard therapy, may have been responsible for the sudden multiplication of the zoster virus which, perhaps in conjunction with the pyoderma microbes, may have caused an SSP.

Schlang B50,092/50: An SSP-L produced by two injections of meningococcus or *E. coli* endotoxin in the rabbit can be prevented by the i.v. injection of nitrogen mustard [Methyl bis (β -chloroethyl) amine HCl] four days before the experiment. Protection of the injected skin by occlusion of the blood vessels with a

specially constructed clamp fails to influence the inhibition. On the other hand, protection of the lower limbs from the nitrogen mustard by temporary aortic occlusion decreases or prevents the inhibition, presumably because the latter depends upon some myelotoxic effect of the drug.

Stetson & Good C69,100/51: Pretreatment with either nitrogen mustard or benzene (both of which cause leukopenia) inhibit the SSP-L normally produced by two injections of meningococcal toxin. Sulfapyridine, which prevents the benzene-induced leukopenia, also tends to prevent its protective effect against the SSP-L. Leukocytic infiltration of the i.c. injection site is the most evident morphologic expression of local "preparation." It is assumed "that polymorphonuclear leucocytes play an essential role in the preparation of the skin for the Shwartzman phenomenon."

Bennett & Cluff B90,942/52: Nitrogen mustard inhibits the SSP-L produced by two injections of *S. marcescens* endotoxin in the rabbit and concurrently produces leukopenia. This protective effect is abolished by cysteine, which also prevents the leukopenia, but not by Thorotrast. The pyrogenic effect of bacterial endotoxin is uninfluenced by nitrogen mustard. Hence, this effect is apparently independent of the presence of normal numbers of circulating leukocytes.

Good & Thomas B80,500/52: The skin and kidney lesions elicited by bacterial toxins i.v. in Thorotrast i.v.-pretreated rabbits (like those of the classical SSP) were completely inhibited by pretreatment with nitrogen mustard in doses sufficient to produce polymorphonuclear leukopenia.

Schlang B69,777/52: An "SSP-L" can be elicited in the rabbit by an antigen-antibody reaction *in vivo*. Meningococcus, *E. coli* or *S. typhimurium* i.c. is used for preparation in rabbits sensitized to human serum and challenged by the same antigen 24 hrs. after i.c. preparation. This response is prevented by nitrogen mustard i.v. given 4 days before i.v. challenge with the antigen.

Schlang B75,461/52: Both cysteine and inflammation, produced by mild irritants, inhibit the leukopenia normally elicited by nitrogen mustard in the rabbit. Simultaneously, the inhibitory effect of nitrogen mustard upon the development of an SSP-L (induced by two injections of *E. coli* endotoxin) is blocked by these agents. These findings furnish additional support for the correlation between the presence of the heterophil granulocyte and the production of the Shwartzman phenomenon."

Thomas & Good E56,605/52: A single i.v. injection of *S. marcescens* or meningococcal toxin is followed by bilateral cortical necrosis and hyaline thrombosis of the glomerular capillaries in the cortisone pretreated rabbit. There are also hemorrhages in the lung, spleen, liver and gastrointestinal tract. Intradermal toxin causes an SSP-L after cortisone pretreatment. All these changes are prevented by nitrogen mustard, but not if the femoral bone marrow is protected by placing a clamp on the aorta during injection.

Thomas & Good B79,249/52: The effect of nitrogen mustard upon the development of the SSP-G depends upon proper timing. "The animals which received the preparing injection of toxin simultaneously with HN_2 , or 12 hours later, showed no inhibition of the generalized Shwartzman reaction. It will be noted that the polymorphonuclear leukocyte counts were within normal limits at the time of preparation in all these animals. In the group receiving the first injection of toxin 72 hours after HN_2 , all showed extreme leukopenia and none developed renal cortical necrosis. When the interval between the injection of HN_2 and preparation with toxin was 6 or 8 days, leukopenia had disappeared and the animals were again fully susceptible to the generalized Shwartzman reaction." The protective effect of the HN_2 is ascribed to the leukopenia resulting from bone-marrow damage, since protection of the femoral bone marrow, by placing a clamp on the aorta during HN_2 injection, prevents both the leukopenia and the protective effect against the SSP-G.

Race & Reed G23,063/53: The SSP-L produced by two injections of meningococcal endotoxin in the rabbit is incompletely suppressed by nitrogen mustard given 3 days prior to the preparatory i.c. injection.

Thomas et al. E52,778/55: Liquoid given i.v. 2 hrs. before an i.v. injection of bacterial endotoxins (meningococcus, *S. marcescens*, *Shigella paradyenteriae*), produces an "SSP-G" with disappearance of blood fibrinogen in the rabbit. The response is prevented by heparin but not by nitrogen mustard or cortisone. The response is attributed to intravascular precipitation of fibrinogen by the polymer.

Thomas et al. G21,281/55: In rabbits prepared by a single i.v. injection of various Gram-negative bacterial endotoxins, subsequent i.v. injection of several acidic polymers (Liquoid, dextran sulfate or sodium polyvinyl alcohol sulfonate) elicits an "SSP-G." Nitrogen mustard, which was previously shown to prevent the SSP-G induced by two injections of

bacterial endotoxin, had no protective effect against this response.

Thomas C27,073/56; C15,187/56; Thomas & Zweifach C13,964/56: The skin necroses produced by epinephrine i.c. in rabbits given *E. coli* endotoxin i.v., are prevented by pretreatment with cortisone, dibenzyline and chlorpromazine, while heparin and nitrogen mustard offers no protection. Indeed, the lesions produced by mixtures of epinephrine and endotoxin i.c. are greatly aggravated by nitrogen-mustard pretreatment.

Rall & Kelly C36,395/57: The SSP-L normally elicited by an i.c. injection of *S. marcescens* endotoxin, followed 24 hrs. later by the administration of epinephrine into the same skin site in rabbits, is not prevented and indeed is probably aggravated by nitrogen mustard (mechlorethamine or mustargen) given 3 days before the preparatory dose of endotoxin. "These findings suggest that the leucocytes play a less significant role in the epinephrine-induced, than in the classic, Shwartzman reaction."

Thomas D1,020/57: Although nitrogen-mustard pretreatment prevents the SSP-G normally produced by two i.v. injections of meningococcal endotoxin, it does not protect against an SSP-G produced by combined treatment with endotoxin and Liquoid.

Johnstone & Howland G22,057/58: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit is inhibited, but not totally prevented, by nitrogen mustard or x-irradiation conducive to severe leukopenia. "It is concluded (a) that the presence of normal numbers of circulating polymorphonuclear leukocytes is not an obligatory prerequisite condition to the localized hemorrhagic necrosis of the Shwartzman phenomenon, and (b) the mechanisms of action of nitrogen mustard and whole body irradiation on body tissues differ in relation to the Shwartzman reaction."

Fine et al. D98,173/59: Nitrogen mustard can prevent the SSP-G produced in the rabbit by a single large i.v. dose of Thorotrast or a smaller dose combined with hemorrhagic shock. This protection is ascribed to the ensuing granulocytopenia. However, the endotoxemia and death that normally result from this type of Thorotrast treatment are not prevented by nitrogen mustard.

Fine et al. D85,444/59: Nitrogen mustard blocks the SSP-G ordinarily produced by a double dose of Thorotrast in the rabbit.

Evers & Brunson C97,146/60: The i.c. injection of, in themselves, well tolerated doses of

epinephrine, norepinephrine or *E. coli* endotoxin produce topical necrosis without hemorrhage, in rabbits exposed to the "rotational shock" in the Noble-Collip drum. The response was more constant when the rotation preceded, than when it followed, the i.c. injections. Similar changes were obtained by phenylephrine, ephedrine and isopropylarterenol administered during rotational shock. These lesions could not be prevented by nitrogen mustard or heparin. They were prevented or attenuated, however, by pretreatment with mixtures of promethazine and promazine.

Gatling C83,022/60: The topical hemorrhage and fibrinoid necrosis of arteries, produced by i.c. injection of epinephrine or norepinephrine in hypersensitive rabbits, is inhibited by heparin and cortisone but not by nitrogen mustard, chlorpromazine or sodium salicylate.

Nakai & Margaretten E45,655/63: The bilateral renal cortical necrosis produced by a single i.v. injection of staphylococcal endotoxin cannot be prevented either by heparin or by nitrogen-mustard pretreatment. Thus, this lesion differs from the typical SSP-G in its responsiveness. Pretreatment with cortisone, on the other hand, protected rabbits both against the renal cortical necrosis and the lethal effects of a single i.v. injection of staphylococcal toxin.

Hall et al. G9,421/64: The administration of nitrogen mustard failed to prevent the development of the classic SSP-L in epinephrine-tolerant rabbits.

Levin & Cluff G25,181/65: In the rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, unlike the SSP this response is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment.

Oxalate. Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by sodium oxalate.

Papain. Thomas & Stetson D70,785/49: An SSP-L can be produced in the rabbit by papain, cysteine or BAL i.c., given 1 hr. after meningococcal toxin i.v.

Pendiomid. cf. Nerve-drugs.

Phenylbutazone. Tigano G28,861/55: The SSP-L normally elicited by two injections of *S. paratyphi* B in the rabbit is not modified by pretreatment with large doses of phenylbutazone.

Physostigmine. cf. Nerve-drugs.

Picryl Chloride. Stetson E74,348/59: An unpublished observation of Gell is quoted, indicating "that picryl chloride serves to prepare the skin for the Shwartzman phenomenon in previously sensitized guinea pigs." [No details are given (H.S.).]

Pilocarpine, Procaine. cf. Nerve-drugs.

Polyvinylpyrrolidone (PVP). Morel et al. G27,497/64: The formation of erythrocyte aggregates and hemorrhages in the microcirculation of the rat meso-appendix can be followed in vivo after the i.v. injection of polyvinylpyrrolidone (PVP) if simultaneously hypotension is induced by hemorrhage.

Praseodymium. Beller D78,036/60: Various rare-earth elements, especially salts of neodymium and praseodymium, have long been used as anticoagulants in clinical medicine. Thrombocyte agglutination and fibrin precipitation are mentioned as occasional side effects.

Protein. cf. Immunity.

Pyridin Derivatives. Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by pyridin, pyridoxine, pyridoxamine or pyridoxal.

Ricin. Flexner E76,861/02: Erythrocyte agglutination thrombi can occur in various infectious diseases of man and animals, in eclampsia, and after i.v. injection of ricin, ether, or dog's serum into rabbits.

Gratia & Linz E65,500/31: Ricin, used both for the preparatory i.c. and for the provocative i.v. injection, does not produce an "SSP-L" but, if ricin is administered i.c., a subsequent i.v. injection of *E. coli* endotoxin does produce this phenomenon.

Gratia & Linz D6,544/32: 24 hrs. following an i.c. injection of a highly diluted ricin solution, *E. coli* filtrate i.v. causes a mild "SSP-L" in the rabbit. Ricin is inactive, however, when given i.v. as the provocative agent 24 hrs. after skin preparation with ricin.

Salicylic Acid. Smith & Humphrey B59,532/49: The SSP-L normally produced by two injections of *E. coli* endotoxin can be prevented in the rabbit by pretreatment with sodium salicylate, while Anthisan is ineffective in this respect.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit can be inhibited by sodium salicylate given i.p. several times prior to preparatory, and after provocative, injections.

Costa B63,283/51: The SSP is inhibited by

sodium salicylate. [This brief report gives no experimental details. (H.S.)]

Shwartzman B63,812/52: The SSP-L produced in rabbits by two injections of meningococcal toxin is inhibited by Na-salicylate only in about 60% of the cases but complete inhibition can be obtained if calcium pantothenate is simultaneously administered. Given alone the latter has no effect.

Gatling C83,022/60: The topical hemorrhage and fibrinoid necrosis of arteries, produced by i.c. injection of epinephrine or norepinephrine in hypersensitive rabbits, is inhibited by heparin and cortisone but not by nitrogen mustard, chlorpromazine or sodium salicylate.

Silver. Freund B78,141/34; B78,142/34: In guinea pigs given typhoid endotoxin i.v. and silver nitrate s.c., the cutaneous injection sites respond with hemorrhagic necrosis.

Starch. Freund & Smith B78,144/34; Freund & Hosmer D85,443/35: In rabbits prepared by *E. coli* endotoxin i.c., subsequent i.v. injection of starch elicits an "SSP-L." However, as a preparatory agent starch is inactive.

Sulfa Drugs. Schneierson E41,986/39: Sulfanilamide and prontosil, which inhibit the growth of meningococci in vitro, can also prevent the SSP-L elicited by two i.v. injections of live meningococci in the rabbit. The sulfa drugs have no effect, however, upon an SSP-L elicited by meningococcal toxin.

Gerber & Gross G22,254/42: Meningococcal endotoxin was coupled with paraaminobenzenesulfonylacetylimide according to a modification of the Landsteiner method. The resulting conjugate was active in producing an SSP-L in rabbits when given either as the preparatory or the provocative injection in conjunction with the original filtrate as the second agent.

Zahl & Hutner E65,415/42: The hemorrhagic necrosis normally produced in mouse sarcoma 180 by the i.p. injection of *S. typhimurium* endotoxin can be prevented by sulfanilamide p.o. It is assumed that the hemorrhage factor is a component of the O antigens of most Gram-negative bacteria. Since sulfanilamide inhibits both the lethal effect and the tumor hemorrhage effect of these antigens, both these actions are assumed to be characteristic of O antigens.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by sulfanilamide, sulfadiazine or sulfathiazole.

Takeo C10,179/55: Sulfapyridine, administered after the challenging injection, dimin-

ishes the intensity of the SSP in the rabbit. [Method of SSP production not mentioned. (H.S.)]

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, and rises in hematocrit and plasma hemoglobin. These changes "apparently result from a sympathomimetic action of endotoxin on the bowel." The syndrome is inhibited by adrenergic blocking agents (chlorpromazine, dibenzyline), artificial hypothermia and, to a lesser extent, by cortisol. Previous sterilization of the intestinal contents by sulfasuxidine and neomycin has no effect, while vasopressor drugs (norepinephrine, metaraminol) "actually potentiate the shock caused by endotoxin by increasing intestinal ischemia."

SY-28. cf. Nerve-drugs.

Talcum. *Bordet G23,544/34; B78,032/36:* Inflammatory reactions in the peritoneum of guinea pigs obtained by i.p. administration of yeast (*Oidium albicans*) become hemorrhagic if the animals are subsequently given an i.p. or i.v. injection of *E. coli* cultures or filtrates. The same response is obtained if talcum is used for the production of peritonitis. Hence, the sensitization is attributed to inflammation as such.

TEAB. cf. Nerve-drugs.

Theophylline. *Franceschini & Mancini G22,358/55:* The SSP-L induced by two injections of *E. coli* endotoxin in rabbits can be inhibited by theophylline i.v. just prior to the provocative injection. The effect is ascribed either to the vasodilator or to the antiallergic action of theophylline.

Niesert & Schneider F32,779/65: Complamin (a nicotinic acid salt of theophyllin which decreases blood fibrinogen and activates fibrinolysis), greatly diminishes the SSP-G normally produced by two i.v. injections of *S. abortus equi* endotoxin.

Turpentine. *Hanger B78,181/27-28:* Turpentine s.c. occasionally prepares for the production of an "SSP-L" by the subsequent i.v. injection of various bacterial endotoxins in the rabbit.

Shwartzman D71,756/27-28: In rabbits topical irritation by turpentine i.c. failed to prepare the skin for the subsequent i.v. injection of *B. typhosus* filtrate.

Fiorito G25,139/33: 24 hrs. following i.c. injection of turpentine, i.v. provocation with *V. cholerae* filtrate produces an "SSP-L" at the prepared skin site. However, this response

is much less constant and intense than that obtained at sites pretreated with *V. cholerae* endotoxin.

Gentile G26,188/34: Preparation of the skin with simple inflammatory irritants such as formic acid or turpentine does not permit the production of an "SSP-L" in rabbits subsequently treated with typhoid filtrate i.v.

Uranium. *Christian & O'Hare G23,264/13:* Uranium nitrate s.c. may cause various types of renal lesions in rabbits including fibrin thrombi in the glomerular capillaries, hyaline droplets in the capillary walls, and hemorrhages.

Urethane. cf. Nerve-drugs.

Vaseline. *Debonera et al. B78,075/32:* In guinea pigs prepared by sterile vaseline i.c., subsequent i.v. injection of *E. coli* endotoxin produces an "SSP-L" at the prepared skin site.

Vincaleukoblastine. *Galton G9,002/64:* In pregnant hamsters, colchicine produces a typical THP-G with characteristic renal glomerular lesions, while vincaleukoblastine (another stathmokinetic drug) and *E. coli* endotoxin are inactive in this respect. Devitalization of intestinal segments is efficacious perhaps owing to the absorption of some special endotoxin from the intestinal flora. [Other stressors have not been tested (H.S.).]

Vitamins

VITAMIN-B-COMPLEX

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal endotoxin in the rabbit is not inhibited by thiamine, folic acid, para-aminobenzoic acid, biotin, choline, riboflavin, nicotinic acid, or inositol. Neither is the SSP-L inhibited by calcium pantothenate alone, but this vitamin augments the suppressive action of simultaneously administered sodium salicylate.

VITAMIN C

Marginesu G21,460/34: The hemorrhagic manifestations of scurvy are aggravated by a single intracardiac injection of *E. coli* endotoxin in the guinea pig.

Pacheco & Para G22,343/38: The SSP-L produced by two injections of *S. typhosa* endotoxin in the rabbit is uninfluenced by vitamin C i.v.

Andervont & Shimkin G21,647/39: In sarcoma-37 bearing mice, *B. prodigiosus* filtrate i.p. produced hemorrhagic necrosis of the neoplasms. This reaction could be prevented by ascorbic acid s.c. The same inhibition was ob-

tained when the endotoxin was administered s.c. and the ascorbic acid i.p. The production of hemorrhage in other tumors by *B. prodigiosus* toxin could likewise be prevented by ascorbic acid.

Merlini G28,394/39: Ascorbic acid i.v. gives little, if any, protection against the induction of an SSP-L by two injections of *E. coli* endotoxin in the rabbit.

Becker B28,260/48; Shwartzman et al. D71,760/50: Vitamin C fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Vita G22,817/50: Combined treatment with desoxycorticosterone and vitamin C i.v. largely inhibits the SSP-L normally produced by two injections of *E. coli* endotoxin.

VITAMIN E

Becker B28,260/48; Shwartzman et al. D71,760/50: Vitamin E fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Stamler C78,006/59: A high percentage of pregnant rats, fed during a vitamin-E-deficient diet with supplements of peroxidized polyunsaturated fatty acids, died with "eclamptic convulsions associated with widespread intravascular thrombosis, affecting especially the lungs and kidneys." . . . "The disease in the rat has clinical and pathologic points of similarity to eclampsia and certain other fatal maternal disorders of human pregnancy." Dietary vitamin-E supplements protect against this syndrome.

Stamler D4,281/61: The eclampsia-like THP-G elicited by progesterone overdosage in late-pregnant rats is not inhibited by vitamin E.

McKay D15,443/62: In pregnant rats, feeding of a vitamin-E-deficient diet containing oxidized lipids induces the SSP-G in association with fibrin thrombi in the placenta, placatitis and fetal death. The response resembles pregnancy toxemia. Large amounts of vitamin E prevent the appearance of this disease.

Kaunitz et al. E29,696/63: In pregnant rats in which an "SSP-G" was produced by a vitamin-E-deficient diet containing ethyl esters of oxidized cod-liver oil, the kidney and perirenal adipose tissue contained more water than in similarly treated rats in which the "SSP-G" was inhibited by supplements of vitamin E. In the sera of the experimental animals, there was an increase in long-chain fatty acids with relative diminution of phospholipids, triglycerides and unesterified fatty acids suggesting an interference with the mobilization of depot fat. The palmitate:stearate and linoleate:

arachidonate ratios of the tissue lipids were also lower in the rats with the "SSP-G" than in those in which the reaction was prevented by vitamin E. Apparently, the SSP-G is associated with a disturbance of fat mobilization and lipogenesis.

Rothenberg et al. G26,181/63: Dietary lipids can partially block the phagocytic ability of the RES and vitamin-E supplements prevent this blockade in the rat. However, pregnancy is associated with a slight increase in the phagocytic activity of the RES and, hence, it presumably "prepares" for the production of a dietary THP-G through some mechanism other than blockade of the RES.

Goldstein & McKay G27,030/65: The fractions of cod-liver oil which produce "experimental eclampsia" in pregnant rats, are rich in lipid peroxides. Pregnant rats, fed fractions derived from molecular distillation of oxidized cod-liver oil, had increased amounts of lipid peroxides in their kidneys, livers and placentas. The erythrocytes of these animals lysed upon contact with hydrogen peroxide and dialuric acid in a manner characteristic of vitamin-E deficiency. "It is concluded that a state of relative vitamin E deficiency exists in these toxemic rats and that the deficiency of the antioxidant properties of vitamin E may be the basis of cellular damage leading to the eclamptic state."

Rothenberg G27,059/65: Electron-microscopic studies of the glomerular capillary thrombi produced in pregnant rats by diets deficient in vitamin E and rich in oxidized lipids showed that fibrin is present in two forms: "1) a fibrillar arrangement having 240 Å periodicity of the cross-striations and 2) an irregular amorphous granular deposit. Thrombi-emboli were always present within capillary lumens, never mural deposits."

VITAMIN K

Pagano-Purpura G28,400/41: Pretreatment with vitamin K i.v. protects the rabbit against the production of an SSP-L by two injections of typhoid endotoxin.

Boquet G20,920/43: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit is not inhibited either by vitamin K or by potent antihistaminics (929 F, 2339 R.P.). "The local hemorrhagic manifestations do not appear to be due exclusively to derangements in blood coagulability or the liberation of histamine by the provocative injection."

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by vitamin K.

Oswald C22,432/56: The SSP-L produced in rabbits by two injections of *S. abortus equi* endotoxin, or i.c. preparation with Pertussis vaccine and subsequent i.v. provocation with *S. abortus equi* endotoxin, is aggravated by the i.v. injection of vitamin K₃ (menadione). On the other hand, if repeated i.v. injections of menadione are given following the production of an SSP-L, the lesions appear to heal more rapidly than in otherwise untreated controls.

VITAMIN P

Merlini G28,241/41: An impure vitamin-P preparation, given i.v., allegedly inhibited the SSP-L normally produced by two injections of *E. coli* endotoxin in the rabbit.

Maratka & Ivy B29,487/48: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit can be inhibited by rutin, hesperidin and citrin.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by hesperidin.

Water. *Gratia & Linz D6,544/32:* Distilled water i.c. or hypertonic NaCl does not prepare for the subsequent elicitation of an "SSP-L" by bacterial toxin.

Shwartzman et al. D71,760/50: The SSP-L produced by two injections of meningococcal toxin in the rabbit is not inhibited by distilled water.

STRESS, PHYSICAL AGENTS, SURGICAL INTERVENTIONS

This section will deal conjointly with the effect of nonspecific, physical and chemical trauma, temperature variations, electricity, ultraviolet and ionizing rays, hemorrhage, nonspecific nervous stimulation and certain stressful surgical procedures such as bilateral nephrectomy. Finally, we shall consider the hemorrhagic stress syndrome described by Jaques and coworkers, which apparently differs from the THP in that it is unaccompanied by thromboses.

Trauma and Nonspecific Chemical Irritation. The classic SSP-L can be prevented if, prior to the provocative i.v. injection, the prepared skin site is mechanically compressed or treated with certain topically irritating substances. This protection has been ascribed to local ischemia which would shield the prepared skin against the blood-borne provoking agent.

Although various nonspecific irritants can prepare the rabbit's skin for a THP-L induced by subsequent i.v. injection of endotoxin, mechanical trauma has no preparatory potency. However, traumatic removal of the mucosa from the rabbit appendix can prepare, perhaps because it permits access of the intestinal flora (particularly *E. coli*) to the submucosal tissues. Mechanical trauma may also sensitize, under certain conditions, if it produces hemorrhage and edema at a time when SSP-active bacteria or endotoxins are abundant in the blood. "Rotational stress" in the Noble-Collip drum produces diffuse hemorrhagic lesions in itself, and aggravates those elicited by concurrent i.v. administration of *E. coli* endotoxin. Furthermore, endotoxin i.c. may induce extensive dermal necrosis in rabbits exposed to rotational stress.

Klein E65,246/31-32: The SSP-L normally produced in rabbits by two injections of meningococcal or *B. dysenteriae* toxin can be prevented if, just prior to the i.v. provocative injection, these same toxins are injected into the prepared skin site. It has previously been thought that this local inhibition might be due to some immunological phenomenon. However, the author found that many substances (adrenalin, pituitrin, normal saline, phenolized saline, formalinized saline, sterile

egg-white solution, immune rabbit serum, normal human serum) injected i.c. just prior to the provocative i.v. injection, exhibit the same inhibitory effect. Indeed, even compression of the skin site with padded clamps can protect it. Hence "it is believed that these agents produce their effects by creating a local ischemia which shields the prepared skin tissue from the injurious agents circulating in the blood stream."

Stolyhwo G21,662/35-36: In rabbits given a provocative i.v. injection of typhoid or paratyphoid filtrate, preparation of skin sites with various nonbacterial proteins (horse serum, cow's milk, etc.) results in a typical SSP-L, while topical trauma to the skin is ineffective.

Horster G22,366/38: If, following preparation with bacterial endotoxin (kind not stated) into the rabbit ear i.c., the root of the ear is compressed to produce venous stasis, the site of preparation responds with hemorrhagic necrosis. It is assumed that vascular factors may be decisive in eliciting the SSP.

Cattabeni G28,397/40: The SSP-L produced in rabbits by two injections of typhoid endotoxin is not significantly influenced by severe trauma (conducive to bone fractures) applied at the time of the provocative injection.

Basile G23,055/41: After a review of earlier work on the production of an SSP-L in the appendix by the local administration of a preparatory endotoxin injection, the following experiment was performed: Under anesthesia, a small oculist's spoon was introduced into the appendix from its base and a piece of mucosa and submucosa removed. The following day, *E. coli* endotoxin was injected i.v. Of 16 rabbits so treated, 5 showed a definite SSP-L at the traumatized region, while the remainder exhibited only minor lesions such as were found also in controls not provoked by i.v. endotoxin. One of the positively reacting rabbits also showed SSP-G-like changes. It is concluded that topical trauma to the mucosa of the appendix can act as a preparatory treatment. In man, foreign bodies in the appendix may produce such trauma, and certain types of fulminating hemorrhagic appendicitis could represent manifestations of the SSP-L.

Miescher & Böhm E53,167/47: Following inoculation with living *E. coli* into the conjunctiva, mechanical trauma to the testes produces a local hemorrhagic necrosis with the appearance of numerous *coli* organisms in the testes. This mechanism may explain the pathogenesis of certain forms of focal infections.

Vincke B24,876/47: According to the method of Dietrich (E55,223/41), jugular vein thrombosis is produced in rabbits by partially constricting the vessel and then giving *E. coli* bacilli into the ipsilateral ear vein followed 24-48 hrs. later by the i.v. administration of *E. coli* filtrate into the contralateral ear vein.

Rempt & Julius G23,512/54; Rempt G23,511/54; G23,068/56: A rabbit is given *E. coli* filtrate i.v. and i.c. Ten to 56 days later, it receives *E. coli* filtrate i.c. in another area and this area is clamped for 4 hrs. by a special

technique 24 hrs. later. After removal of the clamp, an SSP-L develops at the clamped site. Without earlier treatment with colic filtrate, no hemorrhage occurs.

Takeo C10,179/55: "Fracture of a leg" 2 to 3 hrs. after the challenging injection, aggravates the SSP in the rabbit. [Method of SSP production not mentioned (H.S.).]

McKay et al. G9,469/56: In dogs, intra-aortic transfusion of human blood produces multiple thromboses and hemorrhages in the lung, liver, intestine and other organs, accompanied by hyaline thrombosis of the renal glomerular capillaries. When the transfusion was preceded by repeated renal biopsies and unilateral nephrectomy, capillary thromboses in the gastrointestinal tract were prominent, presumably because of topical sensitization through vasoconstriction.

Anderson & Brunson G21,292/59: A single i.v. injection of *E. coli* endotoxin or exposure to stress in the Noble-Collip drum can produce diffuse hemorrhagic lesions in various organs. The lethal effect and the severity of the morphologic changes are appreciably greater in animals given endotoxin together with stress. Furthermore, endotoxin i.c. in association with acute rotational stress results in an extensive area of dermal necrosis. "The results of the study support the hypothesis that adrenal gland hormones participate in the effects produced by endotoxin."

Katz D87,740/59: Hemorrhagic duodenitis associated with intense dilatation of the duodenal microcirculation is frequently seen in patients under severe stress and particularly after myocardial infarction. "It is certainly plausible that hemorrhagic duodenitis represents one part of the shock phase of the alarm reaction."

Long et al. C64,592/59: Review of the literature and personal observations showing that exposure to stress shortens the blood clotting time of the rat. [No mention of thrombosis or hemorrhage (H.S.).]

McKay & Hardaway G26,439/59: Following release of a crush to the muscles of the dog, there was prompt activation of fibrinolytic and fibrinogenolytic enzymes with elevation of circulating fibrinogen and gradual decrease of platelets. No thrombi were observed, wherein the response differs from incompatible blood-transfusion reactions.

Galton G9,002/64: In pregnant hamsters, colchicine produces a typical THP-G with characteristic renal glomerular lesions, while vincaleukoblastine (another stathmokinetic drug) and *E. coli* endotoxin are inactive in this respect. Devitalization of intestinal seg-

ments is efficacious perhaps owing to the absorption of some special endotoxin from the intestinal flora. [Other stressors have not been tested (H.S.).]

Temperature Variations. The fact that burns can produce thrombohemorrhagic lesions was probably first described by Klebs in 1876. It has also long been known that extensive burns can produce acute hemorrhagic ulcers in the gastrointestinal tract, but here we cannot speak of a typical THP.

Frostbite and heat stroke can cause changes similar to the THP.

Artificial hypothermia inhibits the production of the classic SSP-L, but a rise in the surrounding temperature does not strikingly aggravate it.

The fact that pretreatment with various pyrogens can prevent the SSP-L is not necessarily related to the associated increase in body temperature.

Klebs A71,439/1876: This is apparently the first observation of multiple hyaline thrombi in the small vessels. They were observed in patients who suffered extensive burns.

Alexander & Thompson G26,200/25: In a case of chronic leukemia, autohemagglutination occurred when the blood was cooled below body temperature. The agglutinated cells dispersed again when the temperature was raised. The phenomenon may be accompanied by paroxysmal hemoglobinuria.

Zdrodowski G23,346/28: Exposure to heat produces gastrointestinal hemorrhages with a great multiplication of *E. coli* and *B. paratyphosus* in the intestinal contents. These changes resemble those observed by Sanarelli in his reaction.

Kielanowski & Selzer G23,077/34: The capillaries of rabbit skin in a region prepared 24 hrs. earlier by *E. coli* endotoxin, react normally (with dilatation) to the application of heat. In the event of subsequent i.v. provocation, the heated skin region shows only a slightly increased hemorrhagic response. Hence, the phenomenon of preparation is not due to a functional inactivation of microcirculation.

Anderwont G20,972/36: The lethal effect of *B. coli* endotoxin in both tumor-bearing and normal mice, is greatly increased if the animals are kept at 37° C.

Friedman G26,852/45: Detailed review of the pathology of trench foot with numerous personal observations. The essential early changes are characterized by agglutinative thrombosis with subsequent organization or gangrene. The late stages are similar to those of *endangiitis obliterans*.

Friedman & Kritzler G26,517/47: Frostbite, incurred by aviators at high altitudes, is associated with histologic lesions similar to those of trench foot. In the exposed regions, arteri-

McKay E4,788/65: A review of the literature shows that erythrocyte aggregation and microthrombosis is not uncommon in various forms of traumatic shocks.

oles and venules contain erythrocyte agglutination thrombi and hyaline material. The walls of these vessels are also hyalinized and infiltrated with erythrocytes.

Scuderi G22,360/48: Subconjunctival preparation with *B. proteus* endotoxin produces an ocular SSP-L in rabbits following i.v. injection of typhoid endotoxin. This response can be prevented by various pyrogens (vaccines, colloidal sulfur) but not by the anti-histaminic Antistin.

Linke G26,040/50: In some patients, Raynaud's syndrome develops upon exposure to cold, because of cold agglutination of erythrocytes.

Jentzer C5,784/53: The SSP-L normally produced by two injections of *E. coli* endotoxin in the rabbit can be prevented by artificial hibernation.

Brinkhous & Penick G22,790/54: Freezing of the skin with liquid air in the dog results in edema and interstitial fibrin deposition in the adjacent viable tissue. "There are fibrin thrombi in dilated lymphatics. The smaller blood vessels, particularly at the margins, are also thrombosed." The changes are less pronounced in hemophilic animals. Both in normal and in hemophilic dogs, the blood fibrinogen and prothrombin were not grossly altered. However, significant reduction of plasma antihemophilic factor and platelets occurred in the normal animals. It is suggested that local thrombosis may result in the release of thromboplastin from the injured sites with consequent systemic changes in clotting factors.

Ungar G27,785/54: Various stressors, particularly burns, enhance thrombus formation after i.v. injection of thrombin in the rat presumably through interference with the fibrinolytic system. It is concluded that "intravascular clotting is facilitated by systemic stress."

Szilágyi et al. C35,397/56; C37,832/56: Hypothermia induced by exposure to cold completely prevents the SSP-L normally induced by two injections of *E. coli* endotoxin.

Ushitel & Krymski C35,541/56: Both the Shwartzman and the Arthus phenomena can be inhibited in rabbits by artificially induced hypothermia. It is assumed that these phenomena are allergic and that the protective effect of cold may be mediated through the alarm reaction with its stimulating effect upon corticoid production.

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, and rises in hematocrit and plasma hemoglobin. These changes "apparently result from sympathomimetic action of endotoxin on the bowel." The syndrome is inhibited by adrenergic blocking agents (chlorpromazine, dibenzyline), artificial hypothermia and, to a lesser extent, by cortisol.

Burri & Allgöwer F42,960/65: Extensive skin burns produce widespread hemorrhagic lesions in the gastrointestinal tract of the rabbit. Extracts made from the intestines of such rabbits exhibit similar toxic effects when injected into mice. Presumably, the development of these lesions after burns are mediated through the absorption of toxic materials (endotoxins?) from the intestine.

McKay E4,788/65: Disseminated intravascular coagulation is a typical manifestation of

heat stroke. It is associated with a hemorrhagic diathesis, depletion of fibrinogen, platelets, prothrombin, activation of fibrinolysis and heat damage to endothelia all over the body. Obstruction of small vessels by platelet aggregates leads to petechial hemorrhages and thromboses, particularly in the skin, conjunctivae, meninges, brain, pleura, lungs, epicardium, endocardium, peritoneum and gastrointestinal tract, but less frequently also in the heart muscle, spleen, pancreas, periadrenal tissue, renal pelvis and urinary bladder. Cold injury (trench foot, frostbite) may also lead to thrombosis and infarction, perhaps through the release of thromboplastin from frozen tissues with a reduction of circulating antihemophilic factor and platelets.

Hansson G35,342/65: In cats, perfusion of the kidney with cooled blood, homologous blood (ADP) or crushed connective tissue as well as transient mechanical interruption of the renal blood flow "induced a significant drop in thrombocyte counts and when a complete renal blood flow obstruction ensued, the small renal vessels were occluded by aggregated thrombocytes. This was especially easily demonstrated in the glomerular capillaries." Subsequently, the kidneys became edematous and studded with patchy hemorrhages. Apparently, "the renal vascular bed is especially vulnerable to thrombocyte aggregation in the blood, presumably due to the special characteristics of this vascular circuit."

Electricity. Exposure to high-frequency electric currents can cause thrombohemorrhagic lesions in various organs with thromboses in the renal glomerular capillaries.

There is an electric potential difference between the intima and adventitia of the canine aorta. Severe injury reverses this potential and this is often associated with thrombosis. If a current, similar in magnitude to the injury current, is applied across the normal vessel wall using two external platinum electrodes, a thrombus forms under the positively polarized electrode.

A syndrome of intravascular clotting has also been shown to develop in dogs following brief periods of circulatory arrest induced by fibrillating and defibrillating the heart electrically.

Baldwin & Nelson G26,878/28-29: Exposure of rats to high-frequency electric currents causes clot formation in the heart and blood vessels with necroses and hemorrhages in the lung, heart and liver. "The glomeruli of the kidney were dilated and the capillaries of the kidney filled with the clotted blood."

Baldwin & Dondale G26,879/29-30: Exposure of rats to high-frequency currents produces vascular dilatation, leukocytosis and hemorrhages into the villi of the small intestine

particularly the duodenum, but also the pyloric end of the stomach. [No mention of thrombi (H.S.).]

Sawyer & Pate G26,856/53: In dogs a small current flow across the aorta, in a direction to reverse the normal polarity, is followed by thrombosis. "The artificially precipitated thrombus is histologically similar to thrombi produced spontaneously in injured blood vessels. Experiments using a series of guard tubes have shown that a current density as small

as 0.4 μ a/mm² will create a thrombus in the normal aorta in 4½ hrs. This current density is well within the physiologic limits of injury current found across a damaged segment of aorta."

Sawyer & Pate G27,046/53: The electric potential difference of the normal canine aortic wall is from 1 to 5 mv. with the intima negative to the adventitia. After severe injury, the potential difference reverses. If a current similar to an injury current is applied across the normal vessel wall, using two external platinum electrodes, a thrombus forms under the positively polarized electrode.

Crowell et al. G24,212/55: When brief periods of circulatory arrests are induced in dogs by fibrillating and defibrillating the heart electrically, a syndrome of intravascular clotting develops which can be prevented by heparinization.

McKay E4,788/65: Accidental contact with high tension wires may cause severe vascular damage, especially in the pancreas, gastrointestinal tract and kidney. Hemorrhagic necrosis may also be found in the sigmoid colon, esophagus, gastric mucosa and gall bladder. Occasionally, hemorrhagic pancreatitis and infarcts of the liver and kidneys are seen.

Ionizing Rays. X-irradiation inhibits the SSP-L, allegedly because of its leukopenic action. On the other hand, local irradiation of the abdomen may produce diffuse fibrinoid lesions with hyaline thrombi in the renal glomerular capillaries of rabbits subsequently given *E. coli* endotoxin i.v. The mechanism of this response has not yet been clarified, but conceivably ionizing rays exert their inhibitory effect through injury to hemopoietic elements, while their direct action upon tissues is diametrically opposed.

Becker B28,260/48: X-irradiation tends to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Cremer & Watson C37,986/57: The distribution of *S. typhosa* endotoxin in the RES was determined in rabbits by its ability to complex with fluorescein-tagged gamma globulin. Pretreatment with cortisone and x-irradiation did not affect the initial phagocytosis of toxin by the RES-cells of the liver, spleen and lung but inhibited its degradation and elimination after a single i.v. injection, as judged by the rate of its disappearance from the RES-cells.

Jarvis et al. G21,659/58: Diffuse vascular fibrinoid lesions with hyaline thrombi in the renal glomerular capillaries were obtained in rabbits by the i.v. injection of *E. coli* endotoxin following irradiation of the abdominal region with 300-2400 R. "These lesions involved the kidneys, spleen, liver, lungs, and heart. The character and distribution of the

lesions resembled that which occurs in the generalized Shwartzman phenomenon." The optimum time interval between irradiation and endotoxin injection was 24 hrs.

Johnstone & Howland G22,057/58: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit is inhibited, but not totally prevented, by nitrogen mustard or x-irradiation conducive to severe leukopenia. "It is concluded (a) that the presence of normal numbers of circulating polymorphonuclear leukocytes is not an obligatory prerequisite condition to the localized hemorrhagic necrosis of the Shwartzman phenomenon, and (b) the mechanisms of action of nitrogen mustard and whole body irradiation on body tissues differ in relation to the Shwartzman reaction."

Ultraviolet Rays. *Marginesu G21,460/34:* The SSP-L normally elicited by two injections of *E. coli* endotoxin in rabbits can be inhibited by ultraviolet irradiation of the skin.

Hemorrhage. Even extensive hemorrhage fails to prevent the classic SSP-L in the rabbit. On the contrary, massive loss of blood causes hemorrhagic necrosis, sometimes with multiple capillary thrombi in the gastrointestinal mucosa, lungs, liver, kidneys, spleen and pancreas of the dog.

Becker B28,260/48: Extensive hemorrhage fails to prevent the SSP-L produced by two injections of meningococcus endotoxin in the rabbit.

Fine et al. D85,444/59: An "SSP-G" can be produced in the rabbit by pretreatment with Thorotrast i.v. and subsequent induction of a hemorrhagic shock terminated after 90 mins.

by returning all the shed blood. The animals recover but die 24 hrs. later with diffuse hemorrhagic lesions. A similar SSP-G is produced in the rabbit by Thorotrust i.v. followed by endotoxin or by two successive injections of Thorotrust. "Thus, we had produced what we regard as endotoxic shock, without giving endotoxin, and achieved this simply by eliminating the endotoxin-detoxifying power of the reticuloendothelial system." Since endotoxin can be demonstrated in the blood of animals after severe hemorrhage, hemorrhagic shock is attributed to an increased absorption from the intestine and a diminished detoxification by the RES.

Hardaway et al. G26,292/62; Hardaway D12,907/62: Irreversible hemorrhagic shock with intravascular coagulation is produced in dogs by bleeding them through an ion-exchange resin for decalcification without the administration of any anticoagulant. The gas-

trointestinal, renal, hepatic, and other thrombohemorrhagic lesions, produced in this manner, are essentially similar to those elicited by intra-aortic injection of thrombin or *E. coli* endotoxin. The body responds to this form of hemorrhage by heparin—and, in some cases, fibrinolysin—production, but the adaptive changes are too slow to offer significant protection. Exogenous heparin, however, prevents these changes.

Extracorporeal Circulation

Mckay E4,788/65: A hemorrhagic diathesis sometimes follows surgical procedures in which extracorporeal circulation is employed. This is accompanied by fibrinogenopenia, thrombocytopenia, and increased fibrinolytic activity. Here, the initiation of blood clotting is presumably due to the manifold mechanical and chemical manipulations to which the blood is exposed.

Nervous Stimulation. The application of microbial or nonmicrobial irritants to the sympathetic nerves or ganglia, allegedly can produce the Reilly phenomenon (characterized by swelling and hemorrhages in the mesenteric lymph nodes and Peyer's plaques, sometimes with renal capillary thromboses and other manifestations reminiscent of the SSP-G). However, this work needs confirmation and, besides, it is not clear whether the compounds applied to the nerves act merely by virtue of their local stress effect. (Cf. pp. 96, 248.)

Nephrectomy and Other Renal Operations. Decapsulation protects the kidney against the SSP-G.

Bilateral nephrectomy performed in rabbits just prior to two i.v. injections of endotoxin, greatly increases the incidence and severity of the resulting cardiovascular lesions. In any event, it is clear that both the SSP-G and the SSP-L can be induced by the usual procedures in bilaterally nephrectomized rabbits. Hence, the presence of the kidney is not essential for the development of these phenomena. In the dog, bilateral nephrectomy in itself suffices to elicit a syndrome reminiscent of thrombotic thrombocytopenic purpura. This phenomenon may represent a transition between the THP and the hyalinosis syndrome as produced by nephrectomy, the endocrine-kidney procedure, or mineralocorticoid overdosage.

Dessy G28,647/36: Following decapsulation of the kidney, two properly spaced i.v. injections of *E. coli* endotoxin no longer produce glomerular lesions in the rabbit. The protection is ascribed to a change in the vascular system.

Dill & Erickson 91,301/38: An eclampsia-like syndrome occurs in pregnant dogs and rabbits following renal artery constriction.

Waters & DeSuto-Nagy B64,578/49-50: Essentially identical arteriolar necroses with hemorrhages are produced in dogs by i.v. injections of large doses of epinephrine, N-amyl-

amine, citrated compatible canine blood or epinephrine + large amounts of canine blood. Similar lesions are obtained by treatment of nephrectomized dogs with pressor renal extracts. The epinephrine-induced lesions can be prevented by dibenamine.

Gamble & Brunson G21,645/55: Bilateral nephrectomy performed in rabbits before two i.v. injections of meningococcal endotoxin, greatly increases the incidence of fibrinoid within the heart valves and beneath the endothelium of the coronary arteries.

Muirhead C15,392/56: Following bilateral

nephrectomy, occlusive vascular lesions develop in the dog with a syndrome reminiscent of the "thrombotic thrombocytopenia," or Moschcowitz Disease. The small arteries and arterioles throughout the viscera exhibit hyaline thrombi which often appear to be continuous with similar deposits within the necrotic vascular wall and give the histologic reactions of fibrinoid. "It is suggested that several features of the experimental lesion support an origin of the occlusive masses via extrusion or herniation of the necrotic smooth muscle of the media into the lumen."

Sheehan & Davis G21,362/59: Compression of the renal pedicle for 3 hrs. causes ischemic death of the parenchyma and blood vessels of the rabbit kidney. If, at this stage, the vascular occlusion is released, the dead arteries become greatly dilated and numerous hemorrhages occur in their media, but circulation is not re-established. The glomerular capillaries are first dilated with red corpuscles which are then pushed into the intertubular capillaries by a finely vacuolated "microfoam." After about 2 hrs., fibrin is laid down in the microfoam along the endothelial surfaces, and eventually, it may completely occlude the capillaries. Thrombi may also occur in inter-

lobular arteries. Heparinization prevents fibrin deposition in arteries, but not the formation of glomerular thrombi.

Hardaway et al. D9,396/61: Liberation of one kidney from its peritoneal attachments produces a Trueta shunt on both sides and predisposes the dog to the production of glomerular thromboses and renal cortical necrosis following intra-aortal injection of incompatible blood.

Lindberg & Riggins E60,393/63: Typical SSP-G and SSP-L manifestations can be produced by two injections of *E. coli* endotoxin in bilaterally nephrectomized rabbits.

Splenectomy. Niesert & Schneider F32,779/65: Splenectomy slightly diminishes the SSP-G normally produced by two i.v. injections of *S. abortus equi* endotoxin.

Hepatic Lesions. Ema G28,643/64: Liver damage produced by various techniques tends to inhibit the SSP-L normally produced by two injections of *E. coli* endotoxin in the rabbit.

Hysterectomy. Galton F53,009/65: Hysterectomy prevents the "SSP-G" normally produced by colchicine in the pregnant hamster.

The Hemorrhagic Stress Syndrome of Jaques. In animals pretreated with anti-coagulants, exposure to intense stress elicits a syndrome characterized by multiple hemorrhages into organs and body cavities. Since, here, there are no thromboses, the phenomenon is essentially different from the various forms of THPs. It is mentioned here only for comparison.

Lepp et al. E50,544/53; Jaques B98,877/54; D90,214/60; D29,378/61; D92,769/61; F16,537/64; E5,312/65; Jaques & Chubaty C14,736/54; Jaques et al. C28,187/56; Fisher et al. C33,194/57; van Cauwenberge & Jaques C72,748/59; Anonymous D30,697/62; Jaques & Millar G22,304/63: Anticoagulants such as phenylindandione and dicoumarol do not produce hemorrhages by themselves in the rabbit or rat, but if, simultaneously, the animals are exposed to a stressor (frostbite, hypertonic NaCl, Na-salicylate, epinephrine, histamin, insulin, etc.) multiple hemorrhages may develop especially in the subcutaneous tissue, lung, pleural cavity, peritoneum, kidneys, pericardium, etc. The animals also show hematuria and bleeding from the nose and mouth. "Our results demon-

strate that severe spontaneous hemorrhage results from the combination of any two or more procedures which affect more than one hemostatic mechanism." Curiously, heparinization did not prepare the animals for this type of hemorrhagic syndrome perhaps because it "interferes with certain effects of stress at the level of the target organ." In any event, "stress constitutes a hemorrhagic factor" under certain circumstances. In the production of hemorrhage, blood coagulation (fibrin formation), platelet plaque formation, and vascular integrity (capillary resistance, vasoconstriction) play decisive roles and presumably two or more of these factors must be deranged in order to produce a hemorrhagic syndrome.

THE PLURICAUSAL THPs

History

The concept that *every well-characterizable specific disease entity must have its own particular cause* gained acceptance mainly during the nineteenth century.

The emergence of modern bacteriology under the influence of Semmelweis, Pasteur, Koch and their contemporaries furnished countless examples in support of this view as applied to the microbial diseases. It became evident that the characteristic syndrome of any one infectious malady—such as tuberculosis, cholera, typhoid or diphtheria—could be elicited only by its own specific kind of germ.

Soon afterwards, research in the fields of nutrition and endocrinology showed that the same principle is applicable here also. Such previously mysterious diseases as scurvy, pellagra or rickets were each traced to the lack of one specific vitamin, while the most diverse endocrine derangements were found to result either from a lack or an excess of particular hormones, each compound being responsible for one kind of derangement only. These data were readily acceptable, since they agreed with earlier observations in toxicology: it had long been known that poisoning with lead, arsenic or certain plant extracts induces specific syndromes, each characteristic of the particular poison used.

In the face of all this well-documented evidence, it seemed that we must henceforth abandon the vague notions of our predecessors who thought that diverse diseases can result from a single cause and, conversely, that one and the same malady can be produced by different causative agents. The very idea that any one disease, say tuberculosis, might be due, in different patients, to malnutrition, heredity, excessive physical work or emotional shock appeared to be as unscientific as the superstitions of antiquity which attributed the most diverse maladies to the "evil eye" or the jealousy of the gods. Yet, there remained the disturbing fact that certain individuals are uncommonly resistant or susceptible to certain diseases; indeed, these "individual variations in disease proneness" can often be traced to, or even purposely modified by, identifiable factors.

The concept of the "pluricausal diseases" attempts to analyze this "soil factor" by objective and, wherever possible, quantitative experimental techniques. Up to now, one of its most striking contributions has been to show, on many disease models, that a variety of "sensitizing factors" can so prepare the organism that it will respond to certain "challengers" with a stereotyped reaction whose character can be predicted. In each case, the quality of the expectable morbid lesion (e.g., inflammation, necrosis, calcification, thrombohemorrhagic changes) is determined by the sensitizer, but the disease proneness remains latent until a challenger is applied which makes a response manifest and determines its location.

It was in the course of our studies on the mechanism of *stress-induced morbid lesions* that we first became aware of pluricausal diseases. We noted, for example, that the same nonspecific stressor agent (e.g., exposure to cold) could either produce no disease or elicit quite selective lesions in certain organs (e.g., thymus, gastrointestinal tract, kidney), depending upon "conditioning factors." Apparently, these modifying agents (e.g., diet, hormones, prior exposure to stress) can preferentially affect the sensitivity of certain organs and thereby determine the localization of disease.

Inflammation is perhaps the most typical tissue response to nonspecific topical stressors, and its regulation by pro- and antiphlogistic "stress hormones" is another example of humoral conditioning. Here a relative excess of prophlogistic agents can act as the "sensitizer," but it takes an appropriate tissue irritant to

unmask the latent disease proneness thus induced and to determine the location of the resulting inflammatory response.

Later it became possible to sensitize experimental animals for the production of a *syndrome of hyalinosis*, which furnished us with several models of collagen diseases, such as periarteritis nodosa and hypertensive nephrosclerosis. This sensitization was achieved by treatment with mineralocorticoids and dietary supplements of sodium. As yet, little work has been done concerning the challengers necessary for the evocation and localization of hyalinosis at different sites in animals thus sensitized. Yet it has been shown, for example, that unilateral nephrectomy can predispose the contralateral kidney to the development of a hyalinizing malignant nephrosclerosis and hypertension, while partial constriction of peripheral arteries exerts a topically protective effect, presumably because of the local reduction in blood pressure.

All these and many other findings give additional support to the view that a variety of agents are only conditional pathogens whose toxicity and organ affinity depend upon accessory circumstances. In other words, only some diseases are induced by individual specific pathogens (microbes, poisons) while others have no single cause but depend upon pathogenic constellations of events. Indeed, many apparently quite specific disease entities, such as peptic ulcers or hypertension, can result from a variety of concurrently applied potential pathogens, presumably because, in the final analysis, these combinations of agents interfere with the same sets of physiologic mechanisms.

Additional observations of this kind were made in studying the chemical production of cardiac necroses after sensitization by concurrent treatment with both gluco- and mineralocorticoids (or certain halogenated corticoids which possess both gluco- and mineralocorticoid potency). This treatment causes no specific cardiac lesion in itself, but so prepares the organism that it responds to a variety of systemic stressors (restraint, forced muscular exercise, cold, trauma) with large infarctoid necroses specifically localized in the myocardium. Here again, the resulting stereotyped lesion was interpreted as a "*pluricausal cardiopathy*" whose development depends upon the properly coordinated application of several potential pathogens.

More recently, we encountered a similar situation in *calciphylaxis*. Here, parathyroid hormone or vitamin-D derivatives act as "sensitizers," in that they condition the organism so that subsequent treatment with "challengers" will elicit localized tissue calcification. Thus, after pretreatment with a dose of parathyroid hormone which produces a calcinotic diathesis (a latent predisposition for soft tissue calcification), subsequent intravenous challenge with CrCl₃ induces calcium precipitation in the parathyroids, ferric dextran in the pancreas, 5-HT in the salivary glands, etc. In other words, the hypercalcemic agent acts as a general tissue sensitizer for a particular (here calcifying) type of response, but challengers are necessary to make this tendency manifest and to localize the reaction in certain regions.

During these investigations, our attention was accidentally drawn to the fact that *thrombohemorrhagic lesions* can also be predictably elicited in certain target organs by conjoint treatment with appropriate pathogens, none of which is ef-

fective alone. Thus, while we were studying the factors conducive to pluricausal cardiopathies, it was noted that in rats pretreated with 9 α -fluorocortisol (F-COL) + Na₂HPO₄, the subsequent administration of ferric oxide saccharate (Fe-OS) produces thromboses in the capillaries and medium-sized veins of the heart often associated with myocardial necroses. At the same time, iron-containing homogeneous thrombi were formed in the renal glomerular capillaries thus causing a change reminiscent of the SSP-G. Furthermore, cutaneous blood-vessel thrombosis with consequent necrosis was induced at sites where polymyxin was given s.c. in conjunction with Fe-OS i.v. Here, the tissue lesions were reminiscent of the SSP-L.

Subsequently, many forms of THPs became known which are pluricausal in the sense that they depend upon the coordinated effect of multiple pathogenic factors: sensitizers, which act systemically and induce a thrombohemorrhagic diathesis, and challengers, which make this latent disease-proneness manifest and determine the localization of the resulting lesions. We speak of a pluricausal THP-L when the challenger is applied topically to the tissue in which the response is to be elicited, and of a pluricausal THP-G when the challenger is administered systemically. Even in the latter case, it is possible, by appropriate combinations of sensitizers and challengers, to produce thrombohemorrhagic lesions predictably localized in certain organs, such as the heart, kidney, uterus, adrenals, salivary glands or the skin.

In this volume, a special section had to be set aside for the discussion of these pluricausal THPs for several reasons:

1. By definition, they are elicited by the conjoint action of several factors; hence, it was impossible to list them according to any one of these and it would have been redundant to mention them under each constituent of the evocative pathogenic situation.

2. The concept of the pluricausal THPs attempts to analyse thrombohemorrhagic lesions from a new point of view which requires a special classification of the pathogens and syndromes involved.

3. Unlike the work reported in the rest of this book, the experiments on the pluricausal THPs were performed in the same laboratory under conditions especially designed to permit intercomparisons.

Selye 38,798/37; B1,204/46: Detailed description of the general adaptation syndrome as a nonspecific response of the organism to various stressor agents. The distribution and type of the organ lesions are influenced by a variety of factors (diet, hormones, prior exposure to stress) which can modify the standard response.

Selye B40,000/50: The concept of the "pluricausal diseases" is developed on the basis of experiments showing that exposure to the same kind of stress can produce diverse types of "diseases of adaptation" depending upon the simultaneous action of "conditioning factors" which determine the localization of stress-induced morbid lesions. Another example of a pluricausal disease is the periarter-

itis nodosa and hypertensive nephrosclerosis which develops in rats upon combined treatment with mineralocorticoids and dietary supplements of sodium, though neither of these factors is effective by itself.

Pařízek & Záhoř E84,304/56: A single subcutaneous injection of cadmium salts causes hemorrhagic necrosis in the rat testis. [These lesions are associated with thrombosis and changes in the testicular vessels indistinguishable from those of the THP (H.S.).]

Selye C50,810/58; C92,918/61: Conditioning with sodium salts so sensitizes the rat that it responds to certain halogenated corticoids with infarctoid necroses localized in the myocardium. The resulting Electrolyte-Steroid-Cardiopathy with Necrosis (ESCN) is interpreted as a

pluricausal disease. Even stress (restraint, hemorrhage, trauma) can produce infarctoid necroses in the myocardium of rats sensitized by certain corticoids. In all these instances, the development of morbid lesions depends upon the properly coordinated application of several potential pathogens.

Selye & Grasso D4,898/61: In the course of work on the pathogenesis of pluricausal cardiopathies it was noted that rats pretreated with 9 α -fluorocortisol (F-COL) + Fe-OS + Na₂HPO₄ regularly develop thromboses in the capillaries and medium-sized veins of the heart, often associated with myocardial necroses. At the same time, iron-containing homogeneous thromboses were formed in the renal glomerular capillaries similar to those seen in the SSP-G.

Selye D15,540/62: An extensive monograph on calciphylaxis discusses many instances of pluricausal morbid disease. After sensitization with in themselves nonpathogenic doses of vitamin-D derivatives or parathyroid hormone, a variety of otherwise also ineffective mechanical or chemical challengers cause tissue calcification. In the case of topical administration, the challengers induce calcium deposition at the site of their application, while following i.v. injection, they cause selective calcinosis in certain organs for which they possess a special affinity. Thus, the challengers are necessary, not only to make a latent calcinotic tendency manifest, but also to localize the reaction in certain regions.

Selye et al. D24,159/63: Certain experiments on rats suggest that discharged mast cell material can capture blood-borne particulate substances and through this "mastocytopenia" participate in the localization of disease. If the mast-cell discharger polymyxin is given s.c. simultaneously with India ink i.v., the carbon particles are deposited in a halo around the polymyxin-injection site, where discharged mast-cell granules are found in close association with India ink in the connective tissue and the walls of the small blood vessels. If polymyxin is given somewhat prior to the i.v. injection of India ink, there is no topical carbon fixation but many pulmonary capillaries are occluded by thrombi which contain aggregates of India ink. Here, the discharged mast-cell granules may have already been carried from the site of polymyxin injection to the pulmonary circulation by the time the ink was introduced into the circulation, and it is perhaps for this reason that the carbon particles are fixed in the lung. Essentially similar results are obtained when Fe-OS is given i.v. instead of India ink. However, since iron is more toxic, the local pre-

cipitation of Fe-OS tends to cause necrosis and thrombosis, especially in the center of the polymyxin-injection site. "The cutaneous blood-vessel thrombosis with consequent necrosis induced by polymyxin in conjunction with the intravenous injection of Fe-OS is somewhat reminiscent of the local Shwartzman-Sanarelli phenomenon and may help to elucidate the mechanism of such topical hypersensitivity reactions."

Gabbiani G11,111/64: In rats sensitized by the combined administration of 9 α -fluorocortisol and a sodium salt, or by exposure to an intense stressor agent, a single injection of colloidal carbon produces bilateral cortical necrosis of the kidney, with precipitation of fibrin in the glomerular capillaries. The changes resemble those of the SSP-G.

Selye G23,231/66; G23,236/66; G23,239/66: General reviews on the history and present status of the "pluricausal diseases" with special reference to the pluricausal THPs.

Selye & Tuchweber G19,428/64: First description of a nonspecific pluricausal THP by simultaneous combined treatment with various metal salts or agar i.v. and norepinephrine s.c. Thrombohemorrhagic lesions became evident within a few hrs. at the norepinephrine injection site as well as in the heart, duodenum, lung and kidney. The response is nonspecific since it can be elicited by so many combinations of agents; and it is also pluricausal since no one pathogenic factor suffices in itself. This THP could hardly be due to the induction of an altered state of immunological reactivity, since it is elicited without any sensitizing pretreatment. However, "it resembles in some respects certain spontaneous diseases of man (thrombotic thrombocytopenic purpura, anaphylactoid purpura of Schönlein-Henoch, eclampsia, Morbus maculosus Werlhof) and particularly the general and local forms of Shwartzman's "phenomenon of tissue reactivity to bacterial filtrates." The most active i.v. metal combinations were: lead acetate in combination with FeCl₃, Fe-OS or Thorotrust, CeCl₃ in combination with Fe-OS or India ink and LaCl₃ in combination with Fe-OS, all these metal combinations being administered simultaneously with norepinephrine s.c. The production of lesions in the internal organs by any of these agents was greatly aggravated by norepinephrine s.c. which, in addition, produced thrombohemorrhagic changes at the injection site. These topical manifestations of the THP are especially pronounced if the catecholamine is injected into a paw.

Gabbiani G32,006/66: "In the rat cadmium chloride causes a selective hemorrhagic ne-

rosis of the Gasserian ganglion and of the spinal sensory ganglia. Here the nervous cells show synosis of nuclei and lysis of cytoplasm and appear surrounded by hemorrhagic suffusions." [This is a particularly clear-cut ex-

ample of a moncausal THP-G with typical thrombohemorrhagic lesions at a distance from the site where the causative agent is administered (H.S.).]

Comparison of Pluricausal THPs and Calciphylaxis

Among all the pluricausal diseases that have been carefully analyzed up to now, calciphylaxis is probably most comparable to the pluricausal THPs; hence, it may be instructive to confront these two conditions by way of an introduction to our present subject.

1. Although the characteristic tissue lesion is hemorrhagic thrombosis in the THP and calcification in calciphylaxis, both phenomena depend upon the co-ordinated action of two types of pathogens: sensitizers and challengers.

2. There are topical and systemic variants of both the THP and of calciphylaxis.

3. When given by itself (without a challenger), the sensitizer produces either no lesion or changes (hemorrhagic thrombosis or calcification respectively) whose distribution is nonspecific in that it is largely independent of the particular sensi-

COMPARISON OF PLURICAUSAL THPs AND CALCIPHYLAXIS

| Points of Comparison | Phenomena | |
|--|---|---|
| | Pluricausal THP | Calciphylaxis |
| Characteristic lesion | Hemorrhagic thrombosis | Calcification |
| Production | By sensitizer + challenger | By sensitizer + challenger |
| Sensitizer | | |
| Activity when given by itself | Nonspecific distribution of THPs in naturally predisposed organs, especially: heart, kidney, lung, duodenum | Nonspecific distribution of calcification in naturally predisposed organs, especially: heart, kidney, lung, stomach, duodenum |
| Activity when given with topical challenger | THP at sites where challenger is applied (THP-L) | Calcification at sites where challenger is applied (topical calciphylaxis) |
| Activity when given with systemic challenger | THP at sites for which blood-borne challenger has special affinity (THP-G) | Calcification at sites for which blood-borne challenger has special affinity (Systemic calciphylaxis) |
| Challenger | | |
| Variants | Topical and systemic | Topical and systemic |
| Activity when given by itself | Neither topical nor systemic challengers can cause a THP without sensitization | Neither topical nor systemic challengers can cause calcification without sensitization |
| Inhibitors of the phenomena | Cyproheptadine Pretreatment with stressors | Cyproheptadine Pretreatment with stressors |
| Role of metals | Sensitizers | Challengers (Yet in calcergy sensitizers!) |
| Regional predisposition (in rat) | Hind paw predisposed Calvarium resistant | Hind paw resistant Calvarium predisposed |

tizer used and limited to naturally predisposed organs, especially the heart, kidney, lung and gastrointestinal tract.

4. When given by themselves (without appropriate sensitization), neither topical nor systemic challengers are effective in causing THPs or calciphylactic lesions.

5. When given with a topical challenger, the sensitizer permits the elicitation of characteristic lesions (hemorrhagic thrombosis or calcification) at the site where the challenger is applied.

6. When given with a systemic challenger, the sensitizer predisposes to the production of lesions (hemorrhagic thrombosis or calcification) at sites for which the blood-borne challenger has a special affinity.

7. Certain agents (e.g., cyproheptadine, stressors) can prevent the development of both THPs and calciphylactic phenomena under suitable experimental conditions.

8. Metals play a particularly prominent role in the production of both THPs and calciphylaxis, although in the former case they act as sensitizers and in the latter as challengers. (However, in calcergy, as in the THP, metals act as sensitizers.)

9. Finally, it may not be pure coincidence that in calciphylaxis the calvarium of the rat is especially sensitive and the hind paw particularly resistant to topical challenge, while the reverse is true in the THP.

Comparison of Monocausal and Pluricausal THPs

First, it must be pointed out that most of the THPs hitherto considered were monocausal: they depended essentially upon the actions of single pathogens and exhibited a common stereotyped pattern of morbid lesions. The pluricausal THPs are different in both these respects. We have seen, for example, that hemorrhagic thromboses can be produced by the i.v. injection of thrombin, thromboplastin, placental extracts, amniotic fluid, Liquoid, agar, live bacteria or bacterial toxins. In all these instances, the resulting monocausal THP is essentially the same, since the histologic structure and organ distribution of the hemorrhagic thromboses are virtually identical, irrespective of the causative agent. The most commonly affected organs are the kidney, intestine, lung and heart. Although, depending upon circumstances (age, species, dosage, etc.), the resulting lesions may be somewhat more prominent in one or the other of these naturally predisposed sites, the distribution pattern is essentially stereotyped.

It is true that an SSP-G can be elicited by preparation with one, and provocation with another endotoxin, but the classic "Shwartzman-active substances" are both chemically and toxicologically closely related: they merely represent interchangeable members of the same class.

It is also true that occasionally an "SSP" has been produced by preparation with a microbial, and provocation with a nonmicrobial agent, or vice versa. However, here again the lesions are not strictly pluricausal in our sense of the word, since the use of two agents is not a necessary prerequisite for their evocation, identical THPs being produced by two injections of the same endotoxin. In other words, here the nonmicrobial agent was merely regarded as an adjuvant or substitute

for a bacterial endotoxin and not as a qualitatively distinct element of a new pathogenic situation.

In the production of pluricausal THPs, each constituent of a disease-producing constellation has a special role to play. It soon became evident that, in this respect, the causative factors fall into distinct classes: the members of a given class are largely interchangeable but they cannot be replaced by agents of another class. This fact and the protean manifestations of the diverse pluricausal THPs make it necessary to preface our study with a classification both of the pathogenic factors and of the polymorph morbid syndromes elicited by them.

The Pluricausal THP-factors

The factors necessary for the synthesis of a pathogenic situation conducive to a pluricausal THP (just as those required to produce calciphylaxis) can be classified into two principal groups: the "sensitizers" which induce a general predisposition or tissue responsiveness, and the "challengers" which evoke and localize the response in certain predetermined regions.

Sensitizers. These compounds merely create a latent or manifest general thrombohemorrhagic diathesis in which the lesions, if present, are nonspecifically distributed, that is, limited to naturally predisposed organs (heart, lung, kidney, intestine). There are two kinds of sensitizers: incomplete and complete.

Incomplete sensitizers do not manifest their thrombohemorrhagic effect except when given in combination with challengers or other incomplete sensitizers. In the latter case, we may speak of co-sensitizers which, if properly paired, become complete sensitizers. Even such pairs are only irregularly effective, depending upon individual variations in susceptibility whose nature has not yet been elucidated.

Examples of incomplete sensitizers are FeCl_3 , CeCl_3 and India ink. By themselves, these agents do not produce either a THP-L or a THP-G, even when given in fatal doses. However, at least in certain predisposed individuals, their systemic administration can elicit a THP-L at sites prepared by the topical application of a challenger (e.g., epinephrine, norepinephrine, 5-HT or vasopressin).

Complete sensitizers are much more regularly effective, but again only in producing a nonspecific THP-G in which the thrombohemorrhagic lesions are limited to naturally predisposed organs.

Examples of complete sensitizers are agar, InCl_3 or ScCl_3 or combinations of two co-sensitizers (e.g., $\text{FeCl}_3 + \text{CeCl}_3$, $\text{CeCl}_3 + \text{India ink}$, $\text{FeCl}_3 + \text{India ink}$). Agar quite regularly produces a nonspecific THP-G, but since it consists of a mixture of various compounds not yet fully identified, it remains to be seen whether its effect is due to a combination of several co-sensitizers or to a single compound. Single complete sensitizers and pairs of co-sensitizers can produce true pluricausal THP-Gs by themselves, but only occasionally, in especially predisposed individuals. However, any of these complete sensitizers (single compounds or mixtures of co-sensitizers) is regularly effective when administered in combination with a suitable challenger.

Challengers. The chief characteristic of all challengers is that by themselves, even in fatal doses, they are totally ineffective in producing any form of THP but, when given in combination with sensitizers, they can predictably localize throm-

bohemorrhagic lesions in certain regions. Apparently, they create foci of special tissue hypersensitivity.

We distinguish between topical and systemic challengers. Examples of *topical challengers* are catecholamines, vasopressin and 5-HT. In animals systemically pretreated with suitable sensitizers, the s.c. injection of these challengers results in the production of a THP-L, that is, of topical thrombohemorrhagic lesions. The hind paws of the rat are particularly susceptible to the production of such local hemorrhagic thromboses; hence, compounds are usually tested for possible topical localizing potency by injecting them into the hind paws of rats pretreated with a sensitizer i.v.

Examples of *systemic challengers* are dextran, egg white and ACTH. By themselves, these compounds are likewise ineffective in producing a THP but, when given systemically in combination with sensitizers, they produce lesions with predictable localizations. Thus, dextran or egg white i.p., given in combination with sensitizers, can evoke localized thrombohemorrhagic lesions in the anaphylactoid shock organs (snout, ears, paws, tail), that is, an anaphylactoid purpura. Under similar circumstances, ACTH s.c. produces particularly severe thrombohemorrhagic lesions in the adrenals. The chief difference between topical and systemic challengers is that the former evoke the lesions only where these agents are applied, while the latter seek out their target organs, even when administered systemically. Yet, some challengers may act both topically and systemically, depending upon dosage and the route of administration.

As we shall see later, there are many additional sensitizers and challengers, but the few mentioned up to now will suffice to illustrate our classification:

THE PLURICAUSAL THP-FACTORS

| Sensitizers | | Challengers | |
|-------------------|---------------------------------------|----------------|-----------|
| Incomplete | Complete | Topical | Systemic |
| FeCl ₃ | ScCl ₃ | Epinephrine | Dextran |
| CeCl ₃ | CeCl ₃ + FeCl ₃ | Norepinephrine | Egg-white |
| India ink | CeCl ₃ + India ink | 5-HT | ACTH |

For a better understanding of the activities characteristic of individual THP factors, these may be summarized as follows:

ACTIVITY OF PLURICAUSAL THP-FACTORS

| Factors | THP-Activity |
|------------------------------------|--|
| Incomplete sensitizer | 0 |
| Challenger | 0 |
| Incomplete sensitizer + challenger | Irregular and localized |
| Complete sensitizer | Regular (agar) or irregular (two co-sensitizers) but always generalized in naturally predisposed organs. |
| Complete sensitizer + challenger | Regular and severe |

(For original articles relating to the preceding general discussion cf. abstracts following the sections on the pluricausal THP-Ls and THP-Gs.)

The Pluricausal THP-L

Pluricausal THPs can be elicited only by combined treatment with challengers and complete sensitizers or pairs of co-sensitizers. Here again we must distinguish between local and general variants, although the local form may be associated with systemic changes if a sufficiently large amount of the topically administered challenger reaches the circulation. Pluricausal THP-Ls are elicited by combined treatment with systemically applied sensitizers and chemically unrelated topical challengers.

In the most common test procedure, the sensitizers are injected i.v., the challengers s.c. and/or into a hind paw, since the latter is particularly sensitive to the production of a THP-L. In such experiments, *epinephrine* and *norepinephrine* proved to be particularly potent challengers and, with these, especially constant and severe THP-Ls were obtained in the hind paw when topical injection of the catecholamine was preceded by the s.c. administration of a booster dose under the dorsal skin. Here, presumably, after absorption into the blood stream, the catecholamines augment topical responsiveness to a second injection of the same compounds. Using this catecholamine double-challenge procedure, the following sensitizers given i.v. were found to permit the production of a THP-L in the hind paw of the rat:

| | |
|---------------------------------------|--|
| Agar | Fe-OS + Pb-acetate |
| Carrageenin | Fe ₂ (SO ₄) ₃ + Thorotrast |
| CeCl ₃ + FeCl ₃ | InCl ₃ + India ink |
| CeCl ₃ + Fe-OS | InCl ₃ + Thorotrast |
| CeCl ₃ + Fe-sorbitol | India ink (at high dose levels only) |
| CeCl ₃ + InCl ₃ | India ink + tannic acid |
| CeCl ₃ + India ink | LaCl ₃ + tannic acid |
| CeCl ₃ + tannic acid | Na-caseinate + tannic acid |
| CeCl ₃ + Thorotrast | Pb-acetate + tannic acid |
| CrCl ₃ + tannic acid | Pb-acetate + Thorotrast |
| FeCl ₃ + India ink | Polymyxin + tannic acid |
| FeCl ₃ + Pb-acetate | ScCl ₃ |
| FeCl ₃ + tannic acid | Tannic acid (at high dose levels only) |
| FeCl ₃ + Thorotrast | Tannic acid + Thorotrast |
| Fe-dextrin + Thorotrast | Tannic acid + 48/80 |
| Fe-OS + LaCl ₃ | Thorotrast + ZnCl ₂ |

A similar sensitization for the production of a THP-L by norepinephrine can be induced by endogenous sensitizers e.g., by:

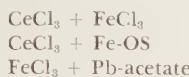
Certain inflammatory exudates

Whole heterologous blood (of dog, cat, rabbit, guinea pig, chicken and man, but not of duck and hamster)

In such experiments, epinephrine can replace norepinephrine and, with either of these catecholamines, the THP-L in the hind paw is usually more pronounced than at the s.c. injection site on the back. Following treatment with most of the sensitizers, the topical lesions are accompanied by more or less pronounced thrombohemorrhagic changes in the naturally predisposed organs such as the kidney and lung. These systemic lesions are especially common and severe when agar is used as a sensitizer, less conspicuous with the metal combinations, and quite exceptional following sensitization by large doses of tannic acid alone (al-

though in this instance splenic hemorrhages and thromboses are occasionally seen).

5-HT can also act as a topical challenger in such experiments, but only after systemic sensitization with certain agents, particularly:



Another interesting difference between the activity of these challengers is that 5-HT, unlike the catecholamines, apparently possesses no potentiating effect upon a second injection of a challenger given at a distance from the first. For example, after sensitization with CeCl₃ + FeCl₃ i.v., norepinephrine injected into one hind paw of the rat augments the thrombohemorrhagic action of a second s.c. injection of either norepinephrine or 5-HT. Conversely, the effect of the latter compound is merely local. However, norepinephrine and 5-HT both potentiate each other's thrombohemorrhagic effects when mixtures of them are injected s.c. into rats sensitized with CeCl₃ + FeCl₃ i.v.

Among a large number of other compounds tested, only some *mast-cell dischargers* (polymyxin, 48/80) were found to possess topical challenging effects under comparable conditions. Hence, the ability of drugs to produce a THP-L in properly sensitized animals, cannot be ascribed merely to tissue damage but must be regarded as comparatively specific.

On the other hand, it is noteworthy that under certain conditions even a physical agent such as *exposure to cold* can produce a THP-L. For example, in a rat forced to walk on ice after an i.v. injection of carrageenin or of tannic acid + Thorotrust, the paws undergo hemorrhagic necrosis with thromboembolic changes in the local vessels not unlike those seen in thromboangiitis obliterans.

It has been noted, furthermore, that *different regions of the body are not equally sensitive to the production of a THP-L*. For instance following sensitization with Na-caseinate + tannic acid, FeCl₃ + CeCl₃, or Thorotrust + tannic acid, challenge with norepinephrine s.c. over the calvarium or the upper part of the back produces little or no local response, while the same amount of this catecholamine given s.c. in the sacral region or in a hind paw elicits a severe THP-L. The knee joint of the rat is particularly sensitive to the production of a THP-L by the topical injection of norepinephrine following suitable sensitization.

VARIOUS SENSITIZERS + CATECHOLAMINES, 5-HT, ETC.

Selye et al. G23,211/65: Following sensitization with agar or CeCl₃ + FeCl₃ i.v., injection of epinephrine, norepinephrine or 5-HT into a hind paw produces a THP-L. Many other agents are ineffective although mast-cell dischargers (48/80, dextran, polymyxin, Thorotrust) can produce an anaphylactoid purpura (not limited to the injection site) under certain conditions. After CeCl₃ + FeCl₃ i.v., epinephrine injected s.c. in the rat also exerts some

distant effect in that it augments the thrombohemorrhagic action of a second s.c. injection of either norepinephrine or 5-HT. Conversely, the effect of the latter compound is merely local. Epinephrine and 5-HT each potentiate the other's local thrombohemorrhagic effect when mixtures of them are injected s.c. into rats pretreated with CeCl₃ + FeCl₃ i.v. Among the combinations of metallic sensitizers that prepare the rat for the production of a THP-L in the hind paw by topical administration of 5-HT, the most effective are: CeCl₃ + FeCl₃, CeCl₃ + Fe-OS, LaCl₃ + Fe-OS, lead acetate +

PLATE I. *Organ changes characteristic of the typical THP-L and THP-G.* 1. Hemorrhagic cutaneous necrosis with hyperemic peripheral halo in rat sensitized by lead acetate + FeCl₃ i.v. and challenged by norepinephrine s.c. 2. THP-L in the left hind paw. Typical hemorrhagic necrosis at the site of norepinephrine challenge in a rat sensitized by agar i.v. 3. Renal changes characteristic of the THP-G. Hyaline thrombi in the glomerular capillaries of a rat given lead acetate + Fe-OS i.v. and norepinephrine s.c. Iron in the capillary thrombi is shown histochemically (Prussian blue, $\times 120$). 4. One of the glomeruli from Fig. 3 at higher magnification ($\times 460$). 5. Characteristic mottled appearance of the renal surface during THP-G elicited by agar i.v. Beginning at the pylorus (*large arrow*), the duodenum is hemorrhagic and edematous. The small arrow points to an exulcerated necrotic area where perforation is prevented by the formation of an omental adhesion. (After Selye & Tuchweber, G19,428/64.)

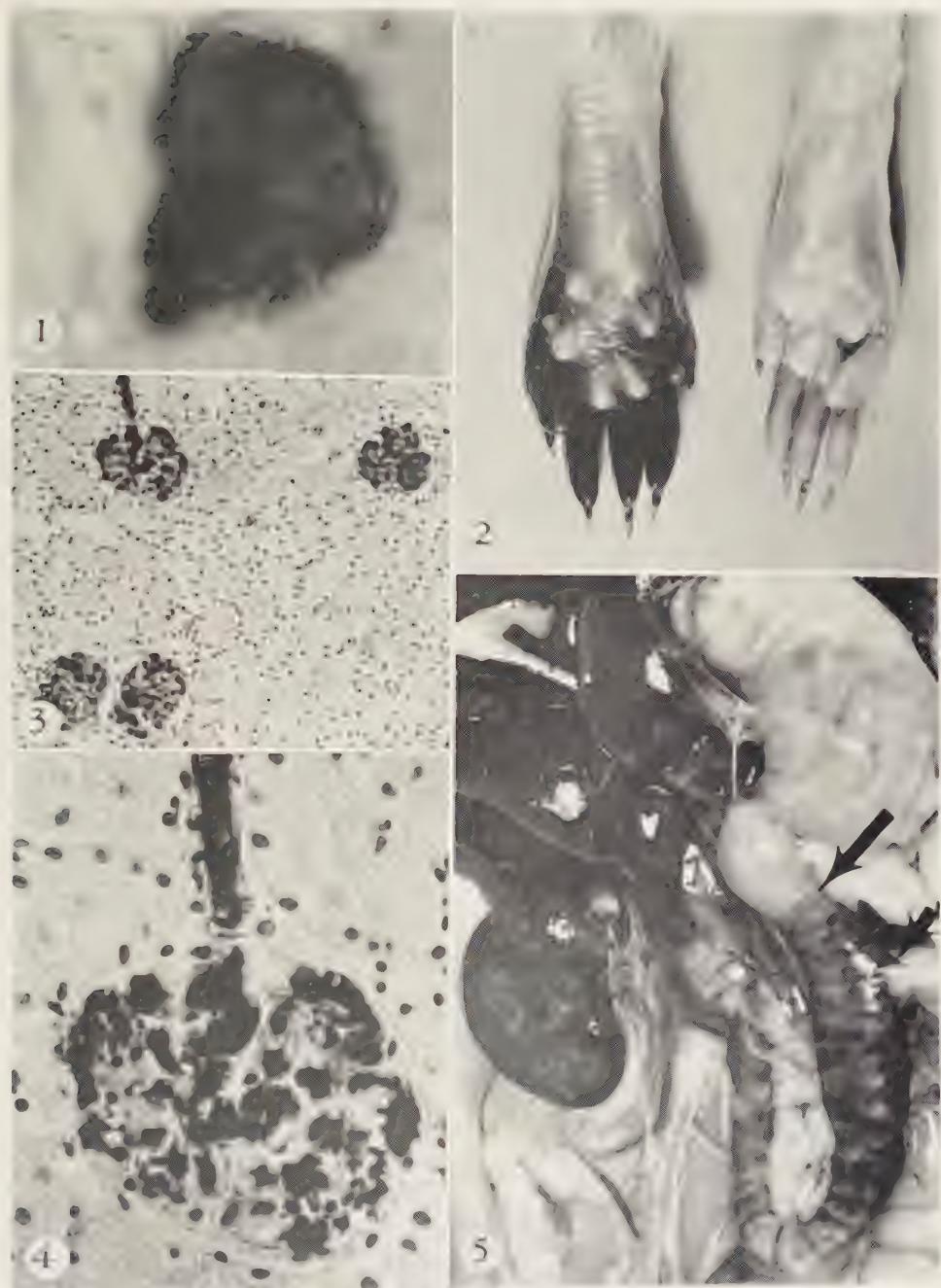


PLATE II. *THP-G affecting adrenals and tumor transplant.* *Top:* Thrombohemorrhagic lesions in the adrenals produced by Thorotrast and restraint. 1. After i.v. injection of Thorotrast alone, the gland has normal appearance. 2. After combined treatment with Thorotrast i.v. and restraint, hemorrhagic spots are visible in the adrenal (*between arrows*) and the bleeding spreads into the perirenal tissue. *Bottom:* Induction of hemorrhagic necrosis in Walker tumor transplants. 3. Normal Walker tumor transplant under the dorsal skin. 4. Hemorrhagic necrosis in a similar transplant induced by sensitization with Thorotrast + tannic acid i.v. and challenge by norepinephrine s.c. at a distance from the tumor. (Figs. 1 and 2 after Gabbiani *et al.*, G19,450/65. Figs. 3 and 4 after Selye, G23,231/66.)

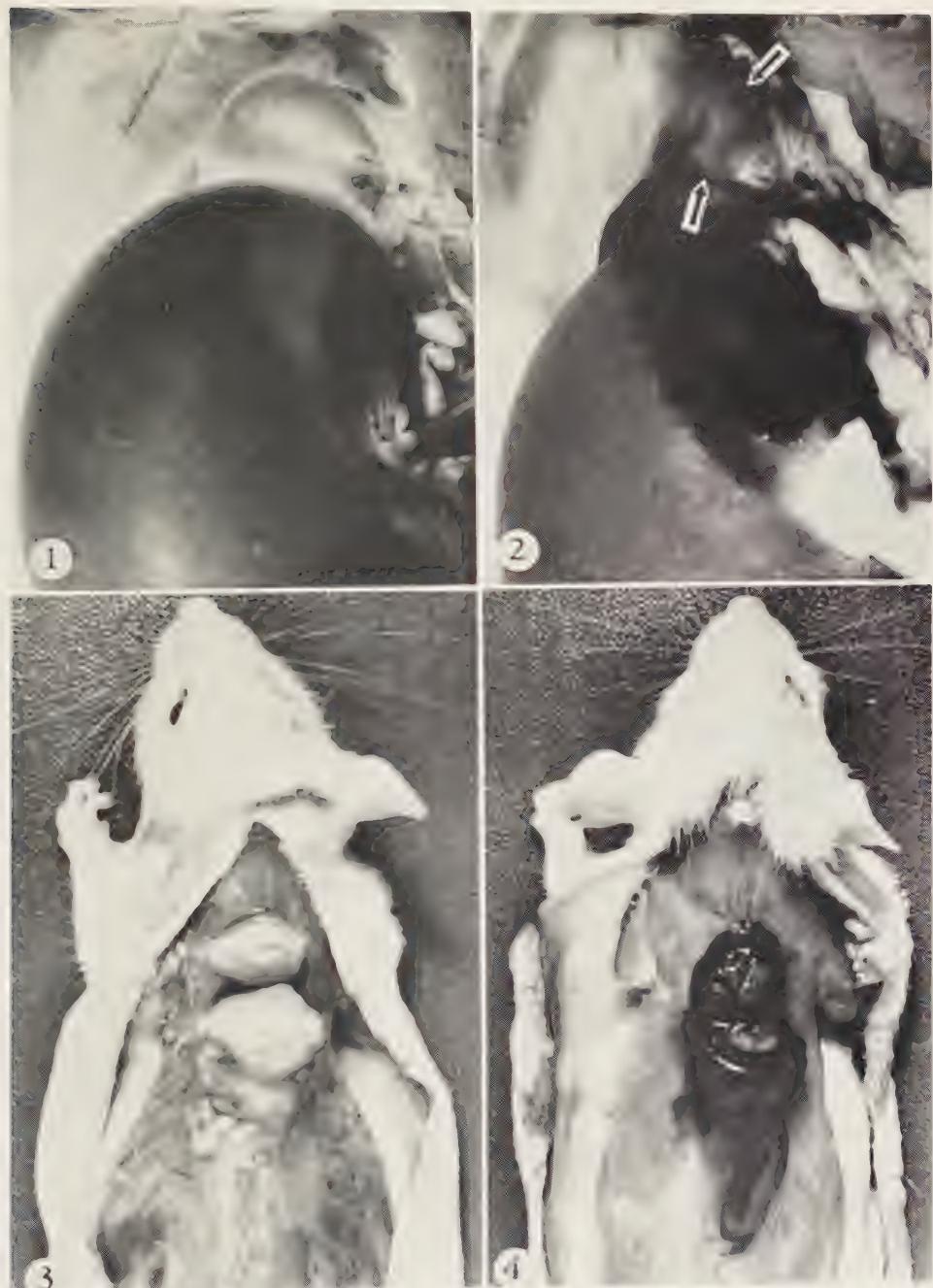




PLATE III. *Induced cold hypersensitivity causing THP in paws and tumor transplants.* 1. Rat sensitized by carrageenin s.c. before exposure to cold. 2. Same rat after exposure to cold shows hemorrhagic necrosis of nose and paws. 3. Murphy rat lymphosarcoma in thigh of carrageenin-sensitized rat. 4. Same animal after exposure to cold exhibits hemorrhagic tumor necrosis. (After Selye, G23,214/65.)



PLATE IV. Selective THP-changes in toes and salivary glands. "Renal shunt." 1. and 2. Advanced hemorrhagic necrosis of the toes (eventually resulting in self-amputation) in a rat sensitized by carrageenin s.c. and challenged by exposure to cold. 3. Selective THP-changes in snout, both external lacrimal glands and left submaxillary salivary gland of a rat sensitized with carrageenin s.c. and challenged with 5-HT i.p. 4. Normal appearance of rat kidney on section. Cortex dark, medulla light. 5. "Renal shunt" produced by sensitization with agar i.v. and exposure to stress (restraint). Medulla dark owing to congestion and thrombosis; cortex light because of anemia and beginning necrosis. Some of the glomeruli are visible owing to capillary thromboses. (Fig. 3 after Selye, G23,231/66.)

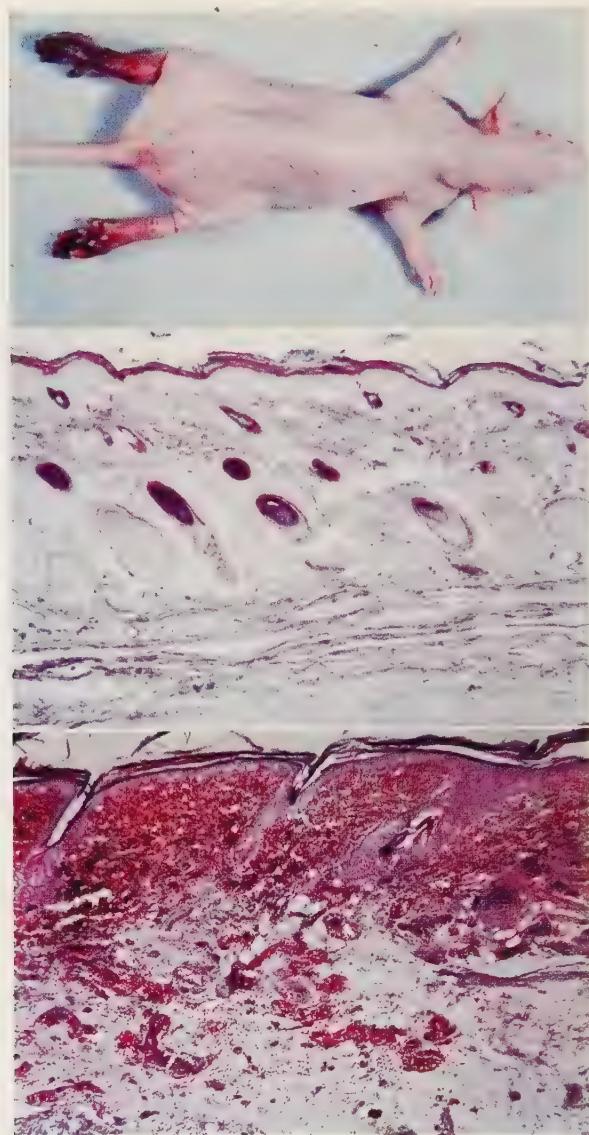


PLATE V. Obliterating thromboangiitis with hemorrhagic gangrene in the caudal extremities. (Plates V-VII illustrate the typical THP lesions that develop following combined treatment with Thorotrust + tannic acid + norepinephrine. All sections stained with multipurpose polychrome technique). *Top:* General appearance of the shaved rat. The left hind paw (which was directly injected with norepinephrine) responds most markedly, but the right hind paw also exhibits severe purple discoloration. *Middle:* Histologic aspect of the hind-paw skin of a normal control rat ($\times 120$). *Bottom:* Similar skin region from the untreated (right) hind paw of a rat which developed the aboral THP syndrome. Multiple thrombi in venules; the mast cells in the loose connective tissue are discharged and hemorrhages infiltrate the dermis up to the epidermal layer ($\times 120$). (After Selye et al., G23,208/65.)

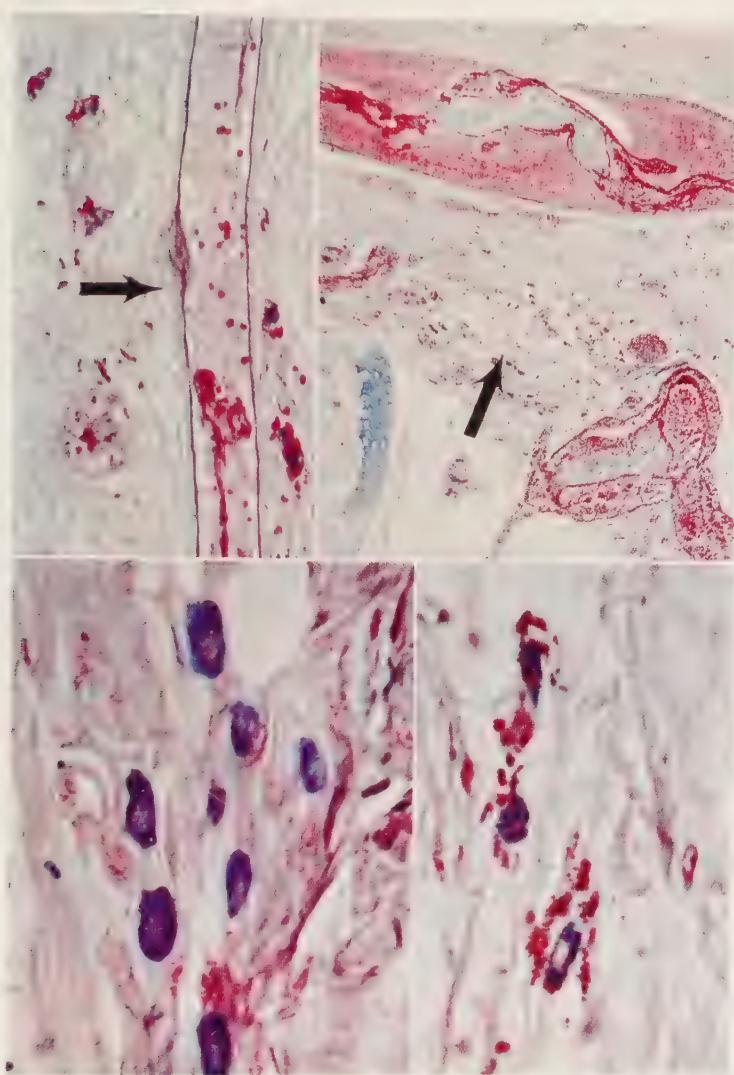


PLATE VI. Obliterating thromboangiitis with hemorrhagic gangrene in the causal extremities (continued). Top left: Medium sized vein containing fibrin threads. The elastica is split up at one point (arrow) and several partly discharged mast cells surround the vessel ($\times 460$). Top right: Several veins around a metatarsal joint contain thrombi composed of Thorotrast (here blue) surrounded by a fibrin precipitate (purple red) and erythrocytes. In adjacent connective tissue many partly discharged mast cells (arrow) ($\times 120$). Bottom left: Normal mast cells of a control animal for comparison ($\times 1000$). Bottom right: Partly discharged mast cells from region marked by arrow in picture above. Intracytoplasmic granules purple blue; extracytoplasmic granules bright red ($\times 1000$).

(After Selye et al., G23,208/65.)

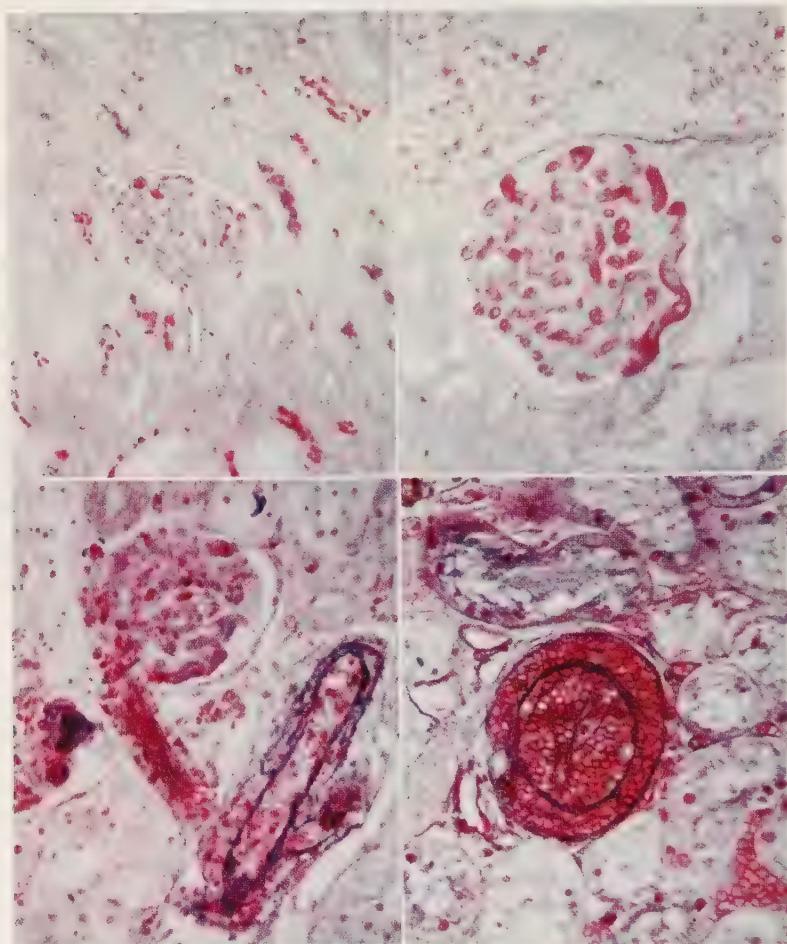


PLATE VII. *Renal changes accompanying experimental obliterating thromboangitis.* *Top left:* Normal renal glomerulus of an untreated control rat. *Top right:* In the experimental rat, some of the glomerular capillaries are completely occluded, others heavily lined ("wire-loop" appearance) by fibrin (here purple red). *Bottom left:* The walls of the interlobular artery and afferent arteriole are infiltrated by erythrocytes and the lumen of the latter as well as some of the glomerular capillaries are occluded by fibrin thrombi. *Bottom right:* Renal arteriole infiltrated with erythrocytes between the elastica interna and externa. The lumen is packed with agglutinated erythrocytes connected by a few fibrin threads. This is the earliest stage of the renal vascular lesion (all 4 Figures $\times 460$).

(After Selye *et al.*, G23,208/65.)

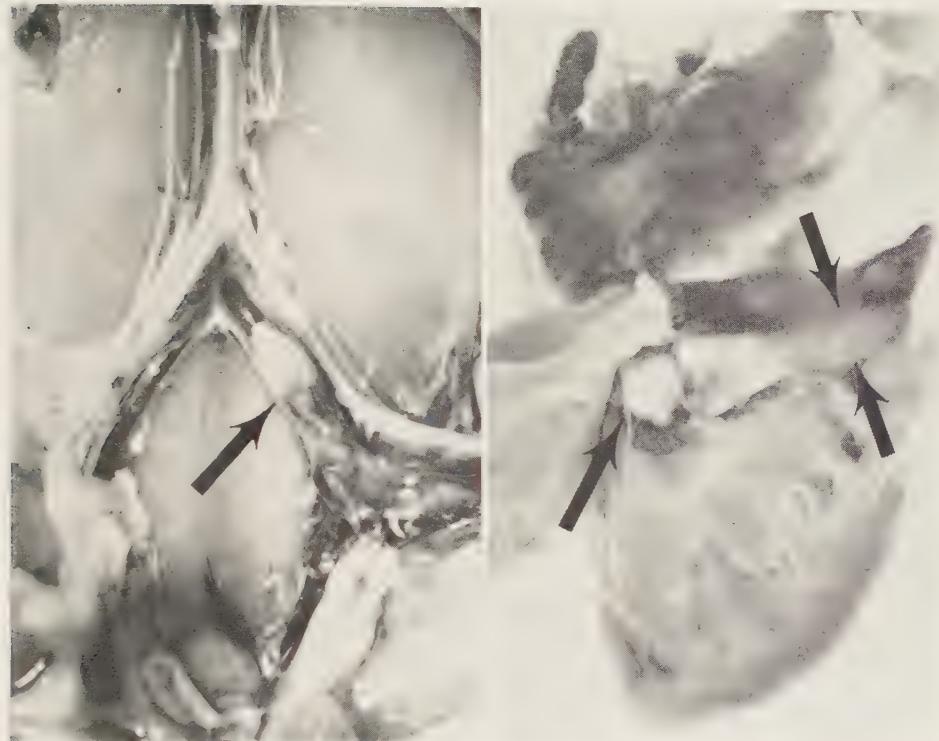


PLATE VIII. Thrombosis in large vein and embolus in pulmonary cone induced by sensitization with $ScCl_3$ i.v. and challenged by epinephrine injected into the musculature adjacent to the iliac vein. 1. Large thrombus occluding the left common iliac vein. The sharp line (arrow) dividing the white "head" from the red "tail" is clearly visible through the vessel wall. 2. Large embolus exposed by reflecting the lateral wall of the right ventricle. The white "head" is lodged in the tricuspid valve (long arrow) while the red "tail" protrudes into the pulmonary cone. (After Selye *et al.*, G32,007/66.)

FeCl_3 , and tannic acid + Thorotrast. In addition, 35 compounds were tested for their ability to produce a THP-L upon injection into the hind paws of rats sensitized with agar or $\text{CeCl}_3 + \text{FeCl}_3$ i.v. Among all these agents, only epinephrine and norepinephrine proved to be fully effective after both types of sensitization. 5-HT induced a very severe THP-L in rats pretreated with $\text{CeCl}_3 + \text{FeCl}_3$, but only minor lesions upon sensitization with agar.

Selye et al. G23,215/65: Screening of numerous compounds (given alone or in combination i.v.) for their ability to sensitize the rat to the production of a THP (locally and/or in internal organs) by norepinephrine injected s.c. on the back and into one hind paw. Several metallic combinations and sulfated polysaccharides proved to be active. Curiously, however, even when given in sublethal doses, only few agents induced sensitivity to the THP-effect of norepinephrine by themselves, while combinations of two appropriately selected metals or of a metal and a nonmetallic compound were highly effective.

VARIOUS SENSITIZERS + NOREPINEPHRINE (REGIONAL DIFFERENCES IN SENSITIVITY)

Gabbiani & Mathur G19,434/65: In rats given $\text{FeCl}_3 +$ lead acetate or $\text{FeCl}_3 + \text{CeCl}_3$ i.v., simultaneous injection of norepinephrine into the cavity of a knee joint produces extraordinarily severe and extensive local thrombohemorrhagic lesions. The authors "conclude that the joints are particularly sensitive to the production by our experimental means of thrombohemorrhagic lesions similar to those of the Shwartzman reaction."

Gabbiani et al. G23,248/65: "Experiments on rats indicate that intravenous administration of any one among 16 rare earth metal trichlorides produces topical thrombohemorrhagic lesions at sites of epinephrine administration. Depending upon dosage and timing, it is possible to produce such lesions either at the epinephrine injection sites alone or also in distant organs, particularly the kidney."

Selye & Tuchweber G23,217/65: In rats sensitized for the production of a pluricausal THP by three techniques (i.v. administration of Th-Din + tannic acid, Na-casenate + tannic acid and $\text{FeCl}_3 + \text{CeCl}_3$), the subcutaneous administration of norepinephrine at various sites showed a definite regional difference in the sensitivity to catecholamine-induced THP-L lesions. In general, responsiveness increased in the craniocaudal direction. The calvarium proved to be almost completely resistant while the tail and hind paw were maximally responsive.

However, the skin of the pubic region was somewhat less sensitive than that of the belly. "At least in the case of three techniques for the induction of a thrombohemorrhagic diathesis, the distribution of cutaneous thrombohemorrhagic reactivity to noradrenaline is essentially independent of the elicitors used." These differences in responsiveness can hardly be attributed to differences in the thickness of the dermis, the density of the collagen fibers, the degree of vascularization or the distribution of mast cells, since it does not parallel any of these parameters; indeed, no known anatomic feature can adequately account for the zones of THP-reactivity to norepinephrine.

Selye & Tuchweber G23,233/65: In rats sensitized with carrageenin s.c., there exist considerable regional differences in reactivity to topically applied norepinephrine. The connective tissue under the skin of the tail, paws, lips and nose is highly susceptible, while that of the groin, lower abdomen, chest, sacrum, interscapular region and over the calvarium is resistant. Among the internal organs, the kidney, pancreas and cecum proved most responsive to this type of challenge, but thrombohemorrhagic lesions have also been produced by topical treatment with norepinephrine in the tongue, quadriceps muscle, thymus, the connective tissue of the hepatic hilus, the salivary glands and the hibernating glands. Other internal organs, such as the preputial glands, the mesenteric lymph nodes, the subconjunctival connective tissue, the sciatic nerve, etc. proved to be irresponsible. It has not been possible to trace these zonal differences in responsiveness to any common structural characteristic of the various territories examined.

Selye & Winandy G23,238/65: Following carrageenin s.c., a single i.p. injection of 5-HT produces severe THP-lesions in the spleen, kidney and pancreas. These changes are frequently accompanied by similar lesions in distant organs (e.g., the submaxillary and external lacrimal glands, the snout and the paws).

BLOOD TRANSFUSION + NOREPINEPHRINE

Selye et al. G23,216/65: Normal rats are extremely tolerant to heterologous blood transfusion, but they respond to norepinephrine s.c. with a severe THP-L at the injection site and a nonspecific THP-G. Among the blood specimens tested, those of the dog, cat, rabbit, guinea pig, chicken and man were especially effective in inducing this type of norepinephrine hypersensitivity. The blood of the duck and hamster, as well as homologous rat blood, proved to be inefficacious.

FE-OS + POLYMYXIN

Selye et al. D24,159/63: Certain experiments on rats suggest that discharged mast-cell material can capture blood-borne particulate substances and through this "mastocytopexis" participate in the localization of disease. If the mast-cell discharger polymyxin is given s.c. simultaneously with India ink i.v., the carbon particles are deposited in a halo around the polymyxin-injection site where discharged mast-cell granules are found in close association with India ink in the connective tissue and the walls of the small blood vessels. Essentially similar results are obtained when Fe-OS is given i.v. instead of India ink. However, since iron is more toxic, the local precipitation of Fe-OS tends to cause necrosis and throm-

bosis especially in the center of the polymyxin-injection site. "The cutaneous blood-vessel thrombosis with consequent necrosis induced by polymyxin in conjunction with the intravenous injection of Fe-OS is somewhat reminiscent of the local Shwartzman-Sanarelli phenomenon and may help to elucidate the mechanism of such topical hypersensitivity reactions."

CARRAGEENIN + COLD

Selye G23,214/65: In rats pretreated with a single s.c. injection of carrageenin, exposure to cold induces a THP in the nose, paws and tail, accompanied by renal glomerular thromboses. The same treatment elicits hemorrhagic necroses in Murphy rat lymphosarcoma transplants.

The Pluricausal THP-G

Nonspecific Distribution. Pluricausal THP-Gs are elicited by combined treatment with systemically applied sensitizers and chemically unrelated, but likewise systemically administered, challengers. Here, as in the THP-L, the most effective challengers so far examined were epinephrine, norepinephrine, 5-HT, mast-cell dischargers and exposure to cold. However, in order to obtain a THP-G, these agents must be so applied that they can easily reach distant organs, for if their effect is essentially limited to the site of administration, at best a THP-L could result.

THP-Gs are designated as nonspecific in their distribution when the thrombohemorrhagic lesions are limited to naturally predisposed sites such as the kidney, heart, intestines and lung.

Selye & Grasso D4,898 61: In the course of work on the pathogenesis of pluricausal cardiopathies, it was noted that rats pretreated with 9 α -fluorocortisol (F-COL) + Fe-OS + Na₂HPO₄, regularly developed thromboses in the capillaries and medium-sized veins of the heart, often associated with myocardial necroses. At the same time, iron-containing homogeneous thromboses were formed in the renal glomerular capillaries similar to those seen in the SSP-G.

Gabbiani et al. G19,450/65: In rats, pretreated with ACTH, fluorocortisol, or stress (restraint), a single i.v. injection of Thorotrast produced thrombohemorrhagic lesions with necrosis in the adrenals and liver, as well as hyaline glomerular capillary thromboses in the kidneys.

Selye G23,214/65: In rats pretreated with a single s.c. injection of carrageenin, exposure to cold induces a THP in the nose, paws and tail, accompanied by renal glomerular thromboses.

Selye & Tuchweber G19,428/65: First description of a nonspecific pluricausal THP by simultaneous combined treatment with various metal salts or agar i.v. and norepinephrine s.c. Thrombohemorrhagic lesions became evident within a few hours at the norepinephrine injection site as well as in the heart, duodenum, lung and kidney. The response is nonspecific, since so many combinations of agents can elicit it, and it is also pluricausal since no one pathogenic factor suffices in itself. This THP could hardly be due to the induction of an altered state of immunological reactivity, since it is elicited without any sensitizing pre-treatment. However, "it resembles in some respects certain spontaneous diseases of man (thrombotic thrombocytopenic purpura, anaphylactoid purpura of Schönlein-Henoch, eclampsia, Morbus maculosus Werlhof) and particularly the general and local forms of Shwartzman's phenomenon of tissue reactivity to bacterial filtrates." The most active i.v.

metal combinations were: lead acetate in combination with FeCl_3 , Fe-OS or Thorotраст, CeCl_3 in combination with Fe-OS or India ink and LaCl_3 in combination with Fe-OS, all these metal combinations being administered simultaneously with norepinephrine s.c. The production of lesions in the internal organs by any of these agents was greatly aggravated by norepinephrine s.c. which, in addition, produced thrombohemorrhagic changes at the injection site. These topical manifestations of the THP are especially pronounced if the catecholamine is injected into a paw.

Selye et al. G19,445/65; Mathur et al. G23, 209/65: Various agar preparations differ markedly in their ability to elicit a THP. Some are wholly inactive whether given alone or in combination with norepinephrine, others, though inactive by themselves, are activated by concurrent treatment with this catecholamine.

Selye et al. G23,215/65: Screening of numerous compounds (given alone or in combination i.v.) for their ability to sensitize the rat to the production of a THP (locally and/or in in-

ternal organs) by norepinephrine injected s.c. on the back and into one hind paw. Several metallic combinations and sulfated polysaccharides proved to be active. However, curiously even when given in sublethal doses, only few agents induced sensitivity to the THP-effect of norepinephrine by themselves, while combinations of two appropriately selected metals or of a metal and a nonmetallic compound were highly effective.

Selye et al. G23,216/65: Normal rats are extremely tolerant to heterologous blood transfusion, but they respond to norepinephrine s.c. with a severe THP-L at the injection site and a nonspecific THP-G in which renal glomerular capillary thromboses are particularly prominent. Among the blood specimens tested, those of the dog, cat, rabbit, guinea pig, chicken and man were especially potent in inducing this type of norepinephrine hypersensitivity. The blood of the duck and hamster, as well as homologous rat blood, proved to be ineffectual.

Organ Specific Distribution. Many THP-Gs are relatively specific in that they show a preponderant localization in certain regions. The following is a list of organs (with examples of evocative techniques in parentheses) that can be more or less selectively affected by thrombohemorrhagic lesions:

Kidney (carrageenin + stress)

Heart ($\text{Fe-OS} + \text{glucocorticoids} + \text{Na}_2\text{HPO}_4$, manucol + norepinephrine)

Vessels (ScCl_3 i.v. + 5-HT near a large vein)

Duodenum, jejunum (agar + age, since this localization is much more readily obtained in older than in young rats)

Cecum (manucol + histamine)

Spleen (carrageenin + norepinephrine, especially if the latter is given i.p.)

Salivary and lacrimal glands (carrageenin + 5-HT)

Adrenals (Thorotраст + ACTH)

Uterus (agar + cyroheptadine)

All anaphylactoid shock organs (agar + egg white)

Certain (aboral) anaphylactoid shock organs (tannic acid + Thorotраст + norepinephrine)

Transplantable tumors (carrageenin + cold)

KIDNEY

Gabbiani G11,111/64: In rats sensitized by the combined administration of 9α -fluorocortisol and a sodium salt, or by exposure to an intense stressor agent, a single injection of colloidal carbon produces bilateral cortical necrosis of the kidney, with precipitation of fibrin in the glomerular capillaries. The

changes resemble those characteristic of the SSP-G.

Selye & Tuchweber G19,431/65: Although normally agar i.v. produces a generalized form of the THP in the rat, particularly severe renal lesions accompanied by water retention occur in the absence of the usual extrarenal changes if: 1. Subthreshold amounts of agar are repeatedly administered i.v., or 2. A small

amount of agar is given i.v. to rats conditioned by unilateral nephrectomy and an excess of NaCl.

HEART

Winandy & Selye G32,001/65: Predominantly cardiac hemorrhages and necroses are obtained in rats given manucol i.v. + norepinephrine s.c.

VESSELS

Selye et al. G32,007/65: In rats sensitized with ScCl₃ i.v., injection of epinephrine, norepinephrine or 5-HT into the musculature adjacent to large veins produces voluminous mixed thrombi in the neighboring vessels. Although the blood of animals thus sensitized shows delayed clotting in vitro, it clots in the vessels much more rapidly after death than that of normal controls. This finding is not easily compatible with the assumption that the hemorrhages that occur upon challenge in animals sensitized for the pluricausal THP with metals, result from a consumption coagulopathy.

DUODENUM, JEJUNUM

Selye et al. G23,204/65: A thrombohemorrhagic form of duodenal and upper jejunal necrosis can be produced by a single i.v. injection of agar in older rats.

CECUM

Winandy & Selye G32,001/65: Thrombohemorrhagic lesions in the cecum are obtained in rats given pullulan i.v. + histamine i.v.

SPLEEN

Selye & Winandy G23,238/65: A single i.p. injection of 5-HT produces splenic hemorrhages and thromboses (frequently accompanied by thrombohemorrhagic phenomena in other organs) following s.c. administration of carrageenin in the rat. [Splenic thromboses are rarely, if ever, the only manifestations of a THP-G but they occur frequently as part of THP-G syndromes produced in various ways (H.S.).]

SALIVARY AND LACRIMAL GLANDS

Selye & Winandy G23,238/65: Following carrageenin s.c., a single i.p. injection of 5-HT produces severe THP lesions in the submaxillary and external lacrimal glands of the rat. These changes are frequently accompanied by similar lesions in various abdominal organs (spleen, pancreas, kidney) and less frequently by an anaphylactoid purpura affecting primarily the snout and the paws.

ADRENALS

Gabbiani et al. G19,450/65: In rats pre-treated with ACTH, fluorocortisol or stress (restraint), a single i.v. injection of Thorotrast produced thrombohemorrhagic lesions with necrosis in the adrenals and liver, as well as hyaline glomerular capillary thromboses in the kidneys.

UTERUS

Selye et al. G19,436/65: Cyproheptadine inhibits the cutaneous manifestations of the anaphylactoid purpura produced in rats by agar + mast-cell dischargers (dextran, ferric dextran, ovalbumen) but simultaneously it aggravates the lesions in various internal organs, particularly the uterus.

ANAPHYLACTOID SHOCK ORGANS

Selye & Tuchweber G19,430/65: In the rat, parenteral administration of various mast-cell dischargers (compound 48/80, dextran, dextrin, egg white, ferric dextran, pepsin extract, polymyxin, thorium dextrin), following agar i.v., induces a type of anaphylactoid purpura characterized by thrombohemorrhagic lesions in the anaphylactoid shock organs, especially the snout, paws and sometimes the root of the tail. As in the Schönlein-Henoch syndrome of man, the experimentally induced cutaneous changes are associated with thrombohemorrhagic lesions in the kidneys and other internal organs.

Selye & Winandy G23,238/65: Following carrageenin s.c., a single i.p. injection of 5-HT produces severe THP-lesions in the submaxillary and external lacrimal glands of the rat. These changes are frequently accompanied by similar lesions in various abdominal organs (spleen, pancreas, kidney) and less frequently by an anaphylactoid purpura affecting primarily the snout and the paws.

Selye et al. G19,445/65; Mathur et al. G23,209/65: Among many agar preparations tested, only one (Anachemia) produced an anaphylactoid purpura (with lesions in the paws, snout and tail) when given by itself. It is assumed that the principle eliciting this form of THP is a contaminant whose concentration varies in the agar preparations used.

ABORAL ANAPHYLACTOID SHOCK ORGANS

Selye et al. G23,208/65: Treatment with various THP-sensitizers, anaphylactoid agents and norepinephrine produces a syndrome of acro-cyanosis and thrombohemorrhagic lesions largely limited to the posterior part of the body. The most effective combination among

those tested is Thorotrast + tannic acid + norepinephrine. This experimental disease exhibits certain similarities to Raynaud's disease, thromboangiitis obliterans and anaphylactoid purpura.

TUMORS

Selye G23,214/65: In rats pretreated with a single s.c. injection of carrageenin, exposure to cold induces hemorrhagic necrosis in Murphy rat lymphosarcoma transplants. Simultaneously THP lesions develop in the nose, paws and tail, accompanied by renal glomerular thromboses.

Selye G23,240/65; G23,237/65: In rats in which the aorta is ligated just caudad from the renal arteries, 5-HT s.c. or exposure to cold

produces an acute and severe muscular dystrophy limited to the posterior part of the body. [In these first publications, the effect of the procedure upon transplantable tumors is not yet mentioned, but the technique has subsequently been used for the induction of hemorrhagic tumor necrosis (H.S.).]

Selye & Tuchweber G23,235/65: When forced to walk on a sheet of ice, carrageenin-pretreated rats bearing two grafts of the same neoplasm (Jensen sarcoma, Murphy rat lymphosarcoma, Walker tumor, TS tumor), one on the back and one in a hind paw, exhibit selective hemorrhagic tumor necrosis only in the latter (refrigerated) graft. Cold or carrageenin alone are ineffectual in producing such changes.

Factors Influencing Pluricausal THPs

The development of pluricausal THPs is readily influenced by a variety of conditioning factors which can aggravate, suppress or alter the distribution of the characteristic lesions. We have already mentioned a few of these modifying circumstances, such as the role played by the *topographic position* of connective tissue in the evocation of a THP-L. We have seen, for example, that in rats sensitized by various agents, the skin over the calvarium, neck and upper part of the thorax is more resistant to challenge by catecholamines or 5-HT than the caudal part of the body, particularly the hind paws. Here, evidently some local factor must be involved in determining this sensitivity gradient.

The modifying effect of *mast-cell dischargers* (dextran, ferric dextran, ovalbumen) upon the THP-lesions normally elicited by rats by i.v. injection of certain sensitizers, such as agar, is usually ascribed to a systemic challenge effect. By causing an anaphylactoid inflammation, the mast-cell dischargers localize the characteristic response in the anaphylactoid shock organs. However, since agar is itself active in producing THP-lesions in internal organs, it is merely a semantic question whether we regard this extension of the changes to the anaphylactoid shock organs as the result of challenge or conditioning by mast-cell dischargers.

Among the more typical conditioning factors, we might mention exposure to *stress*. For example, the duodenal and upper jejunal hemorrhagic necrosis, normally produced in the rat by single i.v. injections of agar, can be prevented by previous exposure to restraint, surgical trauma and various toxic drugs and tissue extracts. On the other hand, in rats sensitized by carrageenin s.c., subsequent exposure to the stress of restraint can produce selective renal cortical necrosis with hemorrhage. Thus, here, as in so many other instances, systemic stress can, under certain circumstances, protect and, under others, predispose to the production of morbid lesions.

Anticoagulants, such as heparin or dicoumarol, protect the rat against the production of pluricausal THPs by various means, presumably because the fundamental lesions depend upon clot formation in the target organs.

Antihistaminics (e.g., Neo-Antergan) and *antiadrenergic* agents (e.g., Dibenamine) exert a similar protective effect, perhaps because they interfere with the

actions of vasoactive substances. It is more difficult to understand why *ciproheptadine* (an antihistaminic and antiserotonin agent) inhibits the cutaneous manifestations of the anaphylactoid THP normally elicited by mast-cell dischargers + agar, while it actually aggravates the associated internal lesions (particularly in the uterus) and the mortality rate. Topical pretreatment of one anaphylactoid shock organ (e.g., a paw) with minute doses of ciproheptadine can even selectively protect the injection site under these conditions. Of course, it is possible, though by no means proven, that this dual effect is due to regional differences in the vascular response to ciproheptadine, since many other vasoactive substances (e.g., vasopressin, catecholamines) are known to induce diametrically opposed actions (vasoconstriction or vasodilation) in different vascular territories.

Finally, the nephrotoxic effect of certain THP-agents (e.g., agar) can be enhanced by *unilateral nephrectomy* or *NaCl*-supplements and particularly by the combined application of both these agents.

Although comparatively little work has been done as yet on factors that modify the course of pluricausal THPs, the few examples just mentioned suffice to show that these responses are highly subject to predictably planned regulation by conditioning agents.

ANTIADRENERGIC AGENTS

Gabbiani et al. G23,248/65: "The thrombohemorrhagic lesions produced by ScCl_3 plus epinephrine are regularly prevented by pretreatment with α -adrenergic blocking agents but not by a series of antihistaminics, anti-serotonins and anticoagulants."

Selye et al. G23,208/65: The aboral anaphylactoid THP produced by Thorotrast + tannic acid + norepinephrine in the rat is inhibited by dibenamine, presumably through its anti-adrenergic action.

CYPROHEPTADINE

Gabbiani et al. G23,248/65: The thrombohemorrhagic lesions produced by ScCl_3 + epinephrine are not prevented by ciproheptadine and various other antiserotonins.

Selye et al. G19,436/65: The anaphylactoid type of PTHP, induced by concurrent treatment with mast-cell dischargers (dextran, ferric dextran, ovalbumen) and agar i.v., is greatly modified by ciproheptadine, a 5-HT- and histamine-blocking agent. The cutaneous manifestations are inhibited while the internal lesions and the mortality rate are aggravated. Topical pretreatment of one anaphylactoid shock organ (e.g., a paw) with minute doses of ciproheptadine can even selectively protect the injection site without significantly affecting the other manifestations of the anaphylactoid THP.

ANTIHISTAMINICS

Gabbiani et al. G23,248/65: The thrombohemorrhagic lesions produced by ScCl_3 + epi-

nephrine are not prevented by antihistaminics.

Selye et al. G23,208/65: The aboral anaphylactoid THP produced by Thorotrast + tannic acid + norepinephrine in the rat is greatly aggravated by pretreatment with the antihistaminic Neo-Antergan.

HEPARIN

Gabbiani et al. G23,248/65: The thrombohemorrhagic lesions produced by ScCl_3 + epinephrine are only slightly diminished by heparin pretreatment.

Selye et al. G19,442/65: Both the ordinary ($\text{CeCl}_3 + \text{FeCl}_3$ or CeCl_3 + India ink, or $\text{Pb-acetate} + \text{FeCl}_3$ i.v. with norepinephrine s.c.) and the anaphylactoid (agar + dextran or agar + egg white) form of the pluricausal THP can be inhibited by pretreatment with heparin in the rat. In all experimental models examined, the inhibition was evident both with regard to the cutaneous and the internal manifestations.

Selye et al. G23,208/65: The aboral anaphylactoid THP produced by Thorotrast + tannic acid + norepinephrine in the rat is inhibited by heparin, presumably through its anticoagulant effect.

DICOUMAROL

Gabbiani et al. G23,248/65: The thrombohemorrhagic lesions produced by ScCl_3 plus epinephrine are not prevented by dicoumarol pretreatment.

Selye & Tuchweber G23,247/65: Dicoumarol p.o. produces localized hemorrhages at sites where carrageein or other inflammatory irri-

tants are applied s.c. Heparinization does not share this effect. Here, we may have an experimental model of the "dicoumarol necroses" which sometimes occur in man following treatment with dicoumarol and related anti-coagulants at sites of local tissue irritation.

STRESS

Selye et al. G23,204/65: The duodenal and upper jejunal THP produced by agar i.v. in

older rats is prevented by complete, but not by incomplete ligation of the common bile duct.

Selye et al. G23,221/65: The THP-G characterized mainly by duodenal and renal lesions, which is produced in adult rats by agar i.v., can be inhibited by pretreatment with a variety of systemic stressors (i.p. or s.c. administration of toxic tissue extracts, formaldehyde or carrageenin, exposure to restraint, spinal-cord transection).

Summary and Classification

It is evident from what we have said before that the development of the pluricausal THPs depends upon a great variety of factors some of which (sensitizers, challengers) are indispensable ingredients of the evocative pathogenic situations, while others (conditioning factors) act merely as modifiers of the response. In order to bring some clarity into this complex field, it may be opportune at this point to summarize the highlights and to attempt at least a provisional classification to show the position of the pluricausal THPs among the many variants of thrombohemorrhagic lesions.

Here, as in any other field of pathology, it is possible to classify morbid phenomena either according to their etiology or their structure. We have tried to delimit our topic by selecting for study only lesions characterized by a combination of thrombosis and hemorrhage. This basic *structural change* is therefore, by definition, common to all the phenomena under discussion; hence, it cannot serve as a basis for their further subdivision into categories. However, we found that, depending upon the evocative procedure, the distribution of the morbid foci varies and—most important—can be made to vary at will. This fact must be taken into consideration in any attempt at classification.

Up to now, the idea of arranging the THPs according to their *etiology* was blocked by the tacit assumption that they are all manifestations of the same "Shwartzman-Sanarelli Phenomenon" (SSP); yet the latter was clearly defined by Shwartzman himself as the hemorrhagic response to two properly spaced injections of certain bacterial endotoxins.

The study of the THP as a possible component in diverse diseases was of course impossible as long as we assumed that this change is essentially always the same in structure and pathogenesis. However, the observations summarized in the preceding pages have made it clear that there are many forms of THPs which differ in their organ distribution and even in the fine structure of the morbid foci depending upon the evocative techniques employed. It has been shown, furthermore, that despite certain common fundamental pathogenetic mechanisms, the manifestations of THPs can be varied at will and that both the causative factors and the different reaction forms can be categorized for a planned systematic analysis.

The following chart is meant to summarize the principal points that have been established and to serve as a preliminary sketch for the classification of both the reaction forms and their evocative agents.

CLASSIFICATION OF THPs *THP*

TIT Class name embracing all thrombohemorrhagic phenomena

| Monocausal | | Pluricausal | |
|---|----------------|---|--|
| Monocausal thrombohemorrhagic phenomena produced by single or repeated treatments with the same or closely related agents | | Pluricausal thrombohemorrhagic phenomena which can be elicited only by combined treatment with sensitizers and challengers | |
| | | General | General |
| <i>Local</i> | | | |
| | <i>General</i> | | |
| | | THPs with general manifestations at a distance from the site where the evocative agent is applied, e.g.: SSP-L <i>The "red infarct"</i> <i>Topical response to Na-metaphosphate</i> | THPs elicited by complete sensitizers or pairs of co-sensitizers + systemic challengers. The resulting syndromes may be non-specific in their distribution (e.g., glucocorticoids + sodium salts + India ink) or show relative specificity by preponderant localization, e.g., in: <i>All anaphylactoid shock organs</i> (agar + egg white) <i>Absorbal anaphylactoid shock organs</i> (Thorotrust + tannic acid + norepinephrine) <i>Uterus (agar + cyroheptadine)</i> <i>Adrenals (Thorotrust + ACTH)</i> <i>Duodenum (agar + age)</i> <i>Heart (Fe-OES + glucocorticoids + Na₂HPO₄)</i> <i>Kidney (carrageenin + stress)</i> <i>Salivary and lacrimal glands (carrageenin + 5-HT)</i> <i>Spleen (carrageenin + norepinephrine i.p.)</i> <i>Tumors (carrageenin + cold)</i> |
| <i>Local</i> | | | |
| | <i>General</i> | | |
| | | THPs with purely local manifestations at the site where the evocative agent is applied, e.g.: Thrombin Amniotic fluid Placental extr. | THPs elicited by combined treatment with sensitizers + topical challengers, e.g. by: <i>Tannic acid + norepinephrine</i> <i>FeCl₃ + CeCl₃ + norepinephrine</i> <i>ScCl₃ + epinephrine</i> |
| | <i>Local</i> | | |
| | | | |

CHAPTER IV

MORPHOLOGIC CHANGES

IN the preceding two chapters, we have discussed the factors which either produce the THP or modify its course; the following pages will be devoted to the organ changes that develop as a consequence of THPs, no matter how produced. A certain degree of overlap with previously mentioned data is therefore unavoidable but here, the structural changes will be our main concern, special attention being given to the conditions which localize a THP in a certain organ.

Skin. In the skin, the morphologic changes elicited by various forms of THP-Ls are essentially the same. At first, a more or less extensive, cutaneous area shows purple discoloration owing to venous stasis. A few hours later, the affected region becomes edematous and intensely hemorrhagic. The central purple area is often surrounded by a bright red hyperemic halo.

Histologically, the outstanding initial change is erythrocyte aggregation in extremely dilated capillaries and small pre- and postcapillary vessels. This first stage is soon followed by the diapedesis of the erythrocytes through the walls of minute vessels into the surrounding tissue. In small arterioles, innumerable erythrocytes are often seen infiltrating all layers of the wall, widely separating the elastica interna and externa. The endothelial cells may become hypertrophic and even vacuolated. Simultaneously, fibrin threads and platelet aggregates enmesh the packed intravascular erythrocyte masses, thereby producing occlusive thrombi. If these lesions are sufficiently severe, hemorrhagic necrosis ensues, the dead skin is rejected and the resulting ulcer gradually heals by granulation. In mild lesions, the thrombi may be removed secondarily by fibrinolysis. In any event, the thrombohemorrhagic region always shows considerable edema and inflammation with local accumulation of polymorphonuclear leukocytes in and around the vessels.

Karsner & Moritz B78,212/34: Detailed description of the histologic changes seen in the skin, stomach, and knee joints of the rabbit when an SSP-L is elicited by the injection of *E. coli* endotoxin, first into these sites and subsequently i.v.

Kielanowski & Selzer D40,967/34: Detailed histologic study of the SSP-L in rabbits given two injections of *E. coli* filtrate. The perivascular polymorphonuclear leukocyte emigration, as well as the thromboses are not characteristic of the SSP-L, since they may be observed after the preparatory injection and before provocation. The characteristic change is a venous engorgement of the capillaries with hemorrhagic infiltration of the adjacent tissues.

The endothelium of the arterioles may become vacuolated.

Gerber B78,161/36: Careful histologic studies of the skin site prepared by typhoid toxin in the rabbit showed only nonspecific inflammation, the intensity of which did not parallel the degree of SSP-“preparedness.” Following i.v. injection of the same toxin, hemorrhagic necrosis ensues which cannot be interpreted as a mere augmentation of the original inflammation.

Lörincz G28,155/36: The SSP-L elicited in the skin (and testis) of rabbits is characterized by parietal thrombi in the blood vessels with extensive hemorrhage, edema and inflamma-

tion. Essentially similar changes are seen in the Arthus phenomenon.

Alechinsky D88,312/39: Detailed description of the histologic changes as they develop during the SSP-L (produced in rabbits by two injections of *E. coli* endotoxin) before and after the provocative injection.

Evers & Brunson C97,146/60: In themselves, well tolerated doses of epinephrine, norepinephrine or *E. coli* endotoxin i.c. produce topical necrosis without hemorrhage in rabbits exposed to "rotational shock" in the Noble-Collip drum. The response was more constant when the rotation preceded than when it followed the i.c. injections. Similar changes were obtained by phenylephrine, ephedrine and isopropylarterenol administered during rotational shock.

Lee & Stetson G21,653/60: Single i.c. injections of *E. coli* or *S. typhosa* endotoxin produce delayed inflammatory reactions in the rabbit. Moderate erythema and leukocytic infiltration appear after 6-12 hrs., reaching a

maximum at 20-24 hrs. By contrast, in rabbits which first received a single i.v. injection of *E. coli* endotoxin, the subsequent i.c. administration of *E. coli* or *S. typhosa* endotoxin produced a greatly accelerated and intensified cutaneous response. Within 1 hr., there was bleb formation with pronounced edema, erythema and leukocytic infiltration although extravasation of erythrocytes and necrosis were rarely conspicuous. The response resembled the Arthus reaction both in general appearance and in being visible within an hour.

Neter et al. C97,516/60: Following i.v. injection of living *S. aureus* organisms or their endotoxins, epinephrine i.c. produces hemorrhagic lesions in the abdomen or back, but not in the ear of the rabbit. The changes can be prevented by dibenzyline.

Stacher E33,582/63: Review of the literature and personal observations indicate that various dicoumarol and indandione derivatives can cause widespread cutaneous necroses which are presumably related to the SSP.

Blood Count. The hematologic changes most characteristic of all forms of THP-G are: thrombocytopenia and leukopenia, followed by leukocytosis with a drop in hemoglobin and erythrocyte count. It is questionable, however, to what extent these changes are really specific for the THP, since quite similar hematologic deviations are seen in the acute phase of the alarm reaction produced by almost any stressor.

In rabbits made tolerant to epinephrine, an SSP-L can be produced by two injections of endotoxin even while there is a considerable drop in polymorphonuclear leukocytes both in the blood and in the challenged area. It has, therefore, been suggested that the presence of leukocytes may not be necessary for the development of the local reaction.

On the other hand, in rabbits in which an SSP-G is elicited by two i.v. injections of *S. enteritidis*, numerous granulated leukocytes appear in the blood which, apparently, carry a sulfated mucopolysaccharide. Possibly, the latter forms an adhesive complex with fibrinogen which participates in the development of SSP-changes.

Sanarelli B78,422/24: If, 24 hrs. after an i.v. injection of a sublethal dose of live cholera vibrios, colitoxin is injected i.v. in the rabbit, there develops a transient fall, followed by a rise in the polymorphonuclear leukocyte count of the blood.

Shwartzman & Gerber B19,259/48: The SSP-L elicited by two injections of meningococcal toxin is often associated with leukopenia, a drop in hemoglobin and erythrocyte count and a decrease in the number of platelets.

Stetson B73,457/51: Following i.v. injection

of meningococcal endotoxin, the total leukocyte count, especially that of the polymorphonuclear leukocytes, drops precipitously within a few minutes in the rabbit. Recovery begins after 4 hrs. and there is a tendency for the total leukocyte count to rise above normal several hours after recovery. Similar blood-count changes were obtained by other SSP-L agents such as *Sh. paradyserteriae* endotoxin, glycogen or agar. [It should be noted, however, that this curve is quite characteristic of the alarm reaction and the author failed to use other stressors as controls (H.S.).]

Thomas & Good B79,249/52: After a preparatory i.v. injection of *S. marcescens* toxin, the polymorphonuclear leukocyte count of the rabbit drops from about 4,000 to about 200 per ml of blood, within 30 min. Then, it gradually rises to about 5-10,000 within the next 48 hrs. After the challenging i.v. injection, the initial drop is followed by an even more pronounced polymorphonuclear leukocytosis, especially in animals which develop renal cortical necrosis.

Berthrong & Cluff D83,712/53: Observations on tissue-culture fragments from the buffy coats of centrifuged blood (using the glass slide method) revealed that *S. marcescens* and *Sh. flexneri* endotoxins i.v. inhibit the migration of leukocytes. The response is obtained both when an SSP-L is produced by two injections and if a single dose is given i.v. Inhibition of the SSP-L by heparin fails to alter this response.

Cluff D79,025/53: Various bacterial endotoxins i.v. inhibit the migration of leukocytes from the buffy coat of centrifuged blood. Repeated daily injections of endotoxin resulted in resistance to this effect. "In view of the participation of the leucocyte in the pathogenesis of the Shwartzman reaction, the presence of leucocytes resistant to endotoxin may be responsible in part for the development of resistance to the Shwartzman phenomenon."

Clark & Batchelor G26,881/57: Various bacterial endotoxins produce degenerative changes in the thrombocytes and heterophil leukocytes of the rabbit *in vitro*. Similar changes may be important in the mediation of endotoxin effects *in vivo*.

McKay & Shapiro D85,442/58: The SSP-G elicited by two i.v. injections of Shear's polysaccharide is accompanied by leukocytosis and thrombocytopenia.

Bokkenheuser & Koornhof E83,027/59: Rabbit erythrocytes coated with very small amounts of endotoxin were inagglutinable in antiserum, whereas those with greater quantities of endotoxin agglutinated readily. A sim-

ilar in vivo sensitization of rabbits was demonstrated by i.v. injection of large doses of endotoxin.

Hall et al. G9,421/64: In rabbits made tolerant to epinephrine, the SSP-L can be produced by two injections of *E. coli* endotoxin even when a considerable drop in polymorphonuclear leukocytes is produced both in the blood and in the area of challenge. These findings "suggest that presence of leukocytes may not be necessary for development of the local reaction."

Horn & Spicer G25,934/64: In rabbits in which an SSP-G is elicited by two injections of *S. enteritidis*, an unusually large number of heterophil leukocytes with distinctive cytoplasmic granules appear in the blood. "These granules, which were histochemically identical to azurophil granules of rabbit bone marrow, stained with azure A above pH 4.0, with aldehyde fuchsin, high iron-diamine, alcian blue, and alcoholic PAS, and were associated with the incorporation of S³⁵-sulfate, indicating the presence of a sulfated mucopolysaccharide. Affinity of the same granules for Biebrich scarlet at highly alkaline pH indicated the presence of a strongly basic protein; blocking reactions suggested that the basic nature of the protein was attributable to high arginine content." The granulated leukocytes appear following the first and the second endotoxin injection used to produce the SSP-G. The authors also report "histochemical and autoradiographic studies indicating that a sulfated mucopolysaccharide is present in the fibrinoid occlusive glomerular lesions of the generalized Shwartzman reaction." . . . "It is tempting to speculate that some pathophysiologic mechanism, e.g., leukocyte sticking in sites of injury, might be related to the coincidence of an acid mucopolysaccharide constituent of the heterophil and locally engendered partially polymerized fibrinogen, leading to the production of an acid polymer-fibrinogen complex with adhesive characteristics."

Hemopoietic and Lymphatic Organs. The lymph nodes draining the area affected by the THP-L show edema, hyperemia, hemorrhage, and swelling of the endothelial cells in the blood capillaries and the lymphatic sinusoids. In the spleen, there is hyperemia and sometimes formation of fibrous nodules within the veins. Essentially similar changes develop in the bone marrow.

Oppenheim G28,484/21; Ceelen G28,482/26: Splenic infarcts are common in patients with typhoid fever. Histologic studies suggest that specific typhoid nodules and endophlebitis,

sometimes with secondary thrombosis, are responsible for these lesions.

Apitz B30,444/34: An SSP-G elicited by two i.v. injections of *E. coli* endotoxin in the rabbit

may cause hyperemia of the spleen with the formation of fibrous nodules within the splenic veins.

Gerber C95,662/36: Detailed description of the splenic, bone-marrow and lymph-node changes in rabbits in which an SSP-G is elicited by two i.v. injections of meningococcal or typhoid toxin.

Patania G19,702/36: An SSP-L can be obtained in the spleen of the rabbit by topical preparation followed by i.v. provocation with *S. typhosa*. Allegedly, an extract prepared from a spleen thus treated and given i.c. mixed with *S. typhosa* endotoxin produces an "SSP-L" without the necessity of i.v. provocation.

Koplik E65,235/37: Characteristic changes occur in the lymph nodes of rabbits in which an SSP-L is produced by the i.v. injection of *B. typhosus* endotoxin following preparation by direct injection of the same material either into the lymph node or into the skin drained by it. The lesions consist of hemorrhages, microthrombi and intense swelling of the endothelial cells.

Ecker et al. G28,154/38: In rabbits in which an SSP-L is elicited in the skin (by two injections of diverse bacterial endotoxins), essentially similar SSP-L changes are noted in the regional lymph nodes.

Alechinsky D88,312/39: Description of the lymph-node changes following two i.v. injections of *E. coli* endotoxin in the rabbit.

Basile G23,055/41: Review of the literature on the production of an SSP-L in the spleen.

Shwartzman & Gerber B19,259/48: If an SSP-L is elicited in the rabbit by two injections

of meningococcal toxin, the regional lymph nodes around the dermal reaction exhibit hemorrhagic necrosis with mural thrombi and extensive hemorrhages in the lymphatic sinusoids.

Race & Reed G23,063/53: "The typical Shwartzman phenomenon tissue reaction, including acute inflammation, thrombosis of small veins, and hemorrhage, was repeatedly observed in the axillary and inguinal lymph nodes of animals in which the phenomenon was produced in the abdominal skin."

Fricsay et al. E77,419/57: Even a single i.v. injection of *S. abortus equi* endotoxin suffices to produce swelling of endothelial cells with accumulation of damaged polymorphonuclear leukocytes and fibrinoid in the renal glomerular capillaries and the splenic sinusoids. This response occurs in the rabbit. "The early pathomorphologic lesions in the spleen and kidney of the rabbit within 8-15 hrs. after 1 or 2 pyrogen injections (generalized Shwartzman phenomenon) differ only quantitatively" being more intense if two properly spaced injections are given.

McKay & Rowe C80,265/60: During the SSP-G elicited by two i.v. injections of Shear's polysaccharide, it is possible to demonstrate the development of large ischemic areas in the lung by the intra-arterial injection of India ink. Ischemia is produced by platelet thrombi and possibly also by arterial spasm. Other areas are blackened owing to dilatation of the alveolar capillaries which trap much of the ink. Similar but less distinct areas appeared in the spleen and liver.

Kidney. The changes most characteristic of the THP-G are erythrocyte aggregation and the formation of hyaline thrombi in the renal glomerular capillaries. In the arterial vessels, especially in the afferent arterioles and the interlobular arteries, there are fibrin and platelet thrombi with erythrocyte diapedesis through the wall into the surrounding tissues. At the same time, the cortex becomes anemic and may undergo extensive necrosis, while the medulla shows hyperemia with hemorrhage, particularly in the regions where arteriolae rectae are plentiful. The tubules show degeneration, vacuolization and often necrosis with more or less pronounced protein precipitation and hyaline-cast formation in the lumina. Although cortical necrosis and hyaline thrombi in the glomerular capillaries are generally considered to be characteristic of the SSP-G, the same lesions have been observed in many other conditions such as scarlet fever and other acute infections, as well as in conjunction with THPs produced by nonmicrobial agents.

It is, allegedly, possible to produce an SSP-L selectively in one kidney by injecting the preparatory material directly into the renal artery or parenchyma. However, the success of such experiments depends upon hitherto unclarified

circumstances; indeed, under certain conditions, the prepared kidney may be protected, the lesions developing more intensely on the contralateral side.

Electron-microscopic studies revealed that the fibrous masses that develop in the glomerular capillaries following two i.v. injections of endotoxin (or one injection of endotoxin followed by Liquoid i.v.) reveal the typical axial periodicity of fibrin.

Essentially the same type of renal lesion develops during the classic SSP-G (elicited by two properly spaced injections of endotoxin) as in other forms of THP-Gs (elicited by single or irregularly spaced injections of microbial products, microbial plus nonmicrobial products, or exclusively nonmicrobial agents). It is true that the relative intensity of glomerular thromboses, "wire-loop" formation, cortical necrosis, medullary hyperemia and hemorrhage vary. Yet, it has not been possible to trace such variations to the evocative agents, and they may well depend upon the speed and intensity of the nephrotoxic effect and on extraneous conditioning factors more than on the chemical nature of the causative factors.

Microbial Products Alone. *Babes G13,239/1890:* Hyaline thrombi may appear in the renal glomerular capillaries in the course of scarlet fever in man.

Flexner E76,861/02: Agglutination of erythrocytes in vivo can occur in various infectious diseases of man and animals.

Duval & Hibbard G22,333/26: In rabbits, *S. scarlatinae* endotoxin i.v. "induced nephritic lesions analogous in kind and variety to those of acute scarlatinal nephritis in man, including the 'epithelial crescent' formation, hyaline thrombi of glomerular capillaries, hemorrhage into capsular space and necrosis of capillary tufts."

Shwartzman E53,222/30: It is possible to produce an SSP-L in the kidney if bacterial filtrate (kind not mentioned) is injected directly into the renal arteries prior to the i.v. injection of the same material.

Duval G21,637/31: Living or killed *S. scarlatinae* or their lysates produce "scarlatinal nephritis" in the dog, with fatty degeneration of the glomerular endothelia and hyaline thrombi in the glomerular capillaries.

Forssman G21,654/32: A single i.v. injection of staphylococcal toxin can produce bilateral cortical necrosis of the kidneys in rabbits. The same material produces cutaneous necrosis when injected s.c.

Patrassi G21,302/32: Single or repeated i.v. injections of diphtheria toxin produces a kind of glomerulonephritis in rabbits which is characterized by hyaline thrombi of the glomerular capillaries associated with a more or less pronounced inflammatory phenomenon. An extensive review of the early literature reveals that similar observations have been made

following treatment with other bacterial toxins, as well as after infections and intoxications with various drugs.

Apitz B30,444/34: The characteristic renal lesions of the SSP-G elicited by two i.v. injections of *B. coli* endotoxin in the rabbit are: cortical necrosis, fibrinoid thrombi in the glomerular capillaries, necrosis of interlobular arteries with fibrin thrombosis and, occasionally, intense lipid deposition in the glomerular capillaries and the tubules. The degenerative changes in the tubules are considered to be manifestations of nephrosis.

Rigdon et al. G21,638/34: A single i.v. injection of a filtrable toxin from a hemolytic *Staphylococcus aureus* produces renal cortical necrosis with hyaline thrombi in the glomerular capillaries.

von Glahn & Weld G21,291/35: A single i.v. injection of *Staphylococcus aureus* produces renal vascular damage with hyalinization and fibrin thrombosis of the afferent arterioles and glomerular loops, sometimes conducive to cortical necrosis, in the cat and rabbit. No significant changes were noted outside the kidney. [The possible relation of the changes to the SSP-G is not mentioned (H.S.).]

Caldarera G8,886/36: An SSP-L with intense hematuria can be elicited in the rabbit by topical treatment of the renal tissue with *E. coli* endotoxin followed by i.v. provocation.

Gerber C95,662/36: Detailed description of the renal changes in rabbits in which an SSP-G is elicited by two i.v. injections of meningococcal or typhoid toxin.

Boone G22,559/37: A specific renal localization of the SSP-L had been obtained even after denervation of the kidney by the injec-

tion of *B. typhosus* endotoxin into its parenchyma (*Loi & Cardia G23,201/34*). These observations could not be confirmed in similar experiments in which *E. coli* endotoxin was injected either into the renal artery or into the renal parenchyma 24 hrs. before the provocative i.v. injection. The renal changes (if they occurred) were always bilateral and could be ascribed to the escape of endotoxin into the blood stream. "In the light of these results, it seems doubtful that the production of a localized Sanarelli-Shwartzman reaction in the kidney is possible." In rabbits, killed a week or more after the production of an SSP-L by two injections of *E. coli* endotoxin, the renal changes were insignificant as compared with those in the liver and myocardium.

Glynn G21,631/37: "There is general agreement that necrosis of the renal cortex is the most constant pathological change occurring in rabbits following the injection of staphylococcus toxin."

Moritz & Weir G22,344/37: In rabbits prepared by *B. aertrycke* endotoxin injected directly into the left renal artery, a subsequent i.v. injection of the same material produced an SSP-G with typical manifestations affecting also the right kidney, while the left kidney remained unimpaired. Even removal of the contralateral kidney did not prevent this "local refractory state" in the injected kidney. The observations are in contradiction to those of Shwartzman (*E53,222/30*).

de Navasquez E63,407/38: Following a review of the earlier literature on the production of bilateral renal cortical necrosis by single injections of staphylococcal toxin, the author describes the histology of the underlying lesions in detail. There is acute necrosis of the media in the interlobular and afferent arteries accompanied by thrombosis with dilatation and obstruction of the glomerular capillaries. "The mechanism of the obstruction is thought to be the rapid loss of plasma through the grossly dilated glomerular capillaries due to heightened pressure in the renal artery. The resulting concentration of red corpuscles leads to circulatory stasis with consequent ischaemic necrosis of the parenchyma."

Shwartzman et al. G21,283/38: Preparation of the kidneys for the SSP-L may be obtained by: 1. the injection of bacterial endotoxin directly into the renal parenchyma; 2. the introduction of endotoxin into the renal artery; 3. the i.v. injection of the same material, which affects the kidney preferentially even if thus given. In all three instances, a provocative i.v. injection must follow the preparatory treatment.

Alechinsky D88,312/39: Description of the renal changes following two i.v. injections of *E. coli* endotoxin in the rabbit.

Outi & Yotuyanagi G27,053/40: Single injections of *E. coli* filtrate, i.v. or directly into the renal artery, produce severe degenerative changes in the tubules with dilatation of the renal vessels but no typical glomerular fibrin thrombi.

Basile G23,055/41: Review of the literature on the production of an SSP-L in the kidney.

Thomas & Good B79,249/52: The SSP-G induced by two i.v. injections of meningococcal toxins in rabbits is associated with fibrinoid thrombi in the glomerular capillaries.

Gamble & Brunson G21,645/55: The blood of donor rabbits in which an SSP-G was elicited by two injections of meningococcal endotoxin or by one injection of meningococcal endotoxin plus Liquoid, was transferred 2-4 hrs. after the last injection into unprepared recipients by carotid-jugular cross transfusion. This resulted in the development of a typical SSP-G in the recipients, except that the renal lesions were somewhat less pronounced than usual. Renal lesions characteristic of the SSP-G were produced by isolated renal perfusion with the use of donor animals prepared with meningococcal endotoxin and Liquoid. Since normally endotoxin is rapidly cleared from the blood, it is unlikely that residual endotoxin in the blood of the donors could be responsible for the observed changes. "The presence of fibrinoid following transfusion in unprepared recipient animals offers considerable evidence for its transfer by way of the blood stream."

Thal D99,792/55: Symmetrical renal cortical necrosis, not regularly associated with glomerular lesions, occurs in rabbits given a single i.v. injection of *Staphylococcus aureus* toxin. The change is ascribed to renal vasospasm.

Booth et al. C12,832/56: Following the production of an SSP-G by two i.v. injections of *E. coli* endotoxin, there developed fibrinoid thromboses in the glomerular capillaries and the afferent arterioles (sometimes also in the peritubular capillaries) of the rabbit kidney. Histochemical studies suggest the presence in this fibrinoid of "multiple ingredients, including neutral fats, fatty acids, cholesterol and its esters, phospholipids, aldehyde groups of polysaccharide origin, free potassium, free carbonyl groups, protein-bound sulphhydryl groups, and sulfuric acid esters of mucopolysaccharide origin." The response is frequently associated with bilateral renal cortical necrosis. The fibrinoid resembles that seen in human

malignant hypertension and similar states in experimental animals.

Black-Schaffer & Garcia-Caceres G28,650/57: Despite earlier observations to the contrary, no SSP-L could be produced in the rabbit kidney by local preparation followed by i.v. provocation. The authors used various techniques of preparation, injecting menigococcal or *S. marcescens* polysaccharides into the renal artery or the renal parenchyma.

Bohle et al. G21,670/57: Electron-histologic studies of the kidneys of rabbits in which an SSP-G was produced by two i.v. injections of *E. coli* endotoxin, were undertaken 8 hrs. after the second injection. Most of the capillary loops were filled with fibrous masses, showing the typical axial periodicity of fibrin after staining with phosphotungstic acid. The mean period was 171.5A.

Fricsay et al. E77,419/57: Even a single i.v. injection of *S. abortus equi* endotoxin suffices to produce swelling of endothelial cells, accumulation of damaged polymorphonuclear leukocytes and fibrinoid deposition in the renal glomerular capillaries and the splenic sinusoids within 8-15 hrs. in the rabbit. "The early pathomorphologic lesions in the spleen and kidney of the rabbit after 1 or 2 pyrogen injections (generalized Shwartzman phenomenon) differ only quantitatively," being more intense if two properly spaced injections are given.

Papas et al. G21,286/58; Bohle et al. E44,801/58: In rabbits, an SSP-G was produced by two i.v. injections of *E. coli* endotoxin or a single dose of endotoxin followed one hr. later by Liquoid i.v. As judged by electron-microscopic studies, the fibrinoid deposited in the renal glomeruli was the same in both types of experiment. The endothelial cells became swollen and exhibited balloon-like vesicles. Subsequently, fibrinoid having a diameter of 200-300 Å and an axial repeating structure of 120 Å, was deposited within the capillary loops. It is suggested that these observations "are compatible with the hypothesis, proposed earlier, that intravascular fibrinoid, in the generalized Shwartzman reaction, is derived from fibrinogen."

McKay & Rowe D14,807/59; C80,265/60: An SSP-G was produced in the rabbit by two i.v. injections of Shear's polysaccharide. "No alteration was noted in the kidney until 2-4 hrs. after the second injection. At this time the glomerular capillaries dilated and filled with ink. This stasis of blood in these vessels precedes or is concomitant with the intravascular deposition of fibrin in the same locations. It is suggested that dilation and stasis of blood in the renal glomeruli may constitute one of the

major mechanisms of preparation in the generalized Shwartzman reaction."

Graber et al. C85,671/60: Injection of *S. marcescens* endotoxin into the surgically isolated renal circulation of the rabbit, followed 18 hours later by an i.v. injection of the same endotoxin, produced death with typical renal glomerular thromboses.

Meili D59,157/63: A single i.v. injection of hemolytic streptococcal toxin produced bilateral renal cortical necrosis with fibrinoid thrombi in the glomerular capillaries of the rat. The sensitivity to the toxin was inversely proportional to the blood antihemolysin titer. Extrarenal manifestations of the SSP-G have not been mentioned, although the renal lesions were quite typical of this response.

Nakai & Margaretten E45,655/63: The observation of Neisser & Levaditi (G23,202/00) that a single i.v. injection of staphylococcal toxin can induce bilateral renal cortical necrosis in rabbits, has been repeatedly confirmed (Glynn G21,631/37; De Navasquez E63,407/38; Thal D99,792/55; Truetta et al. 99,193/47). The authors point out however, that when rabbits are killed at intervals after receiving staphylococcal toxin, renal necrosis is well advanced before the appearance of intravascular thrombi. Hence, "bilateral renal cortical necrosis can no longer be regarded as the hallmark of the generalized Shwartzman reaction."

Emmrich et al. F8,082/64: During the SSP-G, elicited by two i.v. injections of *S. abortus equi* endotoxin, the histochemically demonstrable phosphatase content of the arteries, liver, and kidney show only minor variations.

Cavanagh & Albores G31,619/65: Even single i.v. injections of *E. coli* endotoxin can produce hyaline thromboses of the renal glomerular capillaries in the rabbit.

Horn & Spicer G25,692/65: An SSP-G was produced by two i.v. injections of *S. enteritidis* in the rabbit and the fibrinoid thrombi were stained with the aldehyde-fuchsin and high iron-diamine techniques which are characteristic for sulfated mucopolysaccharides. The staining of fibrinoid by these methods suggests that sulfated mucopolysaccharides may be constituents of fibrinoid. The incorporation of S³⁵-sulfate by fibrinoid was regarded as additional evidence in support of this view. Since numerous leukocytes were present in the renal glomeruli during the early period of fibrinoid deposition, it is postulated that the sulfated mucopolysaccharide, which becomes incorporated into fibrinoid, may originate from circulating leukocytes.

McKay E4,788/65: An extensive review of the literature, and personal observations, sug-

gest that "glomerular capillary dilation occurs after endotoxin administration in all conditions of 'preparation' for the generalized Shwartzman reaction and in all likelihood is important in the localization of the fibrin thrombi."

Nonmicrobial Agents Alone or in Combination with Microbial Products. Pearce D82,984/09; D82,993/13: After a survey of the earliest publications on the production of hemorrhages by snake venoms, the author describes hemorrhagic lesions with fibrin deposition in the glomeruli of rabbits given the venom of *Crotalus adamanteus* i.v. Hyaline masses are deposited in the glomeruli and when these become organized, giant cells appear. There is also tubular damage and hyaline cast formation.

Baehr G22,339/13: As little as 0.35 µg of uranium nitrate i.v. produce fibrin thrombi in the glomeruli with hyalinization of the capillary wall and hemorrhages into Bowman's capsule. Occasionally, syncytial formations surround blood-filled "lacunae."

Wiesel & Hess A25,721/15: Epinephrine i.v., given in combination with uranium nitrate i.p. or potassium chromate s.c., produces glomerulonephritis, often with thromboses of the glomerular loops, in the rabbit. Sometimes, there are glomerular hemorrhages and eventually Bowman's capsule is thickened and the entire glomerulus becomes hyalinized and fibrotic. Neither epinephrine nor the salts alone are effective.

Major G23,260/16-17: In rabbits pretreated with uranium nitrate i.v., repeated subsequent injections of heat-killed *S. pyogenes aureus* i.v. produced a glomerulonephritis which was not elicited by either of these agents when given alone.

Suzuki G22,259/21; G22,258/21: The venom of the Habu viper (*Trimeresurus flavoviridis*) i.v. produces a kind of glomerulonephritis with hyalinizing glomerular capillary thrombi, consisting of fibrin, erythrocytes, leukocytes and platelets. These changes are accompanied by "diphtheroid lesions in the gastrointestinal tract and hemorrhages in the pleura."

Roth & Bloss E80,294/22: Combined treatment with uranium nitrate i.p. and epinephrine i.v. causes a kind of glomerulonephritis with hyaline coagulation necrosis of glomerular loops in rabbits. The changes are reminiscent of those seen during erysipelas suum in hogs. (A review of the literature shows that several earlier investigators produced similar lesions in animals by treatment with a variety of bacterial products and snake venoms.)

Patrassi G21,302/32: Detailed review of the earliest literature concerning the production of hyaline thrombi and glomerulonephritis by treatment with various drugs.

Reyna E24,151/36: Repeated daily i.v. injections of lithium carmine, given during 2-6 days, produce hyaline thrombi in the renal glomerular capillaries with bilateral cortical necrosis. There are also hemorrhages and necroses, sometimes with hyaline thrombi, in the liver, lung and adrenals. [The author emphasizes the similarity of these changes to those of eclampsia and bilateral cortical necrosis in man, but he does not mention the possibility of a relationship to the SSP (H.S.).]

Byrom A8,247/37: Bilateral renal cortical necrosis with media necrosis in the hilar, interlobular and arcuate arteries of the kidney, as well as thrombosis and necrosis of renal glomeruli and focal hepatic necrosis, can be produced in rats by repeated s.c. injections of vasopressin. The changes are reminiscent of eclampsia, malignant hypertension and allergic arteritis. [They are also reminiscent of the SSP-G (H.S.).]

Azevedo & Teixeira G26,897/38: In a patient who died 26 days after being bitten by a cobra (*Bothrops jararaca*), bilateral renal cortical necrosis developed as a consequence of diffuse glomerulonephritis with obliterative arteritis, affecting especially the interlobular, interlobar and arcuate arteries. Glomerular capillary thromboses were not found.

Reilly et al. 99,381/42: Monographic description of the authors' experiments on the production of glomerulonephritis with hemorrhages in association with gastrointestinal hemorrhages in various animals in which the sympathetic nerves were stimulated by the topical application of drugs, bacterial toxins or faradic current.

Jürgens & Studer D38,953/48: Following slow i.v. infusion of thrombin in the rabbit, the blood becomes incoagulable and there is leukopenia, thrombocytopenia and hypofibrinogenemia. Multiple capillary fibrin thrombi develop, especially in the renal glomerular capillaries, the liver and the lung. Polymorphonuclear leukocytes tend to accumulate in these same organs. [The possible implications of this observation in the pathogenesis of the SSP are not discussed (H.S.).]

More & Kobernick G21,660/51: Re-injection of various antigens in specifically sensitized rabbits can produce renal necrosis, glomerular nephritis and a necrotizing arteritis similar to periarteritis nodosa. However, these lesions do not correspond to those seen in human rheumatic fever or in the SSP.

Hausman & Dreyfus C99,073/53: A single i.v. dose of Liquoid causes hyaline thromboses in the renal glomerular capillaries, lungs and adrenals of the rabbit. In the kidneys, "often they lined the walls of the capillaries and formed casts which resembled to some extent the 'wire-loop' lesions seen in disseminated lupus erythematosus."

Brunson et al. C14,440/55: Liquoid i.v., given 12 hrs. after meningococcal endotoxin i.v., produces a typical SSP-G in the rabbit. There is cortical necrosis and thrombosis of the glomerular capillaries by a hyaline, highly birefringent material.

Piel et al. D21,797/55: In rats treated with nephrotoxic serum there developed "fibrin-positive staining thrombi within the glomerular capillary lumina comparable to the capillary lesions of the generalized Shwartzman reaction," a phenomenon frequently observed by earlier students of nephrotoxic nephritis.

Casper & Shulman C19,533/56: Bilateral renal cortical necrosis with thromboses in the interlobular arteries, the afferent arterioles and the glomerular capillaries occurs in infants with favism. This condition is seen especially in individuals of Mediterranean origin following ingestion of fava beans, or even mere approach to a field of fava beans. It is associated with hemolytic anemia and ascribed either to allergy or to some plant agglutinin which acts specifically on erythrocytes in racially predisposed individuals.

Johnstone & McCallum G21,668/56: Repeated i.v. injections of thromboplastin produce fibrin thrombi in the renal glomerular capillaries and pulmonary vessels, combined with hypofibrinogenemia in the rabbit.

Moore G28,864/57: In male weanling rats maintained on a choline-deficient diet, severe renal lesions develop which include cortical necrosis, hemorrhages and fibrin thrombi in arterioles and glomerular capillaries. [Although such capillary thrombi are allegedly pathognomonic of the SSP, the author does not mention the possibility of a relationship to the latter (H.S.).]

Muirhead et al. G21,288/57: Fibrinoid, such as appears in the glomerular capillaries during the SSP-G, is thought to be derived from smooth muscle fibers. Upon autolysis, smooth muscle tissue of the dog's intestine assumes the histochemical characteristic of fibrinoid and, if such autolysates are injected into the renal artery of a dog, fibrinoid thrombi develop in the glomerular capillaries. "The observations recorded are considered to add to the concept that vascular 'fibrinoid' as observed in a variety of conditions is derived

mainly from altered smooth muscle of the media."

Bohle et al. E44,801/58: An SSP-G produced in the rabbit by two i.v. injections of *E. coli* endotoxin, or a single i.v. injection of Liquoid, produces hyaline thrombi in the renal glomerular capillaries, interlobular arteries and interlobular veins. Electron-microscopically, this PS-positive hyaline material shows a fine fibrillar structure with an axial periodicity considered to be characteristic of fibrin.

Merriam & McKay C66,400/59: In rabbits pretreated with cortisone prior to a preparatory injection of bacterial toxin (kind not stated) "4 hours after the first dose of toxin the glomerular capillaries were dilated and packed with ink, an observation compatible with the theory that glomerular capillary dilation is in part responsible for lodgement of fibrin in these vessels in the Shwartzman reaction." India ink was injected into the aorta to check the state of capillary dilatation.

Sheehan & Davis G21,362/59: Compression of the renal pedicle for 3 hrs. causes ischemic death of the parenchyma and blood vessels of the rabbit kidney. If, at this stage, the vascular occlusion is released, the dead arteries become greatly dilated and numerous hemorrhages occur in their media, but circulation is not re-established. The glomerular capillaries are first dilated with red corpuscles which are then pushed into the intertubular capillaries by a finely vacuolated "microfoam." After about 2 hrs., fibrin is laid down in the microfoam along the endothelial surfaces, and eventually it may completely occlude the capillaries. Thrombi may also occur in interlobular arteries. Heparinization prevents fibrin deposition in arteries, but not the formation of glomerular thrombi.

Moore D34,394/62: Renal cortical necrosis with thrombosis in the glomerular capillaries and intra-uterine hemorrhage with fetal death were observed in late-pregnant rats given progesterone and kept on a certain choline-deficient diet. However, choline itself does not appear to be the decisive factor, since supplements of it did not prevent these changes. Still, some dietary factor was important, as no such lesions were observed in similarly treated pregnant rats kept on ordinary rat meal.

Lee G26,187/63: After RES-blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the

appearance of "heparin precipitable fibrinogen" in the circulation.

Margaretten & McKay G3,648/63: Glomerular capillary thrombi similar to those of the SSP-G have been produced in pregnant and nonpregnant rats by the i.v. infusion of thrombin.

Vassalli et al. G14,966/63: Electron-microscopic studies show the deposition of fibrin and fibrinoid in the glomerular capillaries of rabbits injected with Liquoid, thromboplastin or thrombin. Particularly pronounced lesions are obtained following simultaneous treatment with EACA + Liquoid i.v. Phagocytosed fibrin was occasionally observed in swollen endothelial and intercapillary cells.

Margaretten et al. G27,941/64: An "SSP-G" with renal glomerular thrombosis can be produced in rats by slow i.v. infusion of thrombin. In nonpregnant, unlike in pregnant rats, these thrombi rapidly disappear as a consequence of fibrinolysis.

Morard et al. F9,622/64: Carrageenin i.v. produces renal cortical necrosis with fibrin thrombi in the glomerular capillaries of rabbits, rats and guinea pigs. At the same time, there is hemoglobinuria and a decrease in serum complement.

Vassalli et al. E56,313/64: Description of ultrastructural changes in the platelets within the glomerular capillaries of rabbits, following intravenous infusion of thromboplastin or injection of thrombin into the renal artery. Fibrin deposition occurs only secondarily around damaged platelets.

Rodriguez-Erdmann G30,256/65: Following

Lung. The lungs almost constantly exhibit hemorrhages, edema, and microthrombi in the SSP-G and other forms of THP-Gs. A selectively pulmonary localization of the SSP-L has been achieved in the rabbit by intratracheal administration of endotoxin followed by an i.v. injection of the same material. In rabbits pretreated by intratracheal injection of attenuated live microorganisms, subsequent i.v. provocation with homologous or heterologous toxins increased the number of pulmonary abscesses and enhanced virulence. It was concluded that perhaps pulmonary abscesses in man may develop on the basis of an SSP-L.

Pulmonary embolisms can be produced in rabbits by the i.v. injection of epinephrine, or of minute fibrin clots; but only fibrin, especially if combined with epinephrine, causes arteriolitis. It is assumed that pulmonary arteriolitis may be due to the direct effect of fibrin upon the arterial wall.

Shwartzman E53,222/30: It is possible to produce an SSP-L in the lung of the rabbit, if a bacterial filtrate (kind not mentioned) is injected intratracheally prior to the i.v. provocative injection.

blockage of the RES by Thorotrast, the i.v. injection of homogenized fibrin produces renal cortical necrosis with thrombosis of the glomerular capillaries in the rabbit.

Galton F51,263/65: During the THP-G elicited by colchicine in the pregnant hamster, India ink i.v. is trapped by some amorphous deposit in the glomerular capillaries.

Hansson G35,342/65: In cats, perfusion of the kidney with cooled blood, homologous blood (ADP) or crushed connective tissue as well as transient mechanical interruption of the renal blood flow "induced a significant drop in thrombocyte counts and when a complete renal blood flow obstruction ensued, the small renal vessels were occluded by aggregated thrombocytes. This was especially easily demonstrated in the glomerular capillaries." Subsequently, the kidneys became edematous and studded with patchy hemorrhages. Apparently, "the renal vascular bed is especially vulnerable to thrombocyte aggregation in the blood, presumably due to the special characteristics of this vascular circuit."

Urinary passages. *Cataliotti G28,645/38:* An SSP-L can be produced in the urinary bladder of the rabbit by topical preparation followed by i.v. provocation with *E. coli* endotoxin.

Fukui et al. G33,120/64: Allegedly, a "reversed Shwartzman phenomenon" can be produced in rabbits at sites of i.c. *E. coli* endotoxin administration if the animals previously received an i.v. injection of the same endotoxin. An SSP-L in the urinary bladder is obtained under the same circumstances but it is of lesser intensity than in the skin.

Apitz B30,444/34: In the lung of rabbits in which an SSP-G has been elicited by two i.v. injections of *B. coli* endotoxin, focal hemorrhages and edema occur, but fibrin thrombi in the vessels are rare.

Michelazzi G28,166/35: In rabbits pretreated by intrapleural injection of pneumococcus filtrate, subsequent i.v. administration of virulent pneumococci produces acute hemorrhagic lesions in the lung which are ascribed to the SSP.

Gerber C95,662/36: Detailed description of the pulmonary changes in rabbits in which an SSP-G is elicited by two i.v. injections of meningococcal or typhoid toxin.

Weir G22,999/38: A selectively pulmonary localization of the SSP-L can be produced in the rabbit by the intratracheal administration of *B. typhosus* endotoxin followed 24 hrs. later by an i.v. injection of the same material. There is widespread thrombosis of arterioles and venules, dilatation of the capillaries with disruption and swelling of their endothelium. "When bacteria or India ink are injected intravenously at this period, they are fixed within the blood vessels, and the India ink is plastered to the endothelium. The reaction is non-specific, for there is equal fixation of *Staphylococcus aureus* and *B. typhosus* in the lungs at this time." A single intratracheal injection of *B. typhosus* filtrate produces acute alveolitis in the rabbit. If bacteria or India ink are injected i.v., 4 hrs. after the intratracheal injection, they are localized in the alveolar spaces because of an increased permeability of the pulmonary vessels. However, 24 hrs. after the intratracheal injection, when the lung is maximally prepared for the SSP-L, there is no alteration of permeability as judged by the i.v. injection of bacteria or India ink.

Alechinsky D88,312/39: Description of the pulmonary changes following two i.v. injections of *E. coli* endotoxin in the rabbit.

Cohen & Moolten E71,235/43: In rabbits, prepared by an intratracheal injection of attenuated microorganisms resembling bacillus

necrophorus, subsequent i.v. injection of homologous or heterologous toxins increases the number of pulmonary abscesses. With slightly attenuated cultures, the virulence was fully restored. "The anaerobic streptococcus and the anaerobic diphtheroid which are found regularly in cases of putrid abscess of the lung may be suspected as the source of preparatory factor despite their apparent innocuousness." Consequently, it is suspected that pulmonary abscesses in man may, under certain conditions, result from an SSP-L.

Bordet G27,044/58: Influenza virus i.c. does not prepare the rabbit for the production of an SSP-L by the subsequent i.v. administration of *E. coli* endotoxin. However, if the virus is given i.v., provocation with *E. coli* endotoxin 24 hrs. later results in a typical SSP-G with predominant hemorrhagic manifestations in the lung and trachea. Influenza virus was found to be ineffective when used as the provocative agent following preparation with *E. coli* endotoxin.

McKay & Rowe C80,265/60: During the SSP-G, elicited by two i.v. injections of Shear's polysaccharide, it is possible to demonstrate the development of large ischemic areas in the lung by the intra-arterial injection of India ink. Ischemia is produced by platelet thrombi and, possibly, by arterial spasm. Other areas are blackened, owing to dilatation of the alveolar capillaries which trap much of the ink. Similar but less distinct areas appeared in the spleen and liver.

Nityanand & Zaidi F7,183/64: Pulmonary embolisms can be produced in rabbits by the i.v. injection of epinephrine or of minute fibrin clots, but only fibrin, especially in combination with epinephrine, causes arteriolitis. Hence, the latter lesion is ascribed to some direct effect of fibrin.

Cardiovascular System. The blood vessels are undoubtedly the primary target in the development of a THP-G however produced, but here we shall speak only of experiments specifically designed to study cardiovascular responses.

One of the earliest relevant observations was the finding of erythrocyte agglutination thrombi in the small vessels of man during acute infectious diseases.

If one ear of the rabbit is compressed at the base, so as to stop circulation, and endotoxin is injected into the vein distad from the compression, no obvious local change develops upon re-establishment of the circulation. However, if the ear is exposed to heat during contact with endotoxin, a THP-L results around the treated vein. If endotoxin is injected into the marginal vein of a temporarily clamped rabbit ear, a particularly severe hemorrhagic response is obtained on the pretreated side following i.v. provocation. This experiment proved that it is possible to prepare a region by local intravascular application of endotoxin and,

in this case, the critical period is shortened, since provocation is possible almost simultaneously with the preparatory treatment. Localization of an SSP-L to the vascular system has also been achieved by the administration of the preparatory injection directly into the cardiac muscle or into, or around, a femoral artery.

Single i.v. injections of meningococcal endotoxin can produce myocardial and valvular hemorrhage, with muscle necrosis in rabbits. This is often accompanied by fibrinoid deposition in the coronary arteries, and systemic changes reminiscent of the SSP-G.

During the classic SSP-G, cardiac necrosis, hemorrhage, and even calcification may occur. Infection of rabbits with group A streptococci followed by meningococcal or *S. marcescens* endotoxin i.v. can induce fibrinoid deposits in the coronary arteries which bear a certain resemblance to the changes of rheumatic fever, periarteritis nodosa and lupus erythematosus. Of course, fibrinoid deposition is one of the most characteristic features of the SSP-G under any circumstances. With the fluorescent antibody technique, it could be shown that fibrin, or an insoluble derivative of fibrinogen, is a typical constituent of the thrombi formed during the SSP-G. Furthermore, considerable amounts of histochemically demonstrable phosphatase could be detected in the arteries of rabbits exhibiting an SSP-G.

Essentially similar changes are obtained in the cardiovascular system when a THP is produced by nonmicrobial and microbial products in combination, or by nonbacterial materials alone.

Using the rat mesoappendix preparation or the perfused rabbit ear as a test object, it was found that lethal doses of endotoxin induce the terminal arterioles and venules to become completely refractory to epinephrine, while the larger arteries and veins show heightened reactivity. Consequently, stasis and petechial hemorrhages develop in the capillaries and venules. These findings suggested that altered reactivity to catecholamines may be the basic mechanism in the production of thrombohemorrhagic lesions by endotoxin.

In rats kept for many months on diets rich in butter, cholesterol and cholic acid, multiple platelet thrombi developed in the small vessels of the heart. Since this change was associated with thrombocytopenia and anemia, it was regarded as an equivalent of thrombotic thrombocytopenic purpura, despite the absence of ecchymoses.

Single or Variably Spaced Injections of Microbial Products Alone. Flexner E76,861/02: Agglutination of erythrocytes *in vivo* can occur in various infectious diseases of man and animals, in eclampsia, and after i.v. injection of ricin, ether, or dog's serum into rabbits. Such "agglutinative thrombi" were first observed in a vessel of the ileum of a patient who died of typhoid fever. "The vessel was quite occluded by a conglutinated mass made up of globules of different sizes showing different degrees of refraction and varying staining properties. Careful study readily supplied the conviction that the mass was composed of red corpuscles, altered in form, ad-

hesiveness, and staining properties." . . . "When such thrombi are old, or when the agglutination is compact, they may present appearances to which the name of 'hyaline thrombi' has been applied." The "hyaline glomerular thrombi occurring in the kidney in infectious diseases" as well as microthrombi in glaucoma and pulmonary infarction may have a similar origin.

Apitz G25,132/34: Following single or repeated i.v. injections of *E. coli* endotoxin, thrombi develop on the chordae tendineae of the rabbit. It is emphasized, however, that this response is unaccompanied by manifestations of inflammation, and that similar changes

can be obtained during anaphylaxis induced by repeated injections of horse serum. If rabbits are first given *E. coli* endotoxin i.v. and 24 hrs. later cultures of live *staphylococcus aureus* i.v., the course of the resulting septicemia is greatly altered. Depending upon dosage, there may be complete protection against infection, no effect, or a combination of the usual septicemia with endocarditis. Topical protection against infection may also be obtained by pretreatment of the cutaneous inoculation site with endotoxin, as shown by the author's earlier experiments.

Brunson et al. C14,438/55: Single i.v. injections of meningococcal endotoxin produced myocardial and valvular hemorrhages, muscle necrosis and cellular reaction with calcification of muscle fibers in rabbits. There was also edema and vacuolization of the intima and media and a disruption of the endothelial lining with fibrinoid deposition underneath the endothelium of the coronary arteries. In a few animals, renal cortical necrosis or fibrinoid formation in the glomerular capillaries was noted "resembling in all respects that seen in the generalized Shwartzman phenomenon." Pulmonary hemorrhages and thrombi within the branches of the pulmonary arteries were more common. Similar changes were often seen in the liver.

Two Injections of Microbial Products Spaced About 24 Hours Apart. Apitz B30,444/34: Cardiac necroses, hemorrhage and calcification may occur during the SSP-G elicited by two i.v. injections of *B. coli* endotoxin in the rabbit.

Gerber C95,662/36: Detailed description of the cardiac changes in rabbits in which an SSP-G is elicited by two i.v. injections of meningococcal or typhoid toxin.

Alechinsky D88,312/39: If one ear of the rabbit is compressed at the base, so as to stop the circulation, and then *E. coli* endotoxin is injected into a vein distad from the compression, no obvious local change is noted upon re-establishment of the circulation. However, if within 24 hrs. the same filtrate is injected into the marginal vein of the opposite ear, a hemorrhagic response is obtained on the pre-treated side. Thus, it is possible to prepare a region by the local intravascular application of endotoxin. If the ear is prepared in this manner, it responds with hemorrhage even if the i.v. injection is given into the contralateral ear almost simultaneously with the preparatory injection. Thus, the critical period of incubation can be greatly shortened.

Tedeschi & Schlossmann G22,707/41; Tedeschi G22,346/46: In rabbits prepared by meningococcal endotoxin, injected directly into the

cardiac muscle or into or around the femoral artery, an SSP-L developed in the prepared sites following i.v. administration of the same material 24 hrs. later.

Thomas G26,184/52: In rabbits infected with live streptococci i.v., followed 48 hrs. later by meningococcal toxin i.v., cardiac changes occur which resemble those of acute rheumatic fever.

Thomas & Good B79,249/52: In rabbits the SSP-G elicited by two i.v. injections of meningococcal toxin is associated with the development of scattered areas of acute myocardial-fiber necrosis, vacuolization and basophilic staining of portions of the muscle fibers. At the same time, there are hemorrhages and necroses in the lungs, spleen, liver and lymph nodes.

Thomas et al. G21,293/53: Cutaneous and systemic infections with Group A streptococci prepare the rabbit respectively for the SSP-L and SSP-G by subsequent i.v. injection of meningococcal or *S. marcescens* toxin. Under optimal conditions of dosage and timing, fibrinoid deposits appear in the coronary arteries in approximately 50% of the animals. "These are obvious points of resemblance between the vascular lesions of fibrinoid necrosis produced in rabbits and the changes in blood vessels which occur in certain human disease states, characterized by fibrinoid deposition, such as rheumatic fever, periarteritis nodosa, thrombotic thrombocytopenia and disseminated lupus erythematosus."

Thomas et al. G25,140/53: Rabbits, infected by i.v. injection of type 1 streptococci and, two days later, given meningococcal endotoxin i.v., developed "infiltration of the walls of the coronary arteries by homogeneous eosinophilic material resembling fibrinoid, accompanied by varying degrees of necrosis of the arterial walls." . . . "The possibility that rheumatic fever may be a special manifestation of a continuing systemic infection by streptococci has been discussed."

Booth et al. G28,649/55: In rabbits in which an SSP-G was produced by two injections of *E. coli* endotoxin, the hyaline material deposited in various vessels (and especially in the renal glomerular capillaries) was identified as fibrinoid by a variety of histochemical tests. It is indistinguishable from the fibrinoid accumulating in the necrotic arterioles of malignant hypertension in man.

Brunson et al. C14,439/55: Detailed histological and histochemical analysis of the organ lesions in rabbits in which an SSP-G is produced by two i.v. injections of meningococcal toxin. "The important feature of the pathologic changes following such a procedure is the presence of occlusive masses of fibrinoid in

the glomerular capillaries, the splenic sinusoids, beneath the endothelium of the coronary arteries, and within the heart valves. The accumulation of this material in the kidneys and spleen results in the development of renal cortical necrosis and splenic hemorrhages and necrosis." Fibrinoid was found in the hearts and thrombi, necrosis in the liver and pulmonary arteries. The occlusive material has some morphologic and tintorial features of fibrinoid, presumably derived from the circulating blood. "The birefringent properties and reaction of the material to proteolytic enzymes suggest that it is a highly organized protein compound."

Hugues et al. G27,058/58: *S. typhi murium*, given i.p. and 24 hrs. later i.v. to rabbits, produces a peritoneal SSP-L in which the vascular changes can be observed *in vivo* on the exteriorized mesentery. The initial changes are detectable after about 6 min. and consist of ruptures of the veins with hemorrhages, but are unaccompanied by platelet embolisms or leukocyte agglutination. In these respects, they differ from the initial changes of anaphylaxis.

McKay et al. D15,431/59: With the fluorescent antibody technique, it has been demonstrated that fibrin or an insoluble derivative of fibrinogen is a constituent in the thrombi found in the lungs, spleen, liver and kidneys of rabbits in which an SSP-G was produced by two i.v. injections of *S. marcescens* endotoxin.

Scott G22,342/62: Both the SSP-L and the SSP-G elicited by two injections of *E. coli* endotoxin in rabbits are associated with the formation of fibrin thrombi in the lung, liver, kidneys, and sometimes the adrenals and spleen, but the extent of thrombosis is greater in the SSP-G. The presence of coccidiosis, inflammation and tissue damage in an organ predisposes it to the formation of thrombi, presumably through local "preparation." The progressive reduction in the number of thrombi after 4 hrs. suggests the intervention of fibrinolysis.

Coriglione G28,855/64: The ocular SSP-L produced by local preparation and i.v. provocation with typhoid endotoxin in the rabbit, can be prevented by STH, presumably because capillary permeability is diminished as judged by the fluorescein test. [The brief abstract does not permit accurate evaluation of the results (H.S.).]

Emmrich et al. F8,082/64: During the SSP-G, elicited by two i.v. injections of *S. abortus equi* endotoxin, the histochemically demonstrable phosphatase content of the arteries, liver, and kidney shows only minor variations.

Nonmicrobial Agents Alone or in Combination with Microbial Products. Shwartzman E43,557/35: In the rabbit, local reactivity cannot be elicited by a single preparatory i.v. injection of various bacterial endotoxins alone into the clamped (to stop circulation) or non-clamped ear. The SSP-L also fails to appear after such treatment in combination with locally applied cold, xylol, urethane, pilocarpine, atropine, etc. However, such preparatory i.v. injections of toxins are capable of eliciting an "SSP-L" in the rabbit's ear when combined with thermal hyperemia.

Dietrich E55,223/41: If a venous stasis is produced on one side of the neck in rabbits by compression of the jugular vein with a ribbon of fascia and a suspension of *E. coli* bacilli is injected into the marginal ear vein on the same side for preparation, subsequent provocation by the i.v. injection of *E. coli* filtrate into the marginal vein of the opposite ear produces extensive thrombosis in the prepared vein. The lesion is considered to be a close equivalent of spontaneous thromboses as they occur in man.

More & Kobernick G21,660/51: Re-injection of various antigens in specifically sensitized rabbits can produce renal necrosis, glomerular nephritis, and a necrotizing arteritis similar to periarteritis nodosa. However, these lesions do not correspond to those seen in human rheumatic fever or in the SSP.

Brunson et al. C14,440/55: The SSP-G produced by Liquoid alone or by Liquoid plus meningococcal endotoxin i.v. is associated with myocardial necrosis, hemorrhages and calcification. Fibrinoid material is noted beneath the endothelium of the coronary arteries.

Zweifach et al. D15,450/56: Unlike in the rabbit, "repeated attempts to produce skin lesions in the rat with combinations of endotoxin and epinephrine have been uniformly unsuccessful." Using the rat mesoappendix preparation, it was found that lethal doses of endotoxin induce the terminal arterioles and venules to become completely refractory to epinephrine, while heightened reactivity persisted in the larger arteries and veins. "The end result was pooling of stagnant blood in distended capillaries and venules, accompanied by the appearance of petechiae. Topical applications of epinephrine during this stage were followed promptly by an increase in petechial hemorrhage at the site of testing." Analogous results were obtained in perfusion studies of the rabbit ear. Perfusion with small amounts of endotoxin was followed within minutes by potentiation of the epinephrine reactivity. However, larger doses caused com-

plete reversal of this effect, so that epinephrine induced vasodilatation. "It is suggested that abnormal reactions to epinephrine or norepinephrine in the tissues of intact animals may represent a basic mechanism in the intoxicating and tissue-damaging properties of endotoxin."

McKay & Merriam C85,593/60: An SSP-G was elicited in cortisone-pretreated rabbits by bacterial endotoxin (kind not stated) i.v., and the state of the vascular system subsequently examined by intra-aortic administration of India ink. The glomerular capillaries dilated and filled with ink 4 hrs. after the injection of endotoxin. This was accompanied by capillary thrombosis. No change was observed in the distribution of ink in the liver; thrombosis in the hepatic sinusoids and central veins occurred only in 1 of 16 rabbits. "It is suggested

that capillary dilation is an important factor in the localization of thrombi in the generalized Shwartzman reaction and may be considered as an important facet of the phenomenon of 'preparation' for this reaction."

Renaud & Allard D35,261/62: In rats kept on diets rich in butter, cholesterol and cholic acid, there developed, within 1 year, a syndrome characterized by multiple thrombi (presumed to consist of platelets) which were located mainly in the arterioles and capillaries of the heart, but occasionally also in other organs. They "presented a histological picture that resembled thrombotic thrombocytopenic-purpura rather than coronary disease." [Just before death, there developed anemia and thrombocytopenia. However, "ecchymoses were not seen in the thrombotic animals" (H.S.).]

Digestive Tract. Thrombohemorrhagic lesions in the digestive tract are common in THPs elicited by various means. Special attention has been given, however, to the possibility of localizing these changes to certain parts of the gastrointestinal system by topical preparation. Thus, it has been found that, if a preparatory injection of endotoxin (and in some cases of live microbes) is given into the wall of the stomach, esophagus, small intestine, appendix, colon or rectum, a topical SSP-L develops upon subsequent i.v. injection of SSP-active substances. It has been assumed, therefore, that the SSP may participate in the development of hemorrhagic gastrointestinal lesions, particularly appendicitis and ulcerative colitis, in man.

It is noteworthy in this connection, that mere removal (with a sharp spoon) of the mucosa of the rabbit appendix suffices to prepare the animal for the production of a hemorrhagic appendicitis upon subsequent i.v. administration of endotoxin. This preparation has been ascribed to the fact that through the wound surface, the bacterial flora and particularly *E. coli*, gain access to the subjacent tissues. In man, foreign bodies in the appendix could perhaps produce a similar topical sensitization to blood-borne endotoxins and thereby induce fulminating hemorrhagic appendicitis.

Oral Cavity. *Provisionato G28,862/35:* In rabbits, given preparatory injections of *E. coli* endotoxin into the mucosa of the gingiva and tongue as well as i.c., subsequent provocation by the same material i.v. produces an SSP-L in the skin but not in the oral cavity.

Rizzo & Mergenhagen G28,648/60: An SSP-L has been produced both in the skin and in the oral mucosa of the rabbit by topical preparation followed by i.v. provocation with an extract of *Veillonella* organisms.

Stomach and Esophagus. *Appelmans & Vasiliadis D72,056/31:* In rabbits prepared by an *E. coli* or *B. typhosus* endotoxin injection into

the gastric mucosa, the peritoneum, and the skin of the ear, subsequent i.v. injection of the same materials produces an SSP-L only in the ear, and not in the stomach or peritoneum. It is concluded that various sites are not equally susceptible to sensitization and that the stomach and peritoneum are particularly resistant.

Karsner et al. E50,460/31-32; B78,212/34: An SSP-L can be produced in the stomach of the rabbit by the injection of *E. coli* endotoxin into the gastric wall, followed by the i.v. injection of the same material.

Niosi G22,351/39: In rabbits in which a preparatory injection of *E. coli* endotoxin is

injected into the wall of the stomach, a topical SSP-L (often with exulceration of the mucosa) occurs, following the i.v. administration of the same material 24 hrs. later. Similar reactions may explain the pathogenesis of certain peptic ulcers in man.

Basile G23,055/41: Review of the literature on the production of an SSP-L in the gastric mucosa.

Finocchi G22,100/47: In rabbits given an injection of staphylococcus citreus into the wall of the esophagus, subsequent i.v. injection of the same material produces an SSP-L at the site of preparation.

Duodenum, Jejunum and Ileum. Michelazzi D92,869/33: Intestinal loops, removed from rabbits 24 hrs. after E. coli endotoxin i.v. and exposed to the same endotoxin 24 hrs. after preparation, showed no change in their contractility suggestive of any anaphylactic phenomenon.

Franke D45,064/44: Toxic doses of S. marcescens lipopolysaccharide produced hemorrhagic necrosis in the intestine, lymphatic tissue and liver of the dog. "Adrenalin administered after polysaccharide injection augmented the intestinal congestion and hemorrhage and the subendothelial hemorrhages."

Gonçalves G22,359/50: Following preparation by infiltration of the vagus or splanchnic nerves with live herpes simplex virus, the i.v. injection of the same material 2 hrs. later produces gastroduodenal ulcers with local hemorrhages and necrosis. These are interpreted as an SSP-L. Herpes simplex is allegedly common in patients with gastroduodenal ulcers. Perhaps localization of a virus in the autonomic nerves, with a subsequent SSP-L, is involved in the pathogenesis of gastroduodenal ulcers in man.

Jansen G23,254/54: In rabbits, E. coli endotoxin is injected directly into the exteriorized jejunal wall, this being followed the next day by E. coli i.v. A typical SSP-L develops in the prepared intestinal loop.

Fine et al. D98,173/59: In rabbits, transient hemorrhagic shock was produced by bleeding into a heparinized reservoir and then restoring their own blood to effect recovery. If Thorotrast was given i.v. prior to the bleeding, immediate recovery still occurred but was followed, within a few hours, by a second period of shock which terminated in death. At autopsy, hemorrhagic necrosis of the gut was observed, but this was not considered to be an SSP-G.

Selye et al. G23,204/66: A thrombohemorrhagic form of duodenal and upper jejunal necrosis can be produced by a single i.v. injection of agar in the rat.

Appendix. Latteri G22,433/34: An SSP-L can be produced in the appendix of the rabbit by local preparation with E. coli or typhoid endotoxin (injected into the wall of the appendix through a laparotomy) followed 24 hrs. later by the i.v. injection of the same materials.

Horster & Müller G25,124/37: If meningo-coccal endotoxin is injected into the wall of the rabbit appendix, i.v. injection of the same material 24 hrs. later produces a hemorrhagic appendicitis.

Basile G23,055/41: After a review of earlier work on the production of an SSP-L in the appendix by the local administration of a preparatory endotoxin injection, the following experiment was performed in the rabbit: under anesthesia, a small oculist's spoon was introduced into the appendix from its base and a piece of mucosa and submucosa removed. The following day, E. coli endotoxin was injected i.v. Of 16 rabbits so treated, 5 showed a definite SSP-L at the traumatized region, while the remainder exhibited only minor lesions such as were found also in controls not provoked by i.v. endotoxin. One of the positively reacting rabbits also showed SSP-G-like changes. It is concluded that topical trauma to the mucosa of the appendix can act as a preparatory treatment. In man, foreign bodies in the appendix may produce such trauma, and certain types of fulminating hemorrhagic appendicitis could represent manifestations of the SSP-L.

Colon and Rectum. McKay et al. G33,264/55: Pseudomembranous enterocolitis with intravascular clotting in the microcirculation of the bowel can be produced in dogs by the administration of incompatible blood into the aorta with concomitant surgical trauma in the abdomen.

Kirsner & Elchlepp D72,475/57: If S. marcescens endotoxin is injected into the colon of rabbits, an i.v. injection of the same material, 24 hrs. later, results in an SSP-L localized in the injection sites. A similar "ulcerative colitis" can be produced in the rabbit with the Auer procedure.

Goldgraber & Kirsner D10,419/59: An SSP-L can be produced in the colon of rabbits by the injection of S. marcescens endotoxin into the intestinal wall, followed 24 hrs. later by an i.v. injection of the same agent. There develops hyperemia, hemorrhage, thrombosis, necrosis and granuloma formation, sometimes associated with eosinophilic infiltration at the site of the preparatory injections.

Hardaway & McKay G33,251/59: A type of pseudomembranous enterocolitis with multiple thromboses in the microcirculation of the

bowel can be produced in dogs by transfusion of incompatible blood. Heparin prevents this phenomenon.

Patterson et al. C91,249/60: If *E. coli* endotoxin is injected under the submucosa of the rectum and, 24 hrs. later, the same material is given i.v. in the rabbit, an SSP-L is elicited in the rectum and colon.

Hardaway et al. D18,362/61: Intra-aortic injection of incompatible blood, thrombin, or *E. coli* endotoxin, produces hemorrhagic necrosis with intravascular fibrin-clot formation in the dog. The changes resemble pseudo-

Liver and Biliary Passages. In the liver, the changes most characteristic of the SSP-G are the formation of fibrin thrombi (which sometimes become organized fibrous nodules in the walls of the veins) and parenchymal necroses with inflammation and hemorrhage. By topical administration of the preparatory endotoxin injection, it is possible to localize an SSP-L in the liver or the gallbladder.

Apitz B30,444/34: The characteristic hepatic lesions of an SSP-G elicited by two i.v. injections of *E. coli* endotoxin in the rabbit are: fibrin thrombi (sometimes progressing to organization and fibrous nodule formation in the veins) and parenchymal necroses with inflammation and hemorrhage.

Gerber C95,662/36: Detailed description of the hepatic changes in rabbits in which an SSP-G is elicited by two i.v. injections of meningococcal or typhoid toxin.

Divella G27,054/40: An SSP-L can be produced in the gallbladder of the rabbit by topical preparation followed by i.v. provocation with *E. coli* filtrate.

Basile G23,055/41: Review of the literature on the production of an SSP-L in the gallbladder.

Yamagata et al. G22,345/55: Intrahepatic or intraportal injection of *E. coli* endotoxin, followed 24 hrs. later, by i.v. provocation causes an SSP-L in the liver of the rabbit.

McKay & Rowe C80,265/60: During the SSP-G, elicited by two i.v. injections of Shear's polysaccharide, it is possible to demonstrate the development of large ischemic areas in the lung by the intra-arterial injection of India ink. Ischemia is produced by platelet thrombi and possibly also by arterial spasm. Other areas are blackened, owing to dilatation of the alveolar capillaries which trap much of the ink. Similar, but less distinct areas appeared in the spleen and liver. Four hrs. after each injection of endotoxin, ink was almost com-

membranous enterocolitis in man and can be largely prevented by heparin pretreatment.

Patterson et al. D14,188/62: An SSP-L in the colon of the rabbit can be elicited by *E. coli* injected first into the submucosa of the colon and then i.v. However, the authors doubt "that this phenomenon is of importance in the production of chronic ulcerative colitis in man."

Patterson et al. D58,647/63: Rectal manifestations of the SSP-L can be produced in rabbits by the topical injection of a preparatory dose of *E. coli* toxin (either alone or mixed with epinephrine or norepinephrine) followed by i.v. injection of the same toxin.

Liver and Biliary Passages. In the liver, the changes most characteristic of the SSP-G are the formation of fibrin thrombi (which sometimes become organized fibrous nodules in the walls of the veins) and parenchymal necroses with inflammation and hemorrhage. By topical administration of the preparatory endotoxin injection, it is possible to localize an SSP-L in the liver or the gallbladder.

pletely excluded from the center of all hepatic lobules, while the peripheral sinusoids were dilated.

Renaud G31,776/63; G31,557/65: In rats kept on a high-fat diet containing 2% cholic acid and 11% casein as the sole source of protein, a high incidence of massive red infarcts with platelet thrombi in the hepatic veins can be obtained by single i.v. injections of *Proteus mirabilis* or *E. coli* endotoxins. Occasionally, similar thrombi were also found in the lungs, kidneys, spleen, pancreas and cardiac cavities. However, renal glomerular thromboses were not observed.

Emmrich et al. F8,082/64: During the SSP-G elicited by two i.v. injections of *S. abortus equi* endotoxin, the histochemically demonstrable phosphatase content of the arteries, liver, and kidney shows only minor variations.

Renaud F40,451/65: Certain high-fat diets predispose the rat for the development of occlusive thromboses in the large hepatic veins following i.v. injection of *E. coli* or *S. typhosa* endotoxin. No such effect is obtained by the same endotoxins on ordinary diets.

Renaud G31,668/65: In rats made hyperlipemic by prolonged maintenance on a special diet, *S. typhosa* or *E. coli* endotoxin i.v. consistently produce thromboses in the large hepatic veins with consequent red infarcts of the liver. Heparin, hirudin or acenocoumarin given just before the endotoxin considerably lowered the incidence of thrombosis and the mortality rate.

Pancreas. Fulminating hemorrhagic inflammation can also be produced in the pancreas by topical preparation with endotoxin followed by i.v. provocation. The question has been raised whether certain forms of hemorrhagic pancreatitis in man might not be due to the same mechanism.

Reitano & Loi E65,030/34: Hemorrhagic necrosis of the pancreas can be produced in the rabbit by an intrapancreatic injection of typhoid endotoxin followed 24 hrs. later by the i.v. administration of the same material.

Pasquali & Cazzola G28,851/37; G23,074/38: An SSP-L has been produced in the pancreas of the guinea pig by topical preparation and subsequent i.v. provocation with *E. coli* endotoxin.

Bezza G28,396/38: An SSP-L can be elicited in the pancreas of the dog by the injection of *E. coli* endotoxin into the pancreatic duct, followed 24 hrs. later by the i.v. administration of the same material.

Basile B23,055/41: Review of the literature on the production of an SSP-L in the pancreas.

Ackerman 57,770/42: A thrombohemorrhagic pancreatitis develops occasionally in man following transfusion with incompatible blood.

Thal & Brackney B93,944/54: Fulminating hemorrhagic pancreatitis can be produced both in the rabbit and in the goat if *E. coli* endotoxin is first introduced into the pancreatic duct and later i.v. No lesion occurs without the provocative i.v. injection. Histology

logic studies uniformly showed capillary and venular hyaline thromboses, such as also occur in clinical cases of hemorrhagic pancreatitis.

Thal & Molestina C14,784/55: Fulminating hemorrhagic pancreatic necrosis can be produced in the dog by a single intraductal injection of staphylococcal toxin.

Hardaway & McKay D95,869/59: Acute hemorrhagic pancreatic necrosis is produced in dogs by the intra-aortic infusion of human blood. The reaction is associated with intravascular clotting in the pancreas and other organs. A review of the literature shows that hemorrhagic pancreatitis in man is also frequently associated with thrombosis in veins and capillaries, as well as lower nephron nephrosis.

Korn E37,359/63: A necrotizing, hemorrhagic pancreatitis can be produced in the rabbit by injecting *E. coli* or *S. abortus* endotoxin into the pancreatic duct followed 24 hrs. later by the i.v. injection of the same materials.

Seifert F30,647/65: An SSP-L can be elicited in the rabbit pancreas by the injection of *E. coli* or *S. abortus equi* endotoxin into the pancreatic duct followed by i.v. provocation.

Adrenals. Thrombohemorrhagic lesions in the adrenals are uncommon during the classic SSP-G in rabbits, but they occur quite frequently in guinea pigs. In these, hemorrhagic, necrotizing, inflammatory adrenal lesions occur even after single s.c. injections of diphtheria toxin. This change is prevented by hypophysectomy. Apparently, the responsiveness of the adrenal depends upon the trophic influence of ACTH.

In rabbits pretreated with Thorotrast or ACTH, endotoxin i.v. fairly constantly produces adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome. In the rat, prolonged i.v. infusion of thrombin elicits adrenal hemorrhages when accompanied by ACTH treatment. Since the SSP-G resembles the Waterhouse-Friderichsen syndrome in many respects, it may be assumed that the adrenal hemorrhages so characteristic of the latter are conditioned by the stress-induced stimulation of endogenous ACTH secretion which occurs in severe systemic infections.

Gronchi 67,465/34: Injection of *E. coli* into the adrenal of the guinea pig, followed 24 hrs. later by i.v. provocation with the same material, produces an SSP-L in the prepared

adrenal. The adrenal also participates in the SSP-G produced by two i.v. injections of *E. coli* endotoxin in guinea pigs.

Gronchi & Carnielli 30,391/34: The produc-

tion of an SSP-G by two i.v. injections of *E. coli* endotoxin produces particularly conspicuous adrenal hemorrhages in the guinea pig.

Gerber C95,662/36: Detailed description of the adrenal changes in rabbits in which an SSP-G is elicited by two i.v. injections of meningococcal or typhoid toxin.

Reyna E24,151/36: Repeated daily i.v. injections of lithium carmine, given during 2-6 days, produce hyaline thrombi in the renal glomerular capillaries with bilateral cortical necrosis. There are also hemorrhages and necroses, sometimes with hyaline thrombi, in the liver, lung and adrenals. [The author emphasizes the similarity of these changes to those characteristic of eclampsia and bilateral cortical necrosis in man, but he does not mention the possibility of a relationship to the SSP (H.S.).]

Tonutti B48,825/49; B48,887/49; B48,892/50: The hemorrhagic, necrotizing and inflammatory responses that normally occur in the adrenals and at the site of injection following a single s.c. dose of diphtheria toxin, are prevented by hypophysectomy. In the absence of the hypophysis, a topical reaction to skin burns as well as the associated adrenal stimulation are likewise prevented. Apparently, the pituitary conditions nonspecific tissue reactivity presumably through the regulation of corticoid secretion.

Wawersik C31,713/55: An SSP-L, elicited by two injections of meningococcal toxin, produces adrenal hemorrhages in the guinea pig although the preparatory injection is given i.c.

Pirsch et al. G27,360/57: In guinea pigs infected with *Coxiella burnetti* i.p., provocation with *Brucella*, *E. coli* or *S. typhosa* endotoxin, intracardially 3 days later, caused death with adrenal hemorrhages. This was interpreted as an SSP-G, although no characteristic changes were found in the kidneys and hemorrhages in other organs were very inconstant.

Levin & Cluff G8,713/64: Massive bilateral adrenal cortical hemorrhages, develop in rabbits prepared with Thorotrast and injected a few hours later with endotoxin (kind not stated) or ACTH. Administration of multiple doses of cortisol, soon after the Thorotrast or

ACTH injections, suppress the adrenal hemorrhagic reaction, otherwise elicited by endotoxin. It is concluded "that adrenal hemorrhage observed during sepsis, as in the Waterhouse-Friderichsen syndrome, may be attributable to endotoxemia occurring during or shortly after stimulation of the adrenal cortex by infection."

Margareten et al. F3,924/64: Prolonged infusion of thrombin i.v. elicits no adrenal hemorrhage in the rat (changes in other organs are not mentioned). However, if simultaneously ACTH or EACA is infused, adrenal hemorrhages result.

Gabbiani et al. G19,450/65: In rats pretreated with ACTH, fluorocortisol, or stress (restraint), a single i.v. injection of Thorotrast produced thrombohemorrhagic lesions with necrosis in the adrenals and liver, as well as hyaline glomerular capillary thromboses in the kidneys.

Levin & Cluff G25,181/65: In the rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, unlike the SSP, this response is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment. The adrenal hemorrhages are also prevented by certain adrenergic blocking agents such as phenoxybenzamine, alderlin, or 1-(3',4'-dichlorophenyl)-2-(isopropylamino) ethanol. Since ACTH, Thorotrast and *E. coli* endotoxin all increase the blood-cortisol level of the rabbit, it is assumed that the localization of the hemorrhages is connected with increased adrenocortical activity.

Margareten et al. G26,896/65: Hemorrhagic thrombosis of the adrenals often combined with renal cortical necrosis can regularly be obtained in rats by combined treatment with ACTH, EACA and thrombin. It is assumed that thrombin induces a generalized predisposition for thrombosis. ACTH is responsible for the adrenal localization (owing to dilatation of the sinusoids), while EACA prevents fibrinolysis. Treatment with thrombin and EACA or thrombin and ACTH have a similar but less constant effect.

Nervous System. The brain does not participate conspicuously in the SSP-G. It is extraordinarily difficult to produce cerebral thrombohemorrhagic lesions with the usual endotoxins, even by topical preparation followed by i.v. provocation. However, rabbits inoculated intracerebrally with rabies neurovaccine and given the same material subsequently i.v., die with diffuse hemorrhages in the brain and spinal cord, perhaps as a consequence of the specific neurotropic effect of the rabies virus.

Gratia & Linz D7,456/31: Rabbits inoculated intracerebrally with rabies neurovaccine and given the same material two days later i.v., die with diffuse hemorrhages in the brain and spinal cord. *V. cholera* or *E. coli* endotoxins may also be used for provocation, but they induce hemorrhages in the heart, lung, and lymph nodes, without any characteristic SSP-L changes in the brain.

Bock E72,616/32: Subdural or intracerebral injection of *E. coli* endotoxin does not produce an SSP-L at the injection site in rabbits subsequently given an i.v. injection of the same material.

Gonzalez G24,145/32: An SSP-L in the brain could not be obtained either in the rabbit or in the guinea pig by topical preparation followed by i.v. provocation with various endotoxins.

Plaut E41,413/32: If *Spirochaeta pallida* filtrates (proven to be active in producing a cutaneous SSP-L) are given as the preparatory injection into the spinal fluid by suboccipital injection, no hemorrhagic lesions are noted in the brain or the meninges.

Marburg & Shwartzman G22,364/41: Single i.v. injections of meningococcal toxin produce an acute meningococcus encephalitis in the rabbit, but reinjection of the same material i.v. 24 hrs. later does not aggravate this response considerably, nor does it produce hemorrhages characteristic of the SSP-L.

Eye. Changes in the eye of the rabbit can develop during the course of an ordinary SSP-G elicited by two injections of endotoxin. These somewhat resemble diabetic retinopathy in that PAS-positive material appears within dilated veins and sometimes aneurysms develop in the dilated vessels. However, these changes are rarely conspicuous.

Even single i.v. injections of SSP-active endotoxins can produce a "toxic ocular reaction," characterized by iridoconjunctival hyperemia, photophobia, lacrimation, and coagulation of the aqueous humor after its aspiration. However, repetition of the i.v. injection 24 hrs. after the first dose aggravates these manifestations.

An SSP-L cannot be produced in the cornea unless it is vascularized by local irritation; in this event the cornea becomes susceptible to topical preparation and responds with an SSP-L to i.v. provocation. Another technique for the production of an ocular SSP-L is based on the removal of aqueous humor, immediately followed by the i.v. injection of endotoxin, which then localizes in the eye as the fluid content is reconstituted. After this, a second i.v. injection can provoke an ocular hemorrhagic response. Subconjunctival preparation by endotoxin can likewise prepare the eye for the induction of a local SSP-L by a subsequent i.v. injection of the same material.

Waksman & Adams C39,574/57: Experimental allergic encephalomyelitis (EAE) was produced in rabbits by a single injection of nervous tissue in adjuvant. An "SSP-G" was elicited by two properly spaced i.v. injections of meningococcal endotoxin or by a single dose following pretreatment with Thorotrast. 15 of the 63 rabbits receiving this combined treatment "showed full-blown Shwartzman lesions, with hemorrhage and necrosis of the nervous parenchyma, usually superimposed on the pre-existing lesions of EAE. Such hemorrhagic or necrotic lesions were not observed in the control group given toxin alone and occurred in only 2 of the 92 EAE rabbits not given toxin. There was no correspondence between the occurrence of lesions in the central nervous system and the presence or severity of Shwartzman lesions in the major viscera."

Gabbiani G32,006/66: "In the rat cadmium chloride causes a selective hemorrhagic necrosis of the Gasserian ganglion and of the spinal sensory ganglia. Here the nervous cells show pyknosis of nuclei and lysis of cytoplasm and appear surrounded by hemorrhagic suffusions."

Kut F52,393/65: In a woman with septic abortion there was thrombosis of the sagittal sinus and other cerebral veins combined with adrenal hemorrhages, "crush kidney," a hemorrhagic infarct in the lung, cutaneous petechiae and thromboses of the utero-vaginal and femoral veins. The syndrome was interpreted as an SSP-G due to bacterial endotoxins.

Cassuto G28,168/33: An SSP-L can be produced in the conjunctiva or ciliary body of the rabbit by topical preparation followed by i.v. provocation with typhoid endotoxin.

Mossa G2,855/35: By topical preparation followed by i.v. injection of *S. typhosa* endotoxin, it was possible to elicit an SSP-L in the eyelids, conjunctiva, iris and ciliary body of the rabbit, but not in the avascular cornea.

Rossi G28,856/35: Topical preparation followed by i.v. provocation with *E. coli* endotoxin produces an SSP-L in the conjunctiva, iris and ciliary body but not in the cornea, vitreous body or anterior chamber of the rabbit eye.

Fabiani & Gauthier G22,570/37: Normally an SSP-L cannot be produced in the cornea. However, if the cornea is previously vascularized owing to the production of an abscess with living *staphylococcus aureus* cultures, topical preparation of the scar with Shiga toxin followed by the i.v. injection of the same material elicits a typical SSP-L. Apparently, the resistance of the cornea under normal conditions is due not to any special property of its tissue but to the lack of blood vessels.

Alechinsky D88,312/39: If, in a rabbit, the aqueous humor of one eye is removed by puncture and, immediately afterwards, *E. coli* endotoxin is given i.v., the material apparently localizes in the eye, as its fluid content is reconstituted. Consequently, a second i.v. injection of endotoxin, 24 hrs. later, produces a typical hemorrhagic response in the punctured eye.

Sanders G17,733/39: An SSP-L can be produced in the eye of the rabbit by topical preparation followed by i.v. provocation with typhoid but not with gonococcus filtrate. The changes are more severe and constant when the preparatory injection is given into the conjunctiva, than when it is administered intraocularly. In rabbits given only the preparatory injections, the changes were of the same type but much less severe.

Ajó G22,367/41: A single i.v. injection of meningococcus or typhoid toxin in the rabbit produces miosis, photophobia, lacrimation, congestion of the iris and conjunctiva with a marked pericorneal ring of dilated capillaries and in some instances with gross conjunctival hemorrhages. Repetition of the i.v. injection after 24 hrs. aggravates these manifestations. Curiously, "these effects may be considerably diminished by a previous local preparation of rabbits to the Shwartzman phenomenon."

Ear. The external ear of the rabbit has been used for the study of an SSP-L localized in the vascular wall itself. It is easily possible to interrupt the circula-

Basile G23,055/41: Review of the literature on the production of an SSP-L in the eye and its appendices.

Ayo G22,709/43: Among a large variety of bacterial toxins, only those capable of eliciting the SSP-L were found to produce a "toxic ocular reaction" following a single i.v. injection. "The reaction consists of intense iridoconjunctival hyperemia and coagulation of the aqueous humor after its aspiration. It appears several minutes after the intravenous injection of toxin, reaches its maximal intensity in a few hours, and is notably reduced or has completely disappeared in about 12 hrs." Protection against this response can be offered by previous i.c. or i.v. administration of SSP-active filtrates or by moccasin snake venom.

Scuderi G22,360/48: Subconjunctival preparation with *B. proteus* endotoxin produces an ocular SSP-L in rabbits following i.v. injection of typhoid endotoxin. This response can be prevented by various pyrogens (vaccines, colloidal sulfur) but not by the antihistaminic Antistin.

Raus G23,067/56: Vascularization of the rabbit cornea is obtained by injecting alloxan through the sclera into the anterior chamber. After this pretreatment, *B. typhosus* endotoxin injected into the cornea induces an SSP-L if followed by the i.v. administration of the same material. The technique lends itself well to in vivo observation of the development of vascular changes characteristic of the SSP.

Jaeger & Honegger D3,635/60: An SSP-L can be produced in the nictitating membrane of the rabbit by topical preparation with 0.05 µg of *S. abortus equi* endotoxin and subsequent provocation with various macromolecular substances (e.g., Liquoid, dextran, PVP). Under these conditions, preparation and provocation are best applied simultaneously and the response occurs within a few minutes.

Berken D21,841/62: In rabbits in which an SSP-G was produced by two i.v. injections of *E. coli* endotoxin, retinal changes developed which resembled those characteristic of diabetic retinopathy. There was deposition of PAS-positive material within the dilated veins, thickening of small vessel walls and often aneurysmal capillary dilatation. "It is suggested that this reaction may be an etiological factor in the pathogenesis of retinal capillary aneurysms in the diabetic."

Coriglione G28,855/64: An ocular SSP-L is produced by local preparation and i.v. provocation with typhoid endotoxin in the rabbit.

tion temporarily in the rabbit's ear by clamping it at its root; after this, the preparatory endotoxin introduced into the marginal vein remains there long enough to be effective. This type of experiment has been discussed before in connection with the vascular manifestations of THPs (p. 164).

Allegedly, the skin of the ear is less sensitive to preparation than that of the abdomen, but this view has been challenged. Curiously, if endotoxin is injected i.c. into one ear of the rabbit, subsequent i.v. provocation tends to produce petechial hemorrhages in both ears.

It has also been possible to produce an SSP-L in the internal ear, by local provocation with endotoxin.

Gratia & Linz E65,500/31; D6,544/32: If *E. coli* endotoxin is injected i.c. into one ear of a rabbit, a subsequent i.v. injection of the same agent produces not only an SSP-L in the prepared ear but also petechial hemorrhages in the contralateral ear.

Shwartzman E43,557/35: Using various bacterial endotoxins, it has been shown that the rabbit's ear is considerably more resistant than the abdominal skin to preparation for an SSP-L. Curiously, only 10 times the usual provocative dose is required if it is given into the vein of the prepared ear, while 30 times

the normal provocative dose is needed if given into the vein of the non-prepared ear.

Kanyó G28,151/36: The rabbit ear is particularly sensitive to the production of an SSP-L by two injections of *E. coli* endotoxin.

Tsuiki & Kamioka G22,252/52: Following topical application of *B. typhosus* endotoxin to the internal ear, a provocative injection of the same material i.v. elicits an SSP-L in the labyrinth. [Species not mentioned, probably rabbit (H.S.).] It is claimed that this "experiment has offered thus some suggestion as to the etiology of the disease called hydrops or hypertonia labyrinthi."

Nose, Tonsil. An SSP-L limited to the nasal mucosa or tonsil has been obtained by topical preparation followed by i.v. provocation.

Gritti G23,054/36: An SSP-L could be produced in the nasal mucosa of the rabbit by the preparation of the septal mucosa with *B. typhosus* endotoxin, followed next day by an i.v. injection of the same material.

Basile G23,055/41: Review of the literature

on the production of an SSP-L in the nasal mucosa.

Barbera G23,051/42: An SSP-L could be elicited in the tonsil of the dog by topical preparation followed by i.v. provocation on the next day with *B. typhosus* endotoxin.

Male Sex Organs. It is also possible to localize an SSP-L in the testis by the usual technique of local preparation followed by i.v. provocation. However, in the guinea pig, instillation of live *coli* bacilli into the conjunctiva with subsequent clamping of the testis allegedly suffices to produce the same result. Testicular hemorrhages can also be produced in guinea pigs by combined treatment with gonadotrophic hormones and diphtheria toxins.

Gratia & Linz E91,473/31: An SSP-L in the testicle of the rabbit is produced by an intra-testicular inoculation of vaccinia virus followed by the i.v. administration of *E. coli* endotoxin.

Gonzalez G24,145/32: An SSP-L can be obtained in the testis of the rabbit and, less regularly, in that of the guinea pig by topical preparation followed by i.v. provocation with various bacterial endotoxins.

Gentile G26,192/36: If autolyzed staphylococci are injected into the rabbit testicle, a

simple inflammation ensues. If, 24 hrs. later, a broth culture of the same organism is injected i.v., the inflammatory process in the testicle is aggravated and accompanied by necrosis. [The author does not compare this apparently nonhemorrhagic response with the SSP-L (H.S.).]

Lörincz G28,155/36: The SSP-L elicited in the skin and testis of rabbits is characterized by parietal thrombi in the blood vessels with extensive hemorrhage, edema and inflammation. Essentially similar changes are seen in the Arthus phenomenon.

Basile G23,055/41: Review of the literature on the production of an SSP-L in the testis.

Miescher B40,892/47: In rabbits prepared by the injection of *E. coli* endotoxin into the testis, subsequent intracardiac administration of the same material produces a typical SSP-L in the testis. In guinea pigs given a few drops of a suspension of pathogenic *coli* bacilli into the conjunctiva, subsequent clamping of the testis suffices to produce the same result.

Miescher & Böhm E53,167/47: Following preparation of the guinea pig testis by topical injection of *E. coli* filtrate, an i.v. injection of

E. coli 24 hrs. later elicits a typical SSP-L in the testis.

Tonutti B48,887/49; B48,892/50: In guinea pigs simultaneously treated with diphtheria toxin and gonadotrophic hormone, hemorrhagic necrosis occurs in the ovaries and testes, presumably as the consequence of a specific sensitization of these organs.

Pařízek & Záhoř E84,304/56: A single subcutaneous injection of cadmium salts causes hemorrhagic necrosis in the rat testis. [These lesions are associated with thrombosis and changes in the testicular vessels indistinguishable from those of the THP (H.S.).]

Female Sex Organs. Localization of a THP in the female sex organs has been achieved by various techniques. Preparation of the rabbit ear by rubbing it with vaccinia lymph followed by *E. coli* endotoxin i.v., changes the course of the virus infection so that the skin pustules become hemorrhagic; in this event hemorrhages also appear in the internal organs, particularly the uterus and oviducts. In spayed guinea pigs pretreated with estradiol, a single i.v. injection of diphtheria toxin produces marked hemorrhagic necrosis of the uterus. In guinea pigs pretreated with gonadotrophic hormones, diphtheria toxin produces hemorrhagic necrosis of the ovaries. The SSP-L can also be localized in the ovary, uterus, or vagina, by topical preparation followed by the i.v. provocation with endotoxins.

Gratia & Linz E65,231/31: Preparation of the rabbit ear by rubbing it with vaccinia lymph, followed by *E. coli* endotoxin i.v., causes the developing vaccinia pustules to become hemorrhagic and necrotic; their subsequent development is stopped. Apparently, the course of a virus infection can be modified by the SSP. Simultaneously, hemorrhages appear in the inguinal ganglia, lungs, uterus and fallopian tubes. Apparently, topical preparation can result in systemic lesions.

Guarna G28,395/35: An SSP-L can be elicited in the ovary, uterus or vagina of the rabbit by topical preparation and subsequent i.v. provocation with typhoid endotoxin.

Sanarelli G28,164/39: An SSP-G can be produced by the i.v. injection of sterilized human saliva (presumably the result of its bacterial flora) but only if three injections are given at 24 hr. intervals. Here, in addition to the usual intestinal, renal and pulmonary lesions,

hemorrhages occur in the psoas muscles and the uterine horns.

Basile G23,055/41: Review of the literature on the production of an SSP-L in the ovary, uterus and vagina.

Tonutti B48,887/49; B48,892/50: In guinea pigs simultaneously treated with diphtheria toxin and gonadotrophic hormone, hemorrhagic necrosis occurs in the ovaries and testes, presumably as the consequence of a specific sensitization of these organs.

Tonutti B75,807/50: A single intracardiac injection of diphtheria toxin produces marked hemorrhagic necrosis in the uterus of castrate guinea pigs pretreated with estradiol. Progesterone prevents this effect. This is another example of hormonal conditioning for morbid reactions.

McKell et al. D29,283/60: Under the influence of endotoxin (kind not stated) the placenta of the rabbit becomes permeable to trypan blue and colloidal iron.

Joints. An SSP-L localized in a joint is obtained by intra-articular preparation followed by i.v. provocation with endotoxins. However, the attempted comparison between the resulting lesions and those characteristic of rheumatic fever, or of hemophilic arthropathy appears to be somewhat far-fetched.

Moritz & Morley E53,265/31-32: An SSP-L can be elicited in the knee joint of the rabbit by topical injection of *E. coli* or *B. typhosus* filtrate followed by the i.v. injection of the same material. The response is less severe, however, than if the preparatory injection is given i.c.

Karsner & Moritz B78,212/34: An SSP-L can be produced in the joints of rabbits by a topical preparatory injection of *E. coli* endotoxin followed by the i.v. administration of the same material.

Morgan & Bennett G22,350/47: When typhoid endotoxin is injected both i.c. and into the knee joint of a rabbit, the subsequent i.v. injection of the same material produces a

typical SSP-L both in the skin and in the joint. By contrast, repeated intra-articular injections of typhoid endotoxin (without i.v. provocation) produce merely an acute non-hemorrhagic arthritis which gradually becomes chronic.

Raška et al. G23,259/56: In rabbits in which an SSP-L is elicited by means of an extract from streptococcal skin lesions and Streptolysin O, intranasal infection with β -hemolytic streptococci, 3-4 weeks later, produced a polyarthritis. "The clinical and histological aspects of these lesions exhibited a close similarity to the findings in acute rheumatic fever and in the postrheumatic myocardium."

Serosae. Early investigators failed to produce an SSP-L in the pleura or peritoneum of the rabbit by topical preparation followed by i.v. provocation. Yet, under suitable conditions, it is possible, thus, to elicit an SSP-L, at least in the peritoneum. Indeed, this technique furnished valuable data concerning the sequential development of vascular changes which can easily be observed *in vivo* on the exteriorized mesentery after provocation.

Appelmanns & Vassiliadis D72,056/31: In rabbits prepared by an *E. coli* or *B. typhosus* endotoxin injection into the gastric mucosa, the peritoneum, and the skin of the ear, subsequent i.v. injection of the same materials produces an SSP-L only in the ear, but not in the stomach or peritoneum. It is concluded that various sites are not equally susceptible to sensitization and that the stomach and peritoneum are particularly resistant.

Moritz & Morley E53,265/31-32: It is impossible to produce an SSP-L in the pleura or peritoneum of the rabbit by topical injection of *E. coli* or *B. typhosus* toxin, followed by the i.v. injection of the same material.

Hugues et al. G27,058/58; Lecomte et al. C81,517/59: *S. typhi murium*, given i.p. and 24 hrs. later i.v. in rabbits, produces a peritoneal SSP-L in which the vascular changes can be observed *in vivo* on the exteriorized mesentery. The initial changes are detectable after about 6 min., and consist of ruptures of the veins with hemorrhages, but are unaccom-

panied by platelet embolisms or leukocyte agglutination. In these respects, they differ from the initial changes of anaphylaxis.

Cheek Pouch. *Gustafson & Cronberg D61, 874/63:* In hamsters, an SSP-L could be produced in the cheek pouch by preparation with *E. coli* endotoxin followed by i.v. injection of the same agent. The mast cells showed no degranulation until the late stages, when other cells were also damaged. Furthermore, depletion of the local mast-cell population in the cheek pouch (by previous injection of distilled water, protamine or toluidine blue) does not inhibit the ability of the tissue to react with an SSP-L.

Muscles. *Sanarelli G28,164/39:* An SSP-G can be produced by the i.v. injection of sterilized human saliva (presumably the result of its bacterial flora) but only if three injections are given at 24-hr. intervals. Here, in addition to the usual intestinal, renal and pulmonary lesions, hemorrhages occur in the psoas muscles and the uterine horns.

Tumors. An enormous amount of work has been done on the induction of THPs in tumors ever since the nineteenth century, when it was observed that spontaneous infections, especially with erysipelas, can cause regression of malignant neoplasms. Beebe and Tracy (1907) showed that repeated inoculations with various bacteria or their toxins, can cause involution of transplantable canine lymphosarcomas. Later Gratia and Linz (1931) found that hemorrhagic necrosis

occurs in transplantable liposarcomas of guinea pigs, if *E. coli* endotoxin is first injected into the tumor, and 24 hrs. later i.v. However, since even a single i.v. injection of the endotoxin is equally efficacious, it was assumed that neoplastic tissue is permanently in a state of "preparation," perhaps because it contains SSP-active microbes.

These observations have repeatedly been confirmed by a large number of investigators under the most diverse conditions, and it may now be taken as a well-established fact that a variety of microbial endotoxins produce hemorrhagic necrosis both in spontaneous and in transplantable neoplasms. Still, permanent regressions are comparatively rare, and in order to produce hemorrhagic tumor necrosis the endotoxins must be administered in such high doses that most animals die. Hence, considerable work has been done on the purification of the active principle, with the hope that more specifically carcinolytic substances will be found which cause hemorrhagic necrosis and involution of neoplasms without inducing a high mortality. Up to now, these efforts have not been successful, since the preparations most active in producing hemorrhagic tumor necrosis are also the most toxic.

Using a transparent-chamber technique, it was possible to follow the vascular reactions which accompany the production of hemorrhagic necrosis in transplantable murine neoplasms. Irreversible ischemic damage to the tumor capillaries was indicated by stasis, hemorrhage and thrombus formation.

Recently, it has been shown that I^{131} -labeled fibrinogen can be used for the detection of malignant tumors in man because of its great tendency to concentrate in neoplastic tissue. The fact that tumors are normally rich in fibrin and that experimental neoplasms concentrate labeled fibrinogen may be related to the special sensitivity of malignant tissue to thrombohemorrhagic agents.

Although the endotoxins of Gram-negative bacteria were most effective in producing hemorrhagic tumor necrosis, various *yeast extracts*, particularly polysaccharide fractions and zymosan, as well as *extracts of nonneoplastic tissues*, also proved to be effective in this respect. However, recent work in which bacterial contamination was carefully excluded, revealed no tumor-hemorrhage producing potency in extracts of nonneoplastic mammalian tissues, and it is possible that the positive results obtained by earlier investigators were due to the presence of microbes that produce SSP-active substances.

Finally, hemorrhagic tumor necrosis has been produced by a variety of other means such as treatment with *immune bodies*, *histamine*, *colchicine*, *snake venoms*, and *peptone*. Many additional agents, and particularly combinations of agents, share this effect (cf. PTHP).

Microbial Agents Alone. Coley G21,530/1891: Review of the early history of the treatment of sarcomas by infection with erysipelas. Report of several additional successfully treated patients. Inoculations were usually made into the tumor itself. There is no clearcut evidence of hemorrhagic necrosis although many neoplasms involved completely.

Spronck G22,714/1892: Review of the earliest

literature on the effect of infections upon malignant neoplasms. Personal observations suggest that filtrates of streptococcus pyogenes (isolated from cases of erysipelas) can, under certain conditions, cause regression of canine and human malignant tumors.

Beebe & Tracy G23,350/07: Repeated inoculations with various bacteria or their toxins, particularly *B. prodigiosus*, results in involu-

tion of transplantable canine lymphosarcomas.

Shwartzman & Michailovsky E89,870/31-32: Transplants of sarcoma 180 in the mouse undergo hemorrhagic necrosis upon i.v. or i.p. injection of meningococcus toxin.

Gratia & Linz D20,191/31; D6,544/32: In guinea pigs bearing liposarcoma transplants, hemorrhagic necrosis of the tumors may be obtained if *E. coli* endotoxin is first injected into the tumor and 24 hrs. later i.v. However, similar hemorrhagic necrosis is produced even by a single i.v. injection of endotoxin; hence, it appears that the tumor tissue is naturally in a state of "preparation," perhaps because it contains microbes.

Duran-Reynals D93,673/33: Various rapidly growing transplantable malignant tumors of rats and mice undergo hemorrhagic necrosis under the influence of *E. coli* endotoxin i.p. or i.v. Slow-growing malignant tumors, embryomas and granulomas, are not affected in this manner.

Apitz D14,238/34: *E. coli* endotoxin, agar, certain antigen-antibody mixtures, and rabbit anti-mouse serum, induced hemorrhagic tumor necrosis in Ehrlich mouse carcinomas, though only when given in lethal doses. Curiously, none of the active substances produced a generalized hemorrhagic tendency with bleeding outside the tumors.

Duran-Reynals G22,071/34-35: Spontaneous murine mammary carcinomas may undergo involution following single injections of typhoid endotoxin.

Shwartzman G22,682/34-35: In mice infected with *B. enteritidis*, necrosis and regression of sarcoma-180 transplants is frequently observed. Similar results are obtained with filtrates of *B. enteritidis*.

Andervont G20,972/36: The susceptibility of sarcoma-37 and sarcoma-180 to *E. coli* filtrates varies greatly depending upon the strain of mice into which they are transplanted. The filtrates failed to produce hemorrhage in practically all spontaneous mammary carcinomas of mice, as well as in the first transplants of such tumors. However, *E. coli* endotoxin produced hemorrhage regularly in primary dibenzanthracene tumors, sometimes causing their complete regression.

Fogg G22,713/36: Heat-killed cultures or alcohol-insoluble fractions from *B. proteus*, *B. typhosus* or *E. coli*, inhibit the growth of various spontaneous, carcinogen-induced or transplanted malignant neoplasms in mice. In cultures of mouse sarcoma-180, an accidental infection with an unidentified Gram-negative bacillus caused topical dissolution of the neoplastic cells.

Jacobi D28,674/36: By injecting *B. typhosus* endotoxin first into the tumor and then i.v., hemorrhagic necrosis was obtained in: mouse sarcoma-180, Flexner-Jobling rat carcinoma, Walker rat carcinosarcoma-256, and Rous chicken-sarcoma transplants, as well as in the recurrence of an inoperable breast carcinoma in a woman.

Shear & Andervont D38,189/36; Shear E71,736/36: Partial purification of the factor in *E. coli* endotoxin which causes hemorrhagic necrosis of murine sarcoma-37 transplants.

Shwartzman D72,185/36: Spontaneous or experimental infection with *B. enteritidis* inhibits the growth of murine sarcoma-180 transplants. "There exists a definite correlation between the ability of a filtrate of a given microorganism to elicit the phenomenon of local cutaneous reactivity in rabbits and the inhibitory effect of the infecting microorganism on the development of sarcoma-180 in mice."

Shwartzman G19,133/36: Murine sarcoma-180 transplants show hemorrhagic necrosis following single i.v. or i.p. injections of various bacterial endotoxins. "There is observed a decidedly higher death rate following injections of bacterial filtrates in tumor-bearing mice as compared with normal mice." . . . "Mixtures of *B. typhosus* 'agar washings' filtrate with homologous antiserum possess a comparatively low lethal potency and yet elicit prompt and intense hemorrhagic necrosis and subsequent complete regression of sarcoma-180 in a high percentage of mice well above the normal expectancy."

Boyland & Boyland E63,718/37: In murine Crocker-180 tumors and in Jensen rat-sarcoma transplants, hemorrhagic necrosis is induced by the i.p. administration of either colchicine or *B. typhosus* endotoxin.

Sanarelli G23,516/37: The author quotes earlier observations of his assistant, A. Alessandrini, who obtained hemorrhagic reactions by the i.v. injection of *Bacillus proteus* into rabbits bearing myxomas induced by infection with "Sanarellia cuniculi."

Shwartzman B19,913/37: A review of the literature on the production of hemorrhagic tumor necrosis by single injections of bacterial endotoxins.

Andervont & Shimkin G21,647/39: In murine sarcoma-37 transplants, *B. prodigiosus* filtrate i.p. produced hemorrhagic necrosis which could be prevented by ascorbic acid s.c. The same inhibition was obtained when the endotoxin was administered s.c. and the ascorbic acid i.p. The production of hemorrhage in other tumors by *B. prodigiosus* toxin could likewise be prevented by ascorbic acid.

Gardner et al. G22,336/39: In rats bearing Walker tumor transplants hemorrhagic necrosis of both the neoplasms and the host tissues was observed following i.v. injection of carbohydrate complexes prepared from the following organisms: *N. intracellularis*, *Klebsiella pneumoniae*, *Alcaligenes bookeri*, *S. aertrycke*, *S. schottmulleri*, *S. enteritidis*, *E. coli*, *E. communior*, *Aerobacter aerogenes*, *E. typhosa*, *Sh. dysenteriae* and *Sh. parady-enteriae*.

Tulasne G28,162/39: Following repeated i.v. injections of meningococcus or coli endotoxin, various transplantable epitheliomas of the rat and mouse exhibit hemorrhagic necrosis.

Walker & Handman G22,717/39: Various fractions of *S. typhi murium* endotoxin produced an SSP-L when given in two injections as usual to rabbits, but only the nucleoprotein and polysaccharide fractions induced hemorrhagic necroses in murine sarcoma-180 transplants.

Shear & Turner 77,325/40: Brief description of the techniques used for the extraction of tumor hemorrhage-producing material from *E. coli* and *B. prodigiosus*. [The brief abstract gives few experimental details (H.S.).]

Nagasima G24,098/41: *E. coli* endotoxin i.v., i.p. or s.c. produces hemorrhagic necrosis of various transplantable sarcomas and carcinomas in the rat.

Ogata G22,362/41: A single injection of endotoxin (kind not stated), into the tissue of transplantable Bashford carcinomas, Sasaki hepatomas or Fujinawa sarcomas of the rat causes hemorrhagic necrosis in these neoplasms.

Zahl et al. E65,362/42: On the basis of a review of the literature and of personal observations on about 100 strains of bacteria, it is concluded that the organisms producing hemorrhagic necrosis of sarcoma-180 transplants in mice "are characterized by the following common features: (1) they are gram-negative, (2) they contain complex endotoxin antigens, (3) they resemble one another in a type of pathogenesis marked by vascular damage, disturbances in carbohydrate metabolism, and enteric irritation."

Hartwell et al. E61,370/43: Chemical analysis of the material in *S. marcescens* endotoxin, which produces hemorrhagic necrosis of sarcoma-37 transplants in mice.

Hutner & Zahl G21,642/43: Experiments with a very large number of bacterial filtrates revealed that, with few exceptions, hemorrhagic necrosis of sarcoma-180 transplants in mice can be produced only with the endotoxins of Gram-negative forms. "It is concluded that toxins inducing tumor-hemorrhage, and

probably bound up in the complex O antigens, are characteristic of gram-negative bacteria."

Kahler et al. D95,992/43: Ultracentrifugal and electrophoretic analysis of the fraction from *S. marcescens* endotoxin that produces hemorrhagic necrosis in mouse sarcoma-37 transplants.

Shear et al. D38,129/43: Technique for the assay of *S. marcescens* endotoxin extracts which cause hemorrhagic necrosis in murine sarcoma-37 transplants.

Shear & Turner G22,089/43: Extraction from *S. marcescens* of material highly active in producing hemorrhagic necrosis of sarcoma-37 transplants in mice.

Shimkin & Zon E41,798/43: Hemorrhage can be produced in sarcoma-37 transplants in mice by single i.v. injections of *S. marcescens* endotoxin or moccasin venom. Both of these agents elicit marked thrombocytopenia, but this cannot be the cause of the hemorrhage because, if the platelet count drops to the same level as a consequence of anti-mouse-platelet serum, hemorrhagic necrosis of the neoplasms does not occur. It is concluded that "the action of the bacterial filtrate and of the snake venom on the transplanted sarcoma-37 is primarily that of an endothelial toxin."

Zahl & Hutner G22,088/43: The acetone, phenol, and various formamide fractions of *S. typhimurium* endotoxin were active in causing hemorrhagic necrosis in murine sarcoma-180 transplants.

Shear D38,080/44: In sarcomas induced by 3,4-benzpyrene, hemorrhagic necrosis was obtained with single or repeated doses of Shear's polysaccharide (*S. marcescens* endotoxin). However, "some portion of the neoplasm usually escaped destruction and continued to grow progressively until the death of the host. In the few instances in which the entire tumor appeared to have been severely affected, the animals developed symptoms of severe shock and died." Detailed review of the earlier literature on the induction of hemorrhagic necrosis in tumors of animals and man by bacterial products.

Zahl et al. G22,090/45: Hemorrhagic necrosis in murine sarcoma-180 transplants was induced by i.p. injection of killed suspensions of numerous strains and species of microbes. The results are "consistent with the generalization proposed earlier that gram-negative bacteria, as a class, possess a factor usually bound up in the complex O antigen, whose distinguishing physiological characteristic is vascular toxicity as demonstrated by the induction of hemorrhage in implanted mouse tumors." With very few exceptions, Gram-positive bacteria are in-

active. It is pointed out that these exceptional species "are of uncertain taxonomic position and that they are probably unique among gram-positive bacteria having a single terminal flagellum." Protozoan flagellates, 32 types of streptococci, 3 strains of *Pasteurella pestis* and *H. influenzae* were inactive.

Algire et al. G23,094/47: Description of the vascular changes obtained in various transplantable murine tumors (included in transparent chambers) under the influence of *S. marcescens* endotoxin i.p.

Perrault & Shear D7,081/49: A polysaccharide prepared from *S. marcescens* cells was even more effective than one prepared from filtrates in causing hemorrhagic necrosis of sarcoma-37 transplants in the mouse.

Stetson B73,457/51: The i.v. injection of meningococcal endotoxin produces hemorrhagic necrosis in sarcoma-180 transplants in mice, but not in the Brown-Pearce rabbit carcinoma.

Algire et al. G22,055/52: Using the transparent-chamber technique, it was possible to follow the vascular reactions which accompany the production of hemorrhagic necrosis in strain-L sarcoma and sarcoma-37 transplants following single or repeated injections of *S. marcescens* endotoxins i.p. in the mouse. Irreversible ischemic damage to tumor capillaries was indicated by stasis, hemorrhage or thrombus formation. "It is concluded that the tumor-necrotizing effect of this agent is brought about by the ischemia and circulatory stasis induced by hypotension." . . . "There are many indications that the effects on the host of this polysaccharide, as well as of other bacterial endotoxins, are related to the general adaptation syndrome as described by Selye."

Ikawa et al. G26,195/52: A lipopolysaccharide was isolated from *E. coli* cultures which proved highly active in producing hemorrhagic necrosis and regression of murine sarcoma-180 transplants.

Nauts et al. E46,085/53: Detailed description of the studies of William B. Coley who, in 1891, observed that a patient with inoperable sarcoma of the neck recovered after two attacks of erysipelas. Stimulated by this observation, Coley treated inoperable tumor patients with a mixture of *S. marcescens* and erysipelas toxin ("Coley Mixed Toxins" or "Coley's Fluid"). A number of additional cases of patients allegedly cured of malignancies with this mixture or similar preparations have been described.

Rathgeb & Sylvén B98,085/54, B98,086/54, Malmgren B98,087/54: Physicochemical charac-

teristics and purification of the tumor-necrotizing agents from *S. marcescens*.

Havas & Donnelly E26,872/61: The regression of various transplantable, induced and spontaneous tumors which can be obtained in mice by repeated injections of bacterial endotoxins differs from the SSP in that it is unaccompanied by thromboses in the neoplasms and by renal cortical necrosis.

Michael D68,994/63: Pertussis-vaccine treatment increased the susceptibility of mice to the lethal effect of *S. enteritidis* endotoxin while they became more resistant to its necrotizing effect upon sarcoma-37 transplants.

Galton G9,002/64: Hemorrhagic necrosis has been produced in choriocarcinomas transplanted into the cheek pouch of the hamster by a single i.p. injection of colchicine or *E. coli* endotoxin.

Higginbotham & Bass F10,987/64: Both *E. coli* and *S. aureus* endotoxins cause hemorrhagic necrosis in murine S-180 sarcomas.

Yeast and Yeast Extracts. Gardner et al. G22,336/39: Necrosis of Walker tumor transplants was noted in rats treated with carbohydrate complexes prepared from yeast (*Saccharomyces cerevisiae*).

Bradner et al. D1,111/57: In Swiss mice, bearing S-180 sarcoma transplants, a single injection of zymosan i.p. produced necrosis and extrusion in 60% of the animals as compared with 6% in the controls. Zymosan, tested against S-180 tumors in tissue culture, had no direct cytotoxic effect. [No mention is made of any thrombohemorrhagic necrosis in the tumors nor of any possibility that the antineoplastic effect might be related to the SSP-G (H.S.).]

Landy & Shear G21,289/57: Polysaccharides isolated from various animal and plant sources can produce hemorrhagic necrosis of Sarcoma-37 transplants in mice when given i.p. In this respect, they imitate the tumor-necrotizing effect of bacterial endotoxins.

Arndt et al. C82,082/59: Zymosan produces necrosis of sarcoma-180 transplants in Webster-Swiss-strain mice, and this may be due to an SSP. However, this strain did not respond with an SSP-L, even to two injections of *E. coli* endotoxin, which were effective in this respect in other strains of mice. Furthermore, no SSP-L could be elicited with two doses of zymosan in Shwartzman-responsive mice in which two doses of endotoxin proved to be effective under identical conditions. "It is concluded, therefore, that zymosan is ineffective as a reagent for the Shwartzman reaction when used at concentrations effective in causing tumor-necrosis."

Tissue Extracts. *Lewisohn 83,263/38:* Renal and splenic extracts, unlike those of liver, heart, pancreas and testis, can cause hemorrhagic necrosis of murine sarcoma-180 transplants. Histamine s.c. also produces hemorrhagic necrosis in such transplants.

Lewisohn et al. 83,264/40: Murine sarcoma-180 transplants undergo hemorrhagic necrosis following a single i.v. injection of beef spleen extract. Permanent healing of sarcoma-180 transplants by repeated s.c. injections of spleen extract is associated with an enlargement of the spleen. An extract of these spleens causes regression of sarcoma-180 transplants, as well as of spontaneous murine adenocarcinomas of the breast. In this case, the tumor undergoes necrosis but rarely shows hemorrhages. Earlier work on the effect of spleen extract and splenectomy upon tumors is briefly reviewed.

Shear & Perrault C10,276/53: Single injections of purified fractions of polysaccharides prepared from murine spontaneous mammary carcinomas, S-37 sarcomas, or human placenta caused hemorrhagic necrosis of murine S-37 sarcoma transplants.

Horava B85,220/54: A considerable amount of fluid accumulates in the granuloma pouches of rats in which Walker-tumor transplants are introduced into the lumen of the subcutaneous air sacs. This fluid given i.v. produces hemorrhagic necrosis in Walker-tumor transplants.

Perrault & Shear C4,405/55: Hemorrhagic necrosis of intramuscular Sarcoma-37 transplants in CAF₁ mice was obtained with polysaccharides isolated from liver, lung, kidney and stomach of normal strain-C mice. Tumornecrotizing polysaccharides were also found in a variety of tumors (e.g., S-37, C3H Ba, Lymphoma-1, Leukemia-1210, and pooled breast tumors which arose spontaneously in C3H mice). Similar extracts of Harding-Passey mouse melanoma and a spontaneous hemangioma of a dog were inactive. Fresh oysters yielded a negative preparation. The skin of chick embryos contained only inactive material, whereas the abdominal skin of the rabbit gave one of high potency. Some of these preparations were also active in eliciting the SSP-L in the rabbit.

Merler et al. G22,058/60: In contradistinction to earlier reports, no polysaccharides with endotoxic properties could be extracted from various mammalian tissues, including tumors, under conditions in which bacterial contamination was excluded. Such extracts caused no hemorrhagic necrosis in sarcoma-37 transplants in mice.

Other Nonmicrobial Agents. *Apitz D14,238/34:* I.v. injection of histamine, $\text{AuCl}_4\text{Na} + 2\text{H}_2\text{O}$, Witte's peptone or rattlesnake venom, failed to produce hemorrhagic necrosis in

Ehrlich mouse carcinomas. On the other hand, *E. coli* endotoxin, agar, certain antigen-antibody mixtures, and rabbit anti-mouse serum, induced hemorrhagic tumor necrosis, but only when given in lethal doses. Curiously, none of the active substances produced a generalized hemorrhagic tendency with bleeding outside the tumors.

Shwartzman E58,441/35: "Mixtures of *B. typhosus* culture filtrates with homologous antisera possess a high phenomenon-producing and low lethal potency." [No experimental details given (H.S.).] In mice bearing sarcoma-180, a single i.v. injection of such mixtures usually produced prompt hemorrhagic necrosis, and quite often (in 21 of 27 mice) there was "complete regression of tumors with uneventful healing."

Boyland & Boyland E63,718/37: In murine Crocker-180 tumors and in Jensen rat-sarcoma transplants, hemorrhagic necrosis is induced by the i.p. administration of either colchicine or *B. typhosus* endotoxin.

Andervont E69,326/40: Hemorrhagic necrosis can be produced in sarcoma-37 or carcinoma-F transplants in mice given colchicine i.p. The drug acts very much like endotoxins, but combined treatment with colchicine and *E. coli* endotoxin is no more effective than treatment with only one of these agents.

Brues et al. E51,081/40: Murine sarcoma-180 transplants and spontaneous mammary carcinomas undergo involution following treatment with colchicine i.p., but this is not always associated with hemorrhage.

Barrett G21,636/42: In mice bearing sarcoma-37 transplants and sensitized to normal horse serum, reinjection of the same antigen produced hemorrhagic necrosis of the neoplasm. Witte's peptone i.p. and large doses of histamine i.p. exert a similar effect.

Shimkin & Zon E41,798/43: Hemorrhage can be produced in sarcoma-37 transplants in mice by single i.v. injections of *S. marcescens* endotoxin or moccasin venom. Both of these agents elicit marked thrombocytopenia, but this cannot be the cause of the hemorrhage because, if the platelet count drops to the same level as a consequence of anti-mouse-platelet serum, hemorrhagic necrosis of the neoplasms does not occur. It is concluded that "the action of the bacterial filtrate and of the snake venom on the transplanted sarcoma-37 is primarily that of an endothelial toxin."

Algire & Legallais G22,340/51: Hypotension induced by histamine, but also by other stressors (tourniquet shock, hypertonic glucose i.p., anaphylaxis), produces vascular disturbances and hemorrhagic necrosis in a variety of mu-

rine tumor transplants observed by the transparent-chamber technique.

Horava B85,220/54: Fatal stress (forced immobilization) can produce hemorrhagic necrosis of Walker-tumor transplants in the rat.

Galton G9,002/64: Hemorrhagic necrosis has been produced in choriocarcinomas transplanted into the cheek pouch of the hamster by a single i.p. injection of colchicine or *E. coli* endotoxin.

Monasterio et al. G22,078/64: Radioiodinated fibrinogen can be used for the detection of malignant tumors in man because of its great tendency to concentrate in neoplasms. Review

of earlier literature showing that both experimental and human malignant tumors are rich in fibrin and that experimental neoplasms concentrate radioactivity after administration of fibrinogen labeled with I^{131} . [The possible implication of these findings upon the hemorrhagic necrosis of tumors induced by SSP-active substances has not been considered (H.S.).]

Selye G23,214/65: In rats pretreated with a single s.c. injection of carrageenin, exposure to cold induces a THP in the nose, paws and tail, accompanied by renal glomerular thromboses. The same treatment elicits hemorrhagic necroses in Murphy rat lymphosarcoma transplants.

CHAPTER V

CHEMICAL CHANGES

IN this chapter, we shall deal with the comparatively few observations on THPs made with routine chemical techniques. For histochemical changes, the reader is referred to Chapter IV, while derangements in the blood coagulation mechanism are discussed in Chapter VI.

Body Temperature and BMR. The pyrogenic effect of endotoxins is too well known to deserve special attention. It is noteworthy, however, that during an SSP-L the temperature curve does not parallel either the BMR or the intensity of the cutaneous lesions.

Eustatziou et al. D75,628/35: During an SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit, there is a rise in body temperature and BMR. However, the temperature curve does not parallel the BMR and there appears to be no clear-cut connec-

tion between the intensity of the SSP-L and the rise of the temperature and BMR. In rabbits which fail to react with an SSP-L, the rises in BMR and temperature are much less pronounced.

Carbohydrate Metabolism. The lactic acid content of prepared skin is considerably increased during an SSP-L elicited by two injections of endotoxin, presumably because of an increased aerobic glycolysis. The hexose-, hexosamine- and uronic-acid content of the challenged skin is likewise elevated. Apparently both the acid and the neutral polysaccharides rise in this region. As judged by S^{35} incorporation studies, the sulfomucopolysaccharide incorporation into the challenged skin is also much increased.

The blood-sugar concentration diminishes immediately after the provocative injections, but then rises concurrently with the phosphohexoseisomerase activity. The serum content of mucoid, glucosamine, protein-bound hexose, glycoprotein and especially sialic-acid also rises. These changes were thought to reflect the reconstruction of damaged connective-tissue ground substance.

Thomas & Stetson D70,785/49: Rabbit skin prepared for the SSP-L by meningococcal toxin i.c. exhibits a high degree of aerobic glycolysis in vitro. This anomaly is reflected in vivo by an increase in the lactic-acid content of the prepared skin.

Thomas & Good E56,605/52: In rabbits pretreated with *S. marcescens* toxin i.c. and 24 hrs. later given cortisone i.m., the lactic acid content and the degree of aerobic lactic acid production in vitro rose considerably in the prepared skin site. As in the classical SSP-L (produced exclusively with bacterial toxin) these changes are due to the preparatory intradermal injection and occur irrespective of the eliciting systemic cortisone administration.

Kesztyüs et al. G22,097/58: Following the preparatory injection for an SSP-L (produced by two doses of *E. coli* endotoxin in the rabbit) there develops a hypoglycemia, while after the provocative injection hyperglycemia follows and, concurrently, there is a rise in phosphohexoseisomerase activity, possibly owing to muscle damage.

Schulhof & Richter G23,266/59: In rabbits in which an SSP-L was elicited by two injections of typhoid endotoxin, the protein content of the reacting cutaneous area was only slightly increased, while the hexose-, hexosamine- and uronic-acid content was markedly elevated. Apparently, both the acid and the neutral polysaccharides rise in the affected territory.

Berenson & Dalferes G27,362/60: An SSP-L was produced in the rabbit by two injections of *E. coli* endotoxin and quantitative determinations of acid mucopolysaccharides (MPS), hyaluronic acid and chondroitin sulfate were made in the affected cutaneous regions. MPS-changes were observed in vivo by incorporation of glucose C¹⁴ and in vitro by dilution of C¹⁴-labeled MPS. "The results indicate an increased concentration of both MPS fractions in the skin lesions and suggest an increased biosynthesis of the compounds at the site of the lesions. Deposition of chondroitin sulfate from blood may have contributed in part to the concentration of this substance in the lesions. The MPS contribute to the inflammatory state of the Shwartzman phenomenon but the specific roles of these compounds need to be defined by further study."

Kováts et al. G22,096/60: An SSP (-G or -L?) elicited by two injections of *E. coli* endotoxin in the rabbit, is associated with a marked increase in serum glycoproteins, especially sialic acid. The serum mucoid, glucosamine and protein-bound hexose content also rises. These changes are viewed as compensatory reactions intended to assist in the reconstruction of damaged connective-tissue ground substance.

Lipid Metabolism. In eclampsia with retroplacental hemorrhage, the formation of microthrombi is associated with hyperlipemia. Hypercholesterolemia was seen in rabbits in which a THP-G developed following combined treatment with RES-blocking agents and endotoxins i.v. The SSP elicited by two injections of endotoxin is accompanied by an increase in β -lipoproteins, free and esterified cholesterol, as well as total blood lipids. The cholesterol/phospholipid ratio rises, but can be restored to normal by the administration of essential phospholipids. It has been assumed that the hyperlipemia not only accelerates intravascular blood coagulation, but also blocks the RES, thereby preventing effective removal of fibrin derivatives.

In the THP-G induced in pregnant rats by vitamin-E-deficient diets containing supplements of oxidized lipids, the serum contains an excess of long-chain fatty acids, with relative diminution of phospholipids, triglycerides and unesterified fatty acids. All these changes suggest disturbances in fat mobilization and lipogenesis.

Scriver & Oertel 63,237/30: Review of the literature and personal observations reveal that renal cortical necrosis occurs most commonly in eclampsia with retroplacental hemorrhage but that it is also seen after various infections outside of pregnancy. "The very high intravascular fat contents of some of these cases suggest an associated hyperlipaemia." Fibrin thrombi are found in the glomerular capillaries as well as in the afferent and efferent glomerular vessels.

Junge-Hülsing & Wirth G20,938/62: As judged by S³⁵-distribution studies, the sulfomucopolysaccharide incorporation into the challenged skin area is greatly increased during the SSP-L produced in the rabbit by two injections of bacterial endotoxins. Various other topical stressors produce the same effect which is referred to as the "local nonspecific mesenchymal reaction." A similar increase in sulfomucopolysaccharide incorporation occurs throughout the body in the event of exposure to systemic stress and this is designated as the "universal nonspecific mesenchymal reaction." [It is not quite clear whether these "mesenchymal reactions" differ from the L.A.S. and the G.A.S. respectively; they are evidently non-specific (H.S.).]

Hauss & Junge-Hülsing G27,944/63: The incorporation of S³⁵-sulfate into the chondroitin sulfate of connective tissue is greatly increased at the sites where an SSP-L is produced by two injections of *S. abortus equi* endotoxin in rabbits. A less pronounced rise in chondroitin sulfate metabolism is also noted in other cutaneous regions.

Emmrich et al. F8,082/64: During an SSP-G, elicited by two i.v. injections of *S. abortus equi* endotoxin, the hexosamine content of various tissues increases.

Thomas D1,020/57: Hypercholesterolemia similar to that observed after colloidal RES-blocking agents also occurs 24 hrs. after i.v. injection of various bacterial endotoxins in the rabbit.

Kováts et al. E71,740/58: "The Shwartzman phenomenon was elicited in rabbits in the usual way by a culture filtrate of bacterium *coli*" (no details given). This caused an increase in serum β -lipoproteins 6-24 hrs. after the provocative injection. Neither the skin

preparation nor the provocative injection alone exerted such an effect. Since a similar change in lipoprotein pattern is elicited by heparin compounds known to inhibit the SSP, it is assumed that increased endogenous heparin production might play a role in the defence of the organism against the SSP.

Kováts et al. E65,236/61: In rabbits in which an SSP was elicited by two injections of *E. coli* endotoxin (whether this was an SSP-L or an SSP-G is not mentioned), important changes in fat metabolism developed. 3-72 hrs. after the provocation there was a marked increase in β -lipoproteins, free and esterified cholesterol and total blood lipids. The serum phosphates sometimes rose up to three times the normal level within 6 hrs. Conversely, the fat content of the omentum diminished, suggesting lipid mobilization.

Kaunitz et al. E29,696/63: In pregnant rats in which an "SSP-G" was produced by a vitamin-E-deficient diet containing ethyl esters of oxidized cod-liver oil, the kidney and perirenal adipose tissue contained more water than in similarly treated rats in which the SSP-G was inhibited by supplements of vitamin E. In the sera of the experimental animals, there was an increase in long-chain fatty acids with relative diminution of phospholipids, triglycerides and unesterified fatty acids, suggesting an interference with the mobilization of depot fat. The palmitate: stearate and linoleate: arachidonate ratios of the tissue lipids were also lower in the rats with the SSP-G than in those in which the reaction was prevented by vitamin E. Apparently, the "SSP-G" is associated with a disturbance of fat mobilization and lipogenesis.

Protein Metabolism. As might be expected, the severe renal lesions that develop during the SSP-G are associated with a rise in blood NPN. At the same time, there is an increase in the hydroxyproline (collagen) content of various organs. The THP-G elicited by various procedures induces a reversal of the albumin-globulin ratio, due to an increase in globulin which may be related to fibrinoid formation.

Zdrodowski G23,347/31: The serum of rabbits infected with cholera vibrios readily flocculates upon dilution with physiologic saline or distilled water in vitro. This instability is ascribed to the precipitation of globulins and considered to be the fundamental change in the preparation for the SSP.

Bordet E52,527/35: In rabbits in which an SSP-L is produced by two injections of *E. coli* endotoxin, the resorcin test (flocculation of the serum upon addition of resorcin) is often positive.

Hirsch et al. G27,724/64: In rabbits in which an SSP-G is elicited by two i.v. injections of *S. marcescens* or *E. coli* endotoxin, the free fatty acid cholesterol and phospholipid content of the serum increases and fatty livers develop.

Huth et al. G33,036/64: Even the first i.v. injection of endotoxin (kind not stated) produces a pronounced increase in the blood level of total fats, blood lipoproteins, cholesterol and, to a lesser extent, phospholipids. The simultaneous decrease in α -lipoproteins results in a considerable augmentation of the $\beta:\alpha$ -lipoprotein quotient which exhibits a further pronounced increase following the provocative i.v. injection. Administration of essential phospholipids (EPL) increases the survival rate and prevents the accentuated response of the blood-clotting factors to the second i.v. injection of endotoxin. An important causal role in the development of the coagulation defect of the SSP-G is ascribed to changes in blood lipids.

Müller-Berghaus et al. D13,794/64: An SSP-G elicited by two i.v. injections of *E. coli* lipopolysaccharide in the rabbit results in a rise in blood lipids, particularly cholesterol, β -lipoproteins and the cholesterol/phospholipid ratio. Administration of "essential" phospholipids at the proper time restores the cholesterol/phospholipid ratio to normal and renders the second dose of endotoxin ineffective in eliciting the SSP-G. The authors believe that the increased blood lipids not only accelerate intravascular coagulation but also block the RES and thus prevent the effective removal of fibrin and fibrin polymers.

Thomas & Good B79,249/52: The SSP-G induced by two i.v. injections of meningococcal toxin is associated with fully developed renal lesions within 24 hrs. and these are accompanied by a rise in blood NPN.

Fehr & Brunson G21,900/57: In rabbits in which an "SSP-G" was produced by combined treatment with bovine γ -globulin and *E. coli* endotoxin or Liquoid, paper-electrophoretic studies of the serum "showed a reversal of the albumin-globulin ratio due to an increased amount of globulin and the presence of a

para-beta globulin which migrated between the beta and gamma globulin fractions. Although no correlation could be obtained between changes in serum proteins and incidence of fibrinoid lesions, it is possible that the alterations in the serum proteins may have influenced the sites and amounts of fibrinoid formation or deposition."

Schulhof & Richter G23,266/59: In rabbits in which an SSP-L was elicited by two injections

of typhoid endotoxin, the protein content of the reacting cutaneous area was only slightly increased, while the hexose-, hexosamine- and uronic-acid content was markedly elevated. Apparently, both the acid and the neutral polysaccharides rise in the affected territory.

Emmrich et al. F8,082/64: During the SSP-G elicited by two i.v. injections of *S. abortus equi* endotoxin, the hydroxyproline (collagen) content of various organs increases.

Various Other Metabolites. During the classic SSP-L, the *histamine* content of the skin rises, not only in the prepared site, but also at a distance from it, while the blood *potassium* and *calcium* levels drop.

In rabbits given *E. coli* endotoxin i.v. after pretreatment with Thorotrast or ACTH, the development of a Waterhouse-Friderichsen syndrome with adrenal hemorrhages is associated with an increased blood-*cortisol* level.

Silva & Bier G22,094/38: In rabbits in which an SSP-L is produced by two injections of typhoid endotoxin, the *histamine* content of the skin rises considerably not only at the prepared site, but also at a distance from the local reaction.

Kesztyüs et al. G22,097/58: In rabbits in which an SSP-L was produced by two injections of *E. coli* endotoxin, the blood *potassium* and *calcium* concentrations drop considerably.

Davis et al. D25,583/61: *E. coli* endotoxin i.v. causes thrombocytopenia and an increase in plasma serotonin in the rabbit. Serotonin release may play a role in endotoxin shock.

Enoki D60,740/62: The surface tension and the interphase viscosity between the serum and

the intima is increased during the SSP in the rabbit. [Description somewhat obscure (H.S.).]

Lasch F37,812/64: In rabbits in which an SSP-G is produced by two i.v. injections of various endotoxins, the *ATP*, *ADP*, *GTP* and *UTP* content of the thrombocytes is subnormal and consequently clot retraction is diminished.

Levin & Cluff G25,181/65: In rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. Since ACTH, Thorotrast and *E. coli* endotoxin all increase the blood-*cortisol* level of the rabbit, it is assumed that the localization of the hemorrhages is connected with increased adrenocortical activity.

SSP-active Substances. The blood and urine of patients with typhoid fever, and of endotoxin-treated rabbits, contain considerable amounts of SSP-active substances. In rabbits in which an SSP-L is produced, the distribution of p^{32} -marked *E. coli* endotoxin was not significantly changed as compared with normal rabbits. The greatest endotoxin concentrations were found in the liver, lung, kidney and heart, but the prepared skin region exhibited only a moderate and transitory rise in endotoxin content.

Stolyhwo G21,662/35-36; E69,174/36: The urine of patients with typhoid, or of rabbits in which an SSP-L is elicited by two injections of typhoid filtrate, contains substances which can prepare the skin of rabbits for the elicitation of an SSP by a subsequent i.v. injection of typhoid endotoxin. This observation, and the fact that hemorrhagic and necrotic lesions do occur in the intestinal mucosa and skin of typhoid patients suggest that the SSP may participate in the pathogenesis of typhoid fever.

Boquet D18,398/38: Following i.v. administration of *E. coli* endotoxin in rabbits, the serum, withdrawn after 2-4 hrs., still retains much of its preparative effects, as tested by i.c. injection into other rabbits. Yet, it no longer possesses the ability to provoke an SSP-L.

Livchitz 77,816/39: The blood of patients suffering from a variety of infectious diseases (typhus, scarlet fever, etc.) contains substances which can elicit an SSP-L in rabbits when

given i.v. following i.c. preparation with *E. coli* filtrate.

McKinnon et al. G26,513/57: Anaphylactic shock, induced in rabbits by large amounts of antigen and antibody, is associated with the appearance of intravascular amorphous "thrombi" especially in the pulmonary and the hepatic circulation. Apparently, "the intravascular 'thrombi' are antigen-antibody precipitates, since the 'thrombi' were fluorescent only when the challenging fluorescein-labeled antigen was the antigen to which the animal had been sensitized."

Smith et al. E90,550/57: Cr⁵¹-labeled *E. coli* endotoxin distributes itself differently in the organs of prepared and unprepared rabbits: in the former, hepatic uptake is greatly reduced while pulmonary uptake is increased. Renal localization was observed only in rabbits developing bilateral renal cortical necrosis.

Ravin et al. G27,057/58: The toxin that appears in the blood of dogs and rabbits during irreversible hemorrhagic shock resembles bacterial endotoxin in many of its pharmacologic and chemical properties. Concentrates of this toxin can act as the provocative factor of the SSP-G in rabbits prepared by *E. coli* endotoxin or Thorotrust i.v. It is concluded "that the circulating toxin in shock is similar to, or identical with, bacterial endotoxin."

Szabó et al. G21,661/61: Using p³²-marked *E. coli* endotoxin, it could be shown that previous preparation of skin sites does not significantly alter the distribution of i.v. endotoxin in the rabbit. The greatest concentrations of marked endotoxin are found in the liver and (in decreasing order) in the lung, kidney and heart. The prepared skin binds 40%

more endotoxin than adjacent skin 4 hrs. after the i.v. injection but, during the next 24 hrs., the difference vanishes. The distribution in internal organs corresponds approximately to that of other i.v.-injected macromolecular substances. Cr⁵¹-marked endotoxin is not suitable for such observations.

Rubenstein et al. D41,757/62: Following i.v. injection of *E. coli* endotoxin in the dog, it was possible by immunofluorescence to detect endotoxin throughout the walls of the peripheral vascular system, frequently in the endothelium of capillaries and venules, as well as in polymorphonuclear leukocytes, and sometimes free in the lumens of vessels. Occasionally, endotoxin completely filled the renal glomerular capillaries, adrenal medullary sinuses and liver sinuses. It was also abundant in the RES.

Herion et al. F10,884/64: "Endotoxin, injected intravenously in small doses, is removed from the blood of nongranulocytopenic and granulocytopenic, HN₂-treated rabbits at a rate similar to normal controls." . . . "Thus, granulocytes would not appear to contribute significantly to the removal of small doses of endotoxin."

Immune Bodies. *Caruselli G28,860/41:* The SSP-G elicited in rabbits by two i.v. injections of *E. coli* endotoxin is accompanied by changes in the immune-body content of the blood similar to those observed in anaphylaxis: there is a decrease in the bactericidal power of the blood, the complement titer and the opsonic index in normal rabbits and a drop in the agglutinating and precipitating power of the serum in vaccinated animals.

CHAPTER VI

FUNCTIONAL CHANGES

DURING the development of various forms of THPs, the most prominent functional changes are those affecting blood coagulation and the vascular system.

BLOOD COAGULATION

Single or Variably Spaced Injections of Microbial Products. Single i.v. injections of bacterial endotoxins suffice to produce rapid thrombocytopenia and a decrease in blood coagulability. At the same time, there appears in the blood a protein designated as "cryoprofibrin" which is readily precipitated into a gelatinous mass by heparin at low temperatures. The substance is presumed to be an altered fibrinogen because it migrates like fibrinogen in paper electrophoresis and can be partially clotted by thrombin.

Stetson B73,457/51: Meningococcal endotoxin and glycogen i.v. produce rapid thrombocytopenia in the rabbit. This may be important for the production of an SSP by these materials.

Thomas et al. C241/54: Following single i.v. injections of meningococcal, *S. marcescens* or *Sh. paradyserteriae* endotoxin, there appears in the plasma of rabbits a protein which can be precipitated into a gelatinous mass by heparin at low temperatures. The material is presumed to be an altered fibrinogen because it migrates like the latter in paper electrophoresis and can be partially clotted by thrombin. It disappears from the blood within 10 minutes after an i.v. injection of Liquoid.

Clark & Batchelor G26,881/57: Various bacterial endotoxins produce degenerative changes in the thrombocytes and heterophil leukocytes of the rabbit *in vitro*. Similar changes may be important in the mediation of endotoxin effects *in vivo*.

Meneghini D85,262/58: *E. coli* or *S. abortus equi* endotoxin causes fibrinolysis and is of therapeutic value in various thrombo-embolic diseases of man.

Shainoff & Page D53,523/60: "A cold-precipitable, thrombin-coagulable protein, tentatively designated 'cryoprofibrin,' was separated from plasma of rabbits treated with *E. coli* endotoxin. It was shown to contain fibrin-intermediates, consisting of fibrinogen that has lost only a portion of the peptides liberated dur-

ing the conversion of rabbit fibrinogen to fibrin."

Gans & Kravit G28,329/61: Unlike in the rabbit, rapid activation of the plasminogen-plasmin system takes place after *E. coli* endotoxin injection i.v. in the dog. "These observations are interpreted as reasons for the absence of thrombosis in the dog and for the presence of thrombosis in the rabbit."

Hardaway et al. E96,214/61: A single intra-aortic infusion of *E. coli* endotoxin produces an SSP-G-like syndrome in the dog with a decrease in blood coagulability which was ascribed to a consumption of blood-clotting factors, mainly fibrinogen. Heparin pretreatment largely prevents the morphologic changes.

Rodriguez-Erdmann G31,454/64: The characteristic features of the consumption coagulopathy elicited by a single *E. coli* endotoxin injection in pregnant rabbits is a transient increase followed by a decrease in blood thrombin associated with a progressive decrease in fibrinogen, antithrombin III, platelets, factor VIII, factor V and prothrombin. Essentially similar changes occur in the classical SSP-G elicited by two properly spaced injections of endotoxin.

Prose et al. G31,934/65: Following a single i.v. administration of thrombin or *E. coli* endotoxin, fibrin uptake by hypertrophied Kupffer cells can readily be demonstrated with the electron microscope in the rabbit.

Two Injections of Microbial Products Spaced About 24 Hours Apart (the SSP). When a classic SSP-L or SSP-G is produced by two properly spaced injections of SSP-active materials, the changes in blood coagulation are qualitatively similar to those produced by one injection, but usually more severe. There is pronounced thrombocytopenia and the blood becomes incoagulable, just as in anaphylaxis. The blood-heparin content remains normal or rises. The prothrombin time is shortened and, in later stages, the fibrinolytic activity of the serum is increased. Large amounts of cryoprofibrin appear in the plasma and fibrin thrombi are formed in the vessels of various organs. At the same time, there is a decrease in the blood level of prothrombin factors V, VII, VIII, IX and X, as well as thrombocyte factor 3, while the activity of thrombocyte factors 2 and 4 remains unchanged.

The hemorrhagic tendency of the SSP is ascribed to a "consumption coagulopathy," the consequence of a sudden utilization of coagulation factors. Some apparently contradictory findings recorded in the literature are presumably due to the fact that the changes in the blood concentration of the various coagulation factors have been measured at varying intervals following provocation, insufficient attention having been given to their time-dependent differences.

Gratia & Linz E64,450/31; D6,544/32: An SSP-L elicited by *E. coli* endotoxin injected first into the ear and next day i.v. in the rabbit, causes the blood to become incoagulable. The platelet count drops from 700,000 to 70,000 and the red cell count also diminishes. The incoagulable blood can be made to clot by bubbling CO₂ through it. All these phenomena resemble classical anaphylaxis. Furthermore, the production of an SSP-L by *E. coli* in the guinea pig desensitizes the animal to the production of classical anaphylaxis by repeated injections of horse serum. "These observations speak in favor of the anaphylactic nature of the phenomenon."

Hoigné G27,367/51: A thesis on the effect of the SSP-G upon blood coagulation. The antithrombin time, prothrombin activity and blood heparin content are increased, while the factor-V content of the plasma diminishes and thrombocytopenia develops.

Štořek G21,672/51: The SSP-G elicited in the rabbit by two i.v. injections of *E. coli* endotoxin is associated with a certain drop in factor V, thrombocytopenia, and leukopenia. The blood-heparin content remains normal or rises only slightly. The SSP-L elicited by the same endotoxin is accompanied by a definite rise in blood heparin which may last 2-7 days. The thrombocytes and leukocytes decrease during the first two days but then return to normal. The prothrombin time is shortened in both reactions.

Takeo C10,179/55: An increase in the fibrinolytic activity of the serum was observed in

rabbits during the SSP. [Method of production not mentioned (H.S.).]

Volk & Losner G22,356/55: The SSP-L elicited by two injections of meningococcal endotoxin in rabbits is associated with a pronounced delay in the blood-clotting time and a return to normal within about 6 days.

Smith & von Korf D74,067/57: During the SSP-G, there appears in the blood of the rabbit a fibrinogen derivative "characterized by cold-insolubility in the presence of heparin." This material has been regarded as possibly being a precursor of fibrinoid; hence, the chemical characteristics of the corresponding fraction in human blood have been carefully examined.

Kováts et al. E71,740/58: "The Shwartzman phenomenon was elicited in rabbits in the usual way by a culture filtrate of bacterium *coli*" (no details given). This caused an increase in serum β -lipoproteins 6-24 hrs. after the provocative injection. Neither the skin preparation nor the provocative injection alone exerted such an effect. A similar change in lipoprotein pattern is elicited by heparin compounds known to inhibit the SSP; hence, it is assumed that increased endogenous heparin production might play a role in the defense of the organism against the SSP.

McKay et al. G22,384/58: In rabbits in which an SSP-G was produced by two i.v. injections of bacterial endotoxin (kind not stated), fibrin could be demonstrated by staining with fluorescein-labeled antibody to rabbit fibrin in the thrombi, the lungs, liver, spleen and kidney.

"It is concluded that the thrombi of the generalized Shwartzman reaction contain an immunologically active derivative of fibrinogen which is the essential constituent of the thrombi."

McKay & Shapiro D85,442/58: The SSP-G elicited by two i.v. injections of Shear's polysaccharide results in an increase of blood fibrinogen after the first injection and a sudden drop, followed by a secondary increase, after the second injection. A marked decrease in whole blood-coagulation times in silicone occurs 4 hrs. after both injections, but rises to normal after 24 hrs., following each injection. The thrombocytes show a 50% drop after the first injection, remain at this level and then decrease even more after the second injection. During this time no fibrinolytic or fibrinogenolytic activity can be detected, nor is there any significant change in the one stage prothrombin times or antithrombin titers. The marked decrease in circulating fibrinogen at the time of intracapillary thrombosis, suggests that the "hyaline" thrombi of the SSP-G are, in part, fibrin.

Pappas et al. G21,286/58: In rabbits, an SSP-G was produced by two i.v. injections of *E. coli* endotoxin or a single dose of endotoxin followed, one hr. later by Liquoid i.v. As judged by electron-microscopic studies, the fibrinoid deposited in the renal glomeruli was the same in both types of experiment. The endothelial cells became swollen and exhibited balloon-like vesicles. Subsequently, the fibrinoid, having a diameter of 200-300 Å and an axial repeating structure of 120 Å, was deposited within the capillary loops. It is suggested that these observations "are compatible with the hypothesis, proposed earlier, that intravascular fibrinoid, in the generalized Shwartzman reaction, is derived from fibrinogen."

Vazquez D80,507/58: By means of the fluorescent antibody technique, the "fibrinoid" was examined in various human and experimental diseases. Fibrinogen with little or no albumin or gamma globulin was found in the fibrinoid of the SSP-G (rabbit), thrombotic thrombocytopenic purpura and abruptio placentae. On the other hand, in the collagen diseases (lupus erythematosus or rheumatic fever in man, serum sickness in the rabbit), the fibrinoid contained much gamma globulin with little or no fibrinogen or albumin. "It is suggested that a different composition of the fibrinoid in the above studied diseases might indicate a different pathogenesis for the diseases of these 2 groups."

Kliman et al. G26,182/59: In rabbits which develop an SSP-G following two i.v. injec-

tions of *E. coli* endotoxin, thromboplastin generation is impaired. "Except for suggestive poor clot retraction and decrease in platelets, fibrinogen, and perhaps Ac-globulin, no other hemostatic parameters were significantly affected. That the clotting defect was serious, is indicated by the fact that 7 animals died of hemopericardium following cardiac puncture. This is the first demonstration of a clotting abnormality in the Shwartzman reaction which could account for a hemorrhagic tendency."

McKay et al. D15,431/59: With the fluorescent antibody technique, it has been demonstrated that fibrin or an insoluble derivative of fibrinogen is a constituent in the thrombi found in the lungs, spleen, liver and kidneys of rabbits in which an SSP-G was produced by two i.v. injections of *S. marcescens* endotoxin.

Schrader et al. G22,067/59: Following a single i.v. injection of *E. coli* endotoxin, the blood fibrinogen drops moderately below normal within 4 hrs. in the rabbit, but then rises above normal at 24 hrs. If a second injection of toxin is given 24 hrs. after the first, the fibrinogen level drops markedly during the next 4-8 hrs., then returns towards normal.

Kleinmaier et al. C81,035/59: An SSP-G elicited by two injections of various bacterial endotoxins produces a rapid increase in blood thrombin and thrombocytes. This is associated with "viscous metamorphosis" of the latter and transformation of fibrinogen into fibrin. The acute consumption of coagulation factors results in loss of blood coagulability. The latter is regarded as the cause of the hemorrhagic diathesis in the SSP-G.

Lasch et al. G22,059/61: An SSP-G elicited by two i.v. injections of *E. coli* endotoxin in the rabbit increases the blood clotting time and causes a drop in the factors of the prothrombin complex. The anti-blood-thrombokinase activity increases, while the antithrombin-III activity falls. This corresponds to the changes observed in these inhibitory factors during blood clotting in vitro. These observations support the concept that the SSP-G induces intravascular fibrin thrombi and consequently consumes coagulation factors.

Lasch et al. E64,434/61: If, in the course of an SSP-G produced by two i.v. injections of bacterial toxin (kind not stated) in the rabbit, streptokinase is administered, the animals survive a normally fatal response, presumably because of the lysis of microthrombi. However, the mean values for prothrombin factor V, factor VII and blood platelets are not altered by the streptokinase-induced fibrinolysis. When fibrinolysis is inhibited by pretreat-

ment with EACA, two i.v. injections of bacterial endotoxin still elicit a typical SSP-G. At the same time, there is a decrease in the prothrombin factor VII and factor V and platelet content of the blood both in the control and in the experimental animals. On the other hand, the fibrinogen content of the blood is higher in the animals pretreated with EACA. Apparently, fibrinolysis plays no role in the causation of the drop in prothrombin factors VII and V and of blood platelets.

Lasch et al. D43,553/61: An SSP-G elicited by two i.v. injections of *E. coli* or *S. abortus equi* endotoxin causes a diminution of the prothrombin factors V, VII, VIII, IX and X content of the blood. At the same time, there is sudden diminution of blood fibrinogen and intravascular fibrin formation. The hemorrhagic tendency of the SSP-G is ascribed to a "consumption coagulopathy," the consequence of a sudden utilization of coagulation factors. Further evidence in support of this hypothesis is furnished by the observation that the SSP-G is associated with a fall in blood thrombocytes and a particularly pronounced diminution of thrombocyte factor 3. The activity of thrombocyte factors 2 and 4 is unchanged. Similar coagulation defects are noted in patients with hemorrhagic types of coli, meningococcal or staphylococcal sepsis, which can be successfully treated with heparin.

Rodriguez-Erdmann & Lasch E63,756/61: During the first 2-6 hrs. of an SSP (method of production not given) in the rabbit, thrombin activity in the circulating blood increases considerably as tested by its effect upon a fibrinogen solution in vitro, and blood coagulability rises. This is the time when intravasal thrombi are formed. In opposition to earlier investigators, who ascribed clot formation during the SSP to a direct damaging effect of endotoxin upon the fibrinogen molecule, these observations suggest that, during the first phase of the SSP, hypercoagulability of the blood, induced through the enzymatic action of thrombin, is the cause of microthrombus formation. The concept is strengthened by the earlier observations of Jürgens and Studer (*D38,953/48*), who noted that thrombin i.v. causes the formation of fibrin thrombi in the rabbit and simultaneously renders the blood incoagulable. These changes were prevented by heparin. Since antithrombin can be inactivated by a thrombin, the diminution of antithrombin activity during the SSP could be due to increased thrombin formation. The secondary drop in blood thrombin during later phases of the SSP is ascribed to the exhaustion of prothrombin whose blood concentration does, in fact, drop considerably. Thus, the intravasal appearance of thrombin and the consequent

increased utilization and exhaustion of coagulation factors are regarded as the cause of the hemorrhagic tendency. It remains to be seen, however, what causes increased thrombin formation. This cannot be ascribed to a direct action of endotoxin since the latter does not possess any significant thrombokinase-like activity.

Horowitz et al. G33,237/62: Activation and discharge of platelet factor 3 by endotoxin has been demonstrated by incubating platelet-rich rabbit plasma with endotoxin in vitro. This response presumably participates in the clotting defect of the SSP.

Müller-Berghaus et al. D60,636/63: Thromboelastographic studies revealed that, during the classical SSP-G (produced in rabbits by two i.v. injections of *coli* endotoxin), there is no evidence of increased fibrinolysis. The disturbance in blood coagulation is due to excessive fibrin utilization ("Verbrauchskoagulopathie") consequent upon intravascular clotting.

Müller-Berghaus & Lasch G15,504/63: In rabbits in which an SSP-G was induced by two injections of *E. coli* endotoxin, the aorta was removed at different time intervals after provocation to examine the effect of vascular factors upon blood clotting. It was found that "activation of factor V to factor VI is more rapid in aorta preparations obtained during the early and the late phases of SSP than in normal aortas. This effect is attributed to a higher surface activity and is identical in all phases of the SSP." The inactivation of factor V is accelerated in early phase and delayed in late phase aortas. "This could be due to an impoverishment of the aortic wall, which has released its clotting substances, such as vasculokinase, under the influence of the endotoxins. These substances accelerate the intravascular coagulation in the early phase. In the late phase the vessel wall is exhausted. It is also possible that with time thrombin inhibitors (heparin) are released from the wall of the vessels and diminish the effect of the thrombin."

Weber et al. G15,172/63: SSP-G decreases clot retraction time, presumably because energy-rich ATP is lost through damage of thrombocytes. Thrombocyte damage is attributed to intravascular thrombin which starts the viscous metamorphosis.

Jókay et al. G28,485/64: Earlier experiments had shown that in vitro cysteine prevents platelet aggregation and the release of histamine and 5-HT which normally occurs under the influence of endotoxin in rabbit blood. It is now found that simultaneous administration of the provoking dose of *E. coli* endotoxin and

cysteine i.v., in rabbits prepared for the SSP-L, inhibits thrombopenia and enhances leukopenia. At the same time, the resulting SSP-L is aggravated. It is concluded that platelet aggregation is less important than leukopenia in the production of an SSP.

Krecke E4,840/64: In rabbits in which an SSP-G was produced by two i.v. injections of bacterial endotoxins, the renal glomerular capillary thrombi contained fibers with an axial periodicity of about 200 Å, similar to that of fibrin. A single i.v. injection of Liquoid produces the same result. These electron-microscopic studies suggest that the thrombi do in fact contain fibrin.

Lasch F37,812/64: During an SSP-G elicited by two i.v. injections of various endotoxins in the rabbit, there is not only thrombocytopenia but the remaining thrombocytes show qualitative disturbances: their thrombokinase-forming ability is decreased, they produce a diminished amount of lipid factor 3 and—apparently owing to a diminished ATP-content—they induce insufficient clot retraction.

Müller-Berghaus et al. D13,794/64: Following an initial hypercoagulability of the blood, which occurs after both the first and after the second i.v. dose of *E. coli* endotoxin, there ensues a phase of hypocoagulability which manifests itself in a narrowing of the amplitude of the thromboelastogram.

Nonmicrobial Agents Given Alone or in Combination with Microbial Products. Following slow i.v. infusion of *thrombin*, the blood becomes incoagulable and there is thrombocytopenia and hypofibrinogenemia with the formation of multiple capillary thrombi, especially in the renal glomeruli. Thrombin i.v. also provokes the appearance of cryoprotifibrin in the blood. Rapid i.v. infusion of *thromboplastin* elicits the formation of large thrombi in the heart, while slow infusion of the same material results only in a nonfatal afibrinogenemia.

Massive hemorrhage may also produce microthrombi, but this is accompanied by hypercoagulability of the blood, thrombocytosis, accelerated thromboplastin formation and fibrinogenopenia. Yet even here, at the peak of the shock, the platelets, fibrinogen and other coagulation factors are depleted and intense fibrinolysis develops.

Profound depletion of circulating fibrinogen occurs during the THP produced by combined treatment with *endotoxin* and *Liquoid*. Liquoid precipitates fibrinogen from plasma in vitro and the role of the endotoxin might be to cause a change in fibrinogen, perhaps related to the formation of cryoprotifibrin. The THP elicited by single i.v. injections of Liquoid, like the classic SSP-G, is associated with a decrease in the activity of the prothrombin factors V (accelerator globulin), VII and IX/X complex as well as with thrombocytopenia. However, here, the pronounced loss of antihemophilia globulin characteristic of the SSP is not demonstrable.

Schimpf & Cibelius F11,286/64: Upon induction of an SSP-G by two i.v. injections of *E. coli* endotoxin "anti-plasmathromboplastin increases immediately and permanently while antithrombin III activity decreases. Simultaneously a tendency towards increased thrombin formation can be observed. In contrast to this heparin and recalcification times change later. Heparin, titrated with protamin, decreases after ½ hour and remains low (10 hours). The recalcification times also are shortened only after ½ hour, and increase consequently above their normal range."

McKay E4,788/65: A review of the somewhat contradictory literature concerning the mechanism by which endotoxins produce an SSP, leads to the conclusion that "endotoxin acts independently of leukocytes and red blood cells, and does not act as preformed thromboplastin or thrombin." Even *in vitro*, endotoxin causes platelet agglutination.

Scott & Blaszcynski G30,733/65: Plasminogen activator was readily demonstrated in various tissues of the guinea pigs but only with difficulty in those of rabbits. On the other hand, an SSP-G was elicited by two i.v. injections of *E. coli* endotoxin in rabbits, but not in guinea pigs. "This suggested a possible inverse relationship between the production of the generalized Shwartzman reaction and the formation of plasminogen activator in the tissues."

Somewhat related forms of coagulation defects have been noted after the administration of various *drugs, antigens, and incompatible blood*. Even cryoprotin can occur in the plasma following a variety of *inflammatory and necrotizing diseases*; hence, its appearance has been regarded as representing another reaction in the category of the "acute-phase" phenomena. On the other hand, in several *collagen diseases*, plasma cryoprotin drops to unusually low levels, perhaps because the diffuse deposition of fibrinoid depletes the stores.

Combined treatment with *endotoxin and x-irradiation* may elicit a THP-G in which an initial sharp rise in blood fibrinogen is followed by a precipitous fall. The pattern is very similar to that seen after two injections of endotoxin.

Thrombin, Thromboplastin. Jürgens & Studer D38,953/48: Following slow i.v. infusion of thrombin in the rabbit, the blood becomes incoagulable and there is leukopenia, thrombocytopenia and hypofibrinogenemia. Multiple capillary fibrin thrombi develop, especially in the renal glomeruli, the liver and the lung. Polymorphonuclear leukocytes tend to accumulate in these same organs. [The possible implications of this observation in the pathogenesis of the SSP are not discussed (H.S.).]

Ratnoff & Conley G24,129/51: Rapid i.v. infusion of thromboplastin in dogs causes the formation of large thrombi at the mitral and pulmonary orifices of the heart as well as in both ventricles. When the thromboplastin was infused more slowly, a transient, nonfatal afibrinogenemia was induced and blood clotting was prolonged. [No mention is made of microthrombi or hemorrhages (H.S.).]

Lee E41,395/62: Heparin-precipitable fibrinogen (HPF, or "cryoprotin") appears more rapidly in the blood of rabbits given thrombin i.v. than after *E. coli* endotoxin i.v. "The prompt appearance of HPF following thrombin infusion in contrast to the delayed onset after endotoxin injection may well explain the finding of recognizable fibrin deposits as early as 30 minutes after the start of thrombin administration as opposed to the consistent failure to detect fibrin deposits during the first two hours after the challenging injection of endotoxin." The release of endogenous thrombin may be a mediator in the production of HPF by endotoxins.

Lee & McCluskey G33,240/62: Following i.v. injection of thrombin or endotoxin, intracytoplasmic deposition of fibrin can be demonstrated in the hepatic and splenic RES-cells of the rabbit by immunohistochemical methods. Heparin prevents this fibrin storage. "The findings of this study substantiate the hypothesis that fibrin aggregates formed in the circulating blood during low grade intravascular coagulation are largely removed by the reticuloendothelial system."

Hemorrhage. Crowell & Read D79,404/55: During shock produced by massive hemor-

rhage in the dog, microscopic blood clots are formed in small veins. The thrombi remain in place until blood is restored to the animal; then they are washed out and slowly block the pulmonary and portal circulations, thereby causing death. Heparin prevents this response. "It seems probable that irreversible shock produced by hemorrhage may be due to small blood clots formed as the result of excessive stimulation of the blood coagulability control system."

Turpini & Stefanini C73,362/59: Shock induced by severe hemorrhage in rabbits results in hypercoagulability of the blood, as indicated by thrombocytosis, accelerated thromboplastin formation and fibrinogenopenia. At the peak of shock, platelets, fibrinogen and other coagulation factors were depleted and intense fibrinolysis developed. "Histologic studies showed significant intravascular deposition of fibrin, possibly of platelets, in the vessels of lung, kidney and liver. This suggested widespread intravascular clotting."

Liquid. Thomas D1,020/57: A THP with profound depletion of circulating fibrinogen occurs in rabbits treated simultaneously with meningoococcal endotoxin and Liquoid, while neither of these compounds alone is effective in these respects. Injection of endotoxin an hour before the polymer produced death, with fibrinoid thrombi in the glomerular capillaries and fibrinoid deposition in the coronary arteries as well as in the mitral and aortic valves. Liquoid precipitates fibrinogen from plasma in vitro, and the role of the endotoxin in the reaction might be to cause a change in fibrinogen possibly related to the development of cold precipitability by heparin, which renders the fibrinogen more readily precipitated by the acid polymers within the circulating blood *in vivo*.

Rodriguez-Erdmann et al. G22,083/60; Rodriguez-Erdmann & Lasch G24,133/61: A single i.v. injection of Liquoid suffices to produce an "SSP-G" in the rabbit. This syndrome (like that elicited by two i.v. injections of endotoxin) is associated with a decrease in the activity of the factors prothrombin V (acceler-

ator globulin), VII and IX/X-complex with severe acute thrombocytopenia and a diminution of platelet factors 1 and 3. However, the pronounced loss of antihemophilia globulin characteristic of the SSP was not demonstrable. Protamin sulfate largely prevents these changes, including the pathologic lesions. "The similarity between the classical Sanarelli-Shwartzman phenomenon and the coagulopathy induced by Liquoid suggests that in both cases, an analogous mechanism induces intravascular precipitation of fibrin in various organs."

Various. Kusama C70,497/13: Detailed review of the literature up to 1913 and personal observations on the production of multiple thromboses by the i.v. administration of various drugs, antigens and incompatible blood.

Brinkhous & Penick G22,790/54: After freezing of the skin with liquid air in the dog "edema and interstitial fibrin deposits are present in the adjacent viable tissue. There are fibrin thrombi in dilated lymphatics. The smaller blood vessels, particularly at the margins, are also thrombosed." The changes are less pronounced in hemophilic animals. Both in normal and in hemophilic dogs, the blood fibrinogen and prothrombin were not grossly altered. However, significant reduction of plasma antihemophilic factor and platelets occurred in the normal animals. It is suggested that local thrombosis may result in the release of thromboplastin from the injured sites with consequent systemic changes in clotting factors.

Smith D70,806/57: Extensive studies in health and disease on the protein fraction of human plasma, which is characterized by cold-insolubility in the presence of heparin. It is concluded "that normal individuals have low levels of the fraction, that these levels become greatly increased as a result of most acute inflammatory or necrotizing diseases. The appearance of the fraction in increased amounts represents another reaction in the category of 'acute-phase' phenomena." Particularly low values have been found in acute disseminated lupus erythematosus, and in one case of polyarteritis with elevated clottable fibrinogen levels. Presumably, the fibrinogen derivative is depleted as the fibrinoid deposits characteristic of these diseases are being laid down in various organs. However, the occurrence of abnormally high levels in acute rheumatic fever and rheumatoid arthritis does not agree with this interpretation.

Schrader et al. G22,067/59: Following abdominal α -irradiation, there is a gradual rise in the blood fibrinogen of the rabbit. When E. coli endotoxin is given 24 hrs. following x-ray, there is an immediate sharp rise followed by a precipitous drop within 4-8 hrs. These changes correlate well with the resulting fibrinoid lesions of the "SSP-G." The pattern is very similar to that seen after two injections of endotoxin.

Jager E95,817/62: In a man with lymphatic leukemia, there developed an acute illness that included ischemic necrosis of the nose, toes, petechial hemorrhages in the skin, hemorrhagic conjunctivitis and hemorrhage in the vitreous. "The only pertinent laboratory abnormality was a large amount of cold-precipitable fibrinogen in the plasma. Unlike the usual cryofibrinogen, which is demonstrable only upon cooling of heparinized plasma, this protein also appeared when plasma containing citrate, oxalate or edathamil calcium disodium was cooled. It seemed likely that cryofibrinogenemia was a significant factor in the production of thrombosis and hemorrhage." A cryofibrinogen-like substance was also detected in the blood of patients with acute or chronic illness using anticoagulant other than heparin.

Lee G26,187/63: After RES-blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the appearance of "heparin precipitable fibrinogen" in the circulation.

Wilner et al. G5,904/63: The THP-G elicited in pregnant rats by diets rich in oxidized lipids and poor in vitamin E is associated with a sharp drop of the blood-platelet count from about 1 million to 200,000/mm³ owing to accumulation of thrombocytes in the placenta.

McKay & Corey G33,291/64: Brief review of the literature on cryofibrinogen (also referred to as "contractininogen," heparin precipitable fraction or HPF) indicating that the blood concentration of this material rises not only in toxemia of pregnancy but also in rheumatic fever, rheumatoid arthritis, acute bacterial infections, cancer and, to a lesser extent, even in normal pregnancy.

VASOMOTION, BLOOD PRESSURE AND CAPILLARY PERMEABILITY

The SSP-G is associated with a drop in blood pressure and a decrease in capillary resistance. Allegedly, a "capillary permeability promoting" factor appears in the blood.

The THP-L produced in cortisone-pretreated rabbits at sites of i.c. injection of endotoxin decreases capillary permeability in the challenged area, as judged by the fact that i.v. injected dyes stain the skin everywhere, except in the region treated with endotoxin. In this respect, the cortisone-conditioned THP-L is said to differ from the SSP-L and other forms of inflammation in which blood-borne dyes are, on the contrary, concentrated in the affected territories. However, the reported differences may be due to time-dependent variations which could be missed unless complete response-curves are compared.

Sanarelli B78,422/24: If, 24 hrs. following an i.v. injection of a sublethal dose of live cholera vibrios, colitoxin is injected intravenously in the rabbit, there develops an acute nephritis with desquamation of the intestinal epithelium, intestinal hemorrhages and diarrhea, reminiscent of cholera. The blood pressure falls and there develops a transient drop, followed by a rise in the polymorphonuclear leukocyte count of the blood.

Gratia & Linz D6,544/32: When a very severe SSP-L is elicited by two injections of *E. coli* filtrate in the rabbit, there develops a severe hypotension with a fall in thrombocytes, and the blood becomes incoagulable, but its coagulability is restored by exposure to CO₂ in vitro. All these changes are also characteristic of anaphylaxis.

Bier & Planet G28,159/38: Trypan blue given i.v. 1 hr. after the provocative injection, accumulates in the treated skin area of rabbits in which an SSP-L is elicited by two injections of typhoid endotoxin. This finding is contrary to the observations of Burnet (*E42,707/31*) who obtained negative results perhaps because he only examined the outside of the skin where the color is not evident.

Hoigné et al. B63,813/51: During an SSP-L elicited by two injections of *coli* toxin in the rabbit, there is a decrease in capillary resistance and thrombocyte count with an associated increase in the antithrombin level.

Thomas & Good E56,605/52: In cortisone-pretreated rabbits in which an "SSP-L" is produced by i.c. injection of *S. marcescens* toxin,

the i.v. injection 12 hrs. later of trypan blue causes deep coloration of the skin everywhere except in the challenged area. (It was previously observed that skin tissue prepared for the SSP-L by local injection of toxin becomes less permeable to i.v. injected dye and thereby differs from other types of local inflammatory reaction which become more permeable.)

Takeo C10,179/55: The SSP augments the "capillary permeability promoting action" of the blood in the rabbit. [Method of SSP-production not mentioned (H.S.).]

Weil et al. C25,411/56: Analysis of the hemodynamic changes responsible for the hypotension (associated with a rise in portal vein pressure and a fall in systemic venous pressure) elicited in dogs by single i.v. injections of *E. coli* and *Br. melitensis* endotoxins.

Schulhof & Richter G23,266/59: Neither Evans blue nor bromsulphalein i.v. is concentrated in the affected cutaneous territory in rabbits in which an SSP-L is elicited by two injections of typhoid endotoxin.

Enoki D60,740/62: Capillary resistance is greatly decreased (suction cup technique) during the SSP in the rabbit.

Müller-Berghaus & Lasch G15,504/63: The influence of the aortic wall upon blood clotting (measured in vitro) changes considerably during successive stages of an SSP-G induced by two injections of *E. coli* endotoxin in rabbits. But some "vasculokinase" in the aortic wall, which transforms fibrinogen into fibrin, may play a key role in the development of the SSP.

CHAPTER VII

CLINICAL IMPLICATIONS

Reviews on the General Clinical Implications of the SSP

Kielanowski & Selzer D71,895/35
Sanarelli G27,950/35
Gerber C95,662/36
Renaux & Alechinsky G18,585/36
Shwartzman et al. G24,322/36
Albus G23,265/37
Horster G22,366/38
Basile G23,055/41
Albus G23,058/42
Lewi G22,702/49
Black-Schaffer E59,121/49-50

Richter G23,069/50
Hesse D71,863/52
Rempt E72,575/56
Reid G33,238/57
Bohle & Krecke C94,892/59
Hardaway & McKay G33,254/63
Kiss F18,718/64; G23,185/64
Krecke E4,840/64
Penick & Roberts G30,656/64
Hjort & Rapaport G32,971/65
Verstraete et al. G15,997/65
Sise et al. G35,300/62

INFECTIOUS DISEASES

Thrombohemorrhagic lesions, including fibrin thrombosis of the renal glomerular capillaries, occur in various spontaneous infections (pneumonia, peritonitis, infected burns), and it has been suggested that these changes may represent clinical manifestations of the SSP. In fact, it was thought that even normally saprophytic organisms could become pathogenic through the liberation of their endotoxins in a patient "prepared" by some other infection.

These considerations are of particular interest in the interpretation of *focal infections*. Several observations support the thesis that topical treatment with endotoxin in animals, or spontaneously developing infectious foci in man, can so prepare a certain tissue region that it will attract blood-borne toxins or even live bacteria released from another focus. It is very tempting to ascribe such findings to the SSP when the local manifestations are thrombohemorrhagic.

In especially sensitive patients with systemic infections, *chemotherapeutic agents* can produce local thrombohemorrhagic lesions at sites where they are injected. A relationship between such reactions and the SSP has often been suspected but never proven.

There is somewhat more convincing evidence in support of the view that the "secondary syndrome of chemotherapy" or "ninth-day erythema" may be related to the SSP. This syndrome is characterized by a toxic rash, agranulocytosis, nephritis, hepatitis, encephalopathy and thrombohemorrhagic lesions which occur some time (often nine days) after the initiation of chemotherapy in patients with generalized infections. It has been thought that here, the original infection acts as the preparatory agent, while the massive liberation of endotoxin induced by sulfonamides or antibiotics furnishes the provocative stimulus.

This secondary syndrome of chemotherapy resembles the *malignant syndrome* ("syndrome malin") of the French clinicians which occurs in certain infections, especially in severe typhoid fever, diphtheria, influenza, scarlet fever and measles. Its manifestations are strikingly similar, irrespective of the evocative specific pathogen; there is prostration (in infants sometimes with convulsions), fever, cardiovascular collapse, albuminuria, hematuria, dyspnea, diarrhea and vomiting, sometimes with hematemesis and melena. Autopsy reveals intense purple discoloration of the renal pyramids with hemorrhagic infarcts in the lungs and petechial hemorrhages in the pericardium, gastrointestinal mucosa (particularly Peyer's plaques), lymph nodes, meninges, and sometimes along the autonomic nerves. This condition is also reminiscent of Reilly's syndrome and the Waterhouse-Friderichsen syndrome, both of which have been suspected of being manifestations of the SSP. Although a considerable literature has developed under each of these headings, curiously no systematic effort has been made to connect them with each other. Yet they are obviously related, at least in that they represent catastrophic acute exacerbations of generalized infections, in which often fatal thrombohemorrhagic lesions appear whose violence is quite out of proportion to the customary actions of the causative organisms. The fact that the clinicopathologic manifestations of all these syndromes are strikingly similar, and unlike the usual direct effects of the evocative organisms, suggests that here, the microbes do not act directly, but through the evocation of some common pathogenic mechanism which may well be related to the SSP.

The classical *Waterhouse-Friderichsen syndrome* (characterized by purpuric manifestations, bilateral adrenal hemorrhage, hyaline thrombosis of the renal glomerular capillaries and sometimes bilateral renal cortical necrosis) has also been regarded as a special form of the SSP-G. Although it is frequently due to meningococcic septicemia, it can develop in the course of infections by other microorganisms and it is quite closely duplicated in animals by two i.v. injections of various endotoxins administered under certain circumstances. The adrenal hemorrhages, which are particularly characteristic of the Waterhouse-Friderichsen syndrome, can be reproduced most readily by i.v. injections of endotoxin in animals pretreated with such RES-blocking agents as Thorotrust, or after stimulation of the adrenals with ACTH.

Especially striking SSP-like changes are seen in patients with *typhoid fever* (sometimes immediately after typhoid vaccine or nonspecific pyrogen treatment), *scarlet fever*, *cholera*, *purpuric smallpox* and occasionally after *pseudomonas septicemia*. In all these instances the causal participation of the SSP was suspected.

Considerable attention has been given to the possible relationships between the SSP and *tuberculosis*. Tuberculous guinea pigs are especially sensitive to the production of a THP by bacterial endotoxins, and certain forms of hemorrhagic tuberculin reactions are strikingly similar to the SSP-L. The fact that in adults, recurrences of tuberculous lesions usually occur in the immediate vicinity of old foci has also been regarded as due to some SSP-like mechanism.

In this connection, it is noteworthy furthermore that the filtered coelomic fluid of ascaris can produce a typical SSP-L in the rabbit, hence, certain symptoms of patients with *ascariasis* may be due to this type of response.

SSP-like changes have also been seen in some spontaneous diseases of animals such as *hog cholera* and *swine erysipelas*.

Other thrombohemorrhagic lesions possibly related to infections will be discussed in the sections on the Diseases of Pregnancy (septic abortion) and the Digestive Diseases (appendicitis, infantile diarrhea, intestinal gangrene).

Various Spontaneous Infections. *Herzog E73,475/13:* Three cases of widespread fibrin thrombosis in the renal glomerular capillaries following lobar pneumonia, purulent peritonitis and eclampsia respectively. In an eclamptic woman, there was also bilateral cortical necrosis of the kidneys. Earlier pertinent publications are reviewed.

Cohen & Moolten E71,235/43: In rabbits prepared by an intratracheal injection of attenuated microorganisms resembling bacillus necrophorus, subsequent i.v. injection of homologous or heterologous toxins increases the number of pulmonary abscesses. With slightly attenuated cultures, the virulence was fully restored. "The anaerobic streptococcus and the anaerobic diphtheroid which are found regularly in cases of putrid abscess of the lung may be suspected as the source of preparatory factor despite their apparent innocuousness." Consequently, it is suspected that pulmonary abscesses in man may, under certain conditions, result from an SSP-L.

Graber et al. C85,671/60: In a soldier who sustained severe burns, followed by *S. marcescens* septicemia, there developed a typical SSP-G with hyalin thrombi in the renal glomeruli and focal areas of hemorrhage in other organs. "In this case it is postulated that a combination of stress produced by severe trauma followed by the presence of an endotoxemia due to *Serratia marcescens* in the wounds, in the genitourinary tract, and in the blood stream of this patient caused the generalized Schwartzman reaction." Furthermore, "it is suggested that *Serratia marcescens*, a reputed nonpathogen, should be seriously regarded as a potential bacteremic agent in burn trauma."

Naeye C26,518/61: In two patients with disseminated thromboses, presumably induced by infections with unidentified microorganisms, the plasmin and plasminogen levels of the blood were low and the thrombotic diathesis was ascribed to deficient fibrinolysis.

Focal Infections. *Horster & Müller G25,124/37:* If a mild infection is produced by i.c. injection of live staphylococci the local lesion flares up and often becomes hemorrhagic in rabbits upon the subsequent i.v. administration of meningococcal endotoxin. The fact that bacterial products can thus activate an infectious focus is interpreted as evidence supporting the concept of focal infection.

Moritz E65,873/37: After *B. aertrycke* filtrate was given s.c. to rabbits, i.v. injection of living *B. aertrycke* led to the localization of these germs in the developing hemorrhagic cutaneous lesions. The importance of the SSP for the localization of infections in general is emphasized.

Ciambellotti G28,857/38: Review of the literature and the possible relationship between focal infection and the "SSP."

Tommasi G28,858/38: Presentation of a few cases with hemorrhagic cutaneous lesions ascribed to a focal response to *staphylococcus* infection.

Harkavy & Romanoff E41,412/39: Hemorrhagic and necrotic skin reactions result at sites where various vaccines are injected or trauma applied in patients suffering from certain chronic infections.

Sacharow G23,066/41: Using the classical SSP-L procedure in the rabbit, it was possible to show both preparatory and provocative activity in a *Leptothrix lanceolata* Gi₂₈ and an *Actinomyces* culture obtained from the oral cavity of man. It is possible that anaerobic germs of the oral cavity may play a role in focal infection.

Miescher & Böhm E53,167/47: Following inoculation with living *E. coli* into the conjunctiva, mechanical trauma to the testis produces a local hemorrhagic necrosis with the appearance of numerous *coli* organisms in the testis. This mechanism may explain the pathogenesis of certain forms of focal infections.

Kiss D41,976/63: Purely theoretical considerations lead to the conclusion that in various infections (appendicitis, bronchitis, bronchopneumonia, gastroenteritis, furunculosis, focal infections) and particularly in tuberculosis, certain aggravations of inflammatory foci are due to the development of an SSP-L, owing to provocation by bacterial endotoxins. [No original clinical observations or animal experiments are described (H.S.).]

The Secondary Syndrome of Chemotherapy. *Lewi G22,349/48; G21,651/49:* The term "sanergie" is proposed as a group designation for the "secondary syndrome of chemotherapy" characterized by cutaneous rashes and hemorrhagic lesions in the digestive tract, heart, kidney, liver, adrenals, pancreas and brain, following treatment of systemic infections with

chemotherapeutic agents, the Riley phenomenon, and the SSP. The secondary phenomenon of chemotherapy has also been designated as "the syndrome of the ninth day" (Milian) of the "mediate, secondary phenomenon of chemotherapy" (Tzank), since it usually appears secondarily at about the ninth day after institution of chemotherapy.

Boelter & Hatoff G23,052/49: In a 10-year-old girl who was given several injections of penicillin in oil into the buttocks, the subsequent administration of regular penicillin intramuscularly at another site elicited urticarial wheals surrounding the puncture sites of the previous penicillin-in-oil injections. The phenomenon is ascribed to an SSP-L.

Suchett-Kaye G22,095/50: The "secondary syndrome of chemotherapy" ("ninth-day erythema," toxic rash, agranulocytosis, nephritis, hepatitis, encephalopathy, etc.) is thought to be related to the SSP. In a personally observed case, sensitization to sulfonamide was thought to be responsible for this condition.

Hasselmann et al. G22,335/51: In guinea pigs given repeated i.m. injections of BAL, subsequent infections with various bacteria produce thrombohemorrhagic necroses at the BAL injection sites. Similar observations have been made in the pig, as well as in patients treated with BAL for various infectious diseases. The phenomenon is ascribed to the SSP.

Rubens G23,062/51: In a baby who had received procaine-penicillin into the buttocks 6 weeks earlier for an upper respiratory infection, reinjection with the same preparation into the right buttock produced a large local hemorrhagic necrosis. "Arthus phenomenon, Shwartzman phenomenon, and embolia cutis medicamentosa are discussed as possible diagnoses."

Hesse D71,863/52: The hemorrhagic necrotic changes sometimes induced by BAL in patients receiving arsenobenzol therapy are tentatively ascribed to the development of an SSP.

The Malignant Syndrome. *Marquézy E65-247/58:* The malignant syndrome or "syndrome malin" of the French clinicians is characterized by prostration (in infants sometimes with convulsions), fever, cardiovascular collapse, albuminuria, hematuria, dyspnea, diarrhea and vomiting, often with hematemesis and melena. At autopsy, the renal pyramids are seen to have assumed a deep purple color, there are hemorrhagic infarcts in the lungs, petechial hemorrhages underneath the pericardium; hemorrhages in the gastrointestinal mucosae sometimes with intussusception, swelling and hemorrhage in the lymph nodes, particularly those of the mesentery, as well as Peyer's plaques. Histologically, erythrodiapepsis,

swelling of the vascular endothelia thromboses, especially in the veins, and hyperplasia of the reticulo-endothelial system are most striking. Congestion of the meninges and punctate hemorrhages in the brain as well as along the thoracic sympathetic and vagus nerves are common. The syndrome tends to develop especially in the course of severe typhoid fever, diphtheria, influenza, scarlet fever and measles. The typical syndrome of signs and symptoms reappears "with impressive similarity whatever the age of the patient, whatever the etiology." [In this publication, nothing is said about renal glomerular lesions, nor of any possible relationship of the malignant syndrome to the SSP-G; but Reilly's syndrome is considered to be the experimental counterpart of the malignant syndrome (H.S.).]

Rapin G27,052/63: Detailed description of the hemorrhagic "malignant syndrome" which can occur in the course of various infectious diseases, particularly scarlet fever, typhoid and many other septicemias due to gram-negative organisms, but also in viral infections such as influenza, rubeola, poliomyelitis and varicella. It can even occur in parasitic infestations with Plasmodium falciparum. This condition is perhaps related to the general adaption syndrome, Reilly's syndrome and the Shwartzman phenomenon, but a definite interpretation of its pathogenesis is not yet possible.

The Waterhouse-Friderichsen Syndrome. *Black-Schaffer et al. E61,157/47:* Washed meningococci, living or dead, are capable of producing an SSP-L in the rabbit. At the same time, hemorrhages and necroses occasionally occur in internal organs, particularly the adrenals, the renal cortex and the heart. In rabbits given repeated i.v. injections or i.c. deposits of live meningococci, a generalized cutaneous purpura developed with renal glomerular thrombosis, bilateral renal cortical necrosis and adrenal hemorrhages reminiscent of the Waterhouse-Friderichsen syndrome. "Meningococcic purpura has been produced in rabbits. The lesions are interpreted as a cutaneous manifestation of a generalized Shwartzman phenomenon. The syndrome of Waterhouse and Friderichsen, which may complicate meningococcemia, has been reproduced in a rabbit. The adrenal lesions are considered to be a by-product of a general toxemia and not necessarily a resultant of the Shwartzman mechanism. It is believed that the appearance of bilateral renal cortical necrosis in experimental meningococcemia is evidence of the ability of the washed bacteria to produce the general Shwartzman reaction."

Hill & Kinney B45,566/47: "The cutaneous lesions of meningococcemia are the results of

vascular damage, which consists of endothelial damage, inflammation of the vessel wall, necrosis and thrombosis." There are also perivascular hemorrhages and meningococci can readily be demonstrated in the endothelial cells.

Sternberg et al. G22,091/51: Purpuric meningococcemia is not identical with the Waterhouse-Friderichsen syndrome, since it is only rarely associated with adrenal necrosis. In a child with purpuric meningococcemia, a necrotizing hemorrhagic skin lesion over the buttocks was interpreted as an SSP-L.

Rostenberg G21,665/53: Numerous observations are quoted in support of the view that "bilateral renal cortical necrosis and the Waterhouse-Friderichsen syndrome, arise on the basis of a Shwartzman mechanism."

Coste et al. E50,611/57: In a case of severe staphylococcal septicemia, there developed diffuse hemorrhages characteristic of Reilly's syndrome of "generalized sympathetic irritation" but at the same time there were fibrinoid thromboses in the glomerular capillaries and adrenal hemorrhages more characteristic of the SSP-G and of the Waterhouse-Friderichsen syndrome. A relationship between these conditions is suspected.

Margareten & McAdams C62,086/58: Bilateral renal cortical necrosis developed in 3 out of 52 fatal cases of meningococcal infection under circumstances suggesting a causal relationship to corticoid therapy. This observation, and the apparent causal role of thrombosis in the production of hemorrhagic cutaneous and adrenal lesions in the Waterhouse-Friderichsen syndrome "suggest that the Shwartzman phenomenon may be responsible for certain manifestations of fulminant meningococcemia."

Bohle & Krecke C94,892/59: SSP-G-like changes were observed in 4 cases of meningococcal sepsis conducive to the Waterhouse-Friderichsen syndrome.

May D83,972/60: Critical review of data concerning the possible relationship between the SSP and the Waterhouse-Friderichsen syndrome.

Montgomery & Olafsson D84,266/60: A case of Waterhouse-Friderichsen syndrome due to varicella in an adult.

Stuber & Hitzig G33,276/61: In patients with the Waterhouse-Friderichsen syndrome, "the post-mortem findings of fibrin deposits in the capillaries in parenchymatous organs of these patients suggest intravascular coagulation processes very similar to the experimental Sanarelli-Shwartzman phenomenon."

Neuman et al. G33,274/62: "Three cases of Waterhouse-Friderichsen syndrome with

Shwartzman-like phenomenon were reported. All 3 showed varying degrees of skin sloughs and gangrene with resulting deformities." Review of several additional cases in which survivors of the Waterhouse-Friderichsen syndrome suffered spontaneous amputations of fingers or entire extremities.

Ratnoff & Nebehay D23,901/62: Afibrinogenemia and other coagulation defects were detected in a fatal case of Waterhouse-Friderichsen syndrome due to pneumococcus.

Tabbara et al. G24,134/62: A case of fatal septic abortion with hemorrhagic infarction of the adrenals and renal medullary congestion was interpreted as a Waterhouse-Friderichsen syndrome induced by the combined effect of pregnancy and stress of infectious origin.

Margareten et al. E22,659/63: In a series of 51 children with adrenal hemorrhage associated with bacterial infection (Waterhouse-Friderichsen syndrome), the pathogens most commonly found were *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aerobacter aerogenes*, *Escherichia coli* and *Hemophilus influenzae*. The adrenal changes were often accompanied by the formation of fibrin thrombi in the renal glomeruli, renal cortical necrosis, and other lesions characteristic of the SSP-G. A localization of the thrombi in the hyperemic adrenal glands "may be an accident of the stress response to infection." . . . "Histologically, and by context, the lesion resembles the generalized rather than the local Shwartzman reaction."

Levin & Cluff G87,713/64: Massive bilateral adrenal cortical hemorrhages appeared in rabbits which were prepared with Thorotrust and injected a few hours later with endotoxin (kind not stated) or ACTH. Administration of multiple doses of cortisol, soon after the Thorotrust or ACTH injections, suppresses the adrenal hemorrhagic reaction, otherwise elicited by endotoxin. It is concluded "that adrenal hemorrhage observed during sepsis, as in the Waterhouse-Friderichsen syndrome, may be attributable to endotoxemia occurring during or shortly after stimulation of the adrenal cortex by infection."

Coury et al. G26,520/65: Review of the literature with personal observations showing that acute stress can be the cause of bilateral adrenal hemorrhages and the Waterhouse-Friderichsen syndrome, especially in patients having received anticoagulant therapy.

Gunschera F39,653/65: On the basis of a literature review and of personal observations, the Waterhouse-Friderichsen syndrome is considered to be a manifestation of the SSP, complicated by extreme adrenal stimulation as part of a general adaptation syndrome to

the massive infection. Consequently, cortisone treatment has been used, apparently with success.

Levin & Cluff G25,181/65: In rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, unlike the SSP this response is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment. The adrenal hemorrhages are also prevented by certain adrenergic blocking agents such as phenoxybenzamine, alderlin, or 1(3',4'-dichlorophenyl)-2-(isopropylamino) ethanol. Since ACTH, Thorotrast and *E. coli* endotoxin all increase the blood-cortisol level of the rabbit, it is assumed that the localization of the hemorrhages is connected with increased adrenocortical activity.

Typhoid Fever. *Herz G24,641/17:* Detailed description of the hemorrhagic form of typhoid and paratyphoid as observed during the First World War in the Austrian army. The salient manifestations were hemorrhages from the nose, gingiva, stomach and intestine with hemorrhagic transformation and blister formation in the exanthema, hemoptysis, and melena. The bleeding time was normal, blood coagulation often accelerated and there was thrombocytopenia. Histologic examination showed damage to the endothelia of capillary and precapillary vessels with diapedesis of erythrocytes.

Stolyhwo G21,662/35-36: Attention is called to the fact that in patients with typhoid fever, there are hemorrhagic and necrotic lesions, not only in the intestinal tract and lung, but also in the skin; thus the picture is very similar to that of the SSP. A relationship between typhoid and the SSP is also suggested by the observation that the urine of patients with typhoid fever contains substances that can prepare the skin of the rabbit for the elicitation of an SSP-L by a subsequent i.v. injection of typhoid toxin.

Stolyhwo E69,174/36: The urine of rabbits given *B. typhosus* endotoxin i.v., as well as that of patients suffering from typhoid, contains SSP-active substances. If such urine is injected i.c. into rabbits 24 hrs. prior to the i.v. injection of *B. typhosus* endotoxin, typical hemorrhagic skin lesions result. This observation, and the fact that hemorrhagic and necrotic lesions do occur in the intestinal mucosa and skin of typhoid patients suggest that the SSP may participate in the pathogenesis of typhoid fever.

Urbach et al. B19,915/44: In a patient who received three doses of typhoid vaccine at 24

hr. intervals as a treatment for infectious arthritis, a typical SSP-G developed with widespread cutaneous and visceral petechiae as well as renal, hepatic and adrenal necrosis. Although several similar cases could be gathered from the literature, this appears to be the first report in which the SSP-G has been recognized as such in man.

Love & Driscoll B19,916/45: A patient received two injections of antityphoid vaccine with a 24 hr. interval for nonspecific therapy. He died with generalized petechiae throughout the parenchymal organs, with massive necrosis of the liver and kidneys indicating an SSP-G.

Rössle G17,852/46: Typhoid vaccination performed during the incubation stage of typhoid is often associated with generalized hemorrhagic necrosis, especially in the intestine, mesentery, spleen, and in typhoid granulomas of the liver. The response resembles the SSP-G.

Hansen G21,299/47: In several patients suffering from typhoid, treatment with typhoid vaccine was followed by a generalized hemorrhagic reaction, interpreted as an SSP-G.

Honecker G21,298/47: In a patient who received three subcutaneous injections of typhoid-paratyphoid vaccine, pronounced hemorrhagic necrosis developed at the injection site following the last injection. The phenomenon is interpreted as an SSP-L.

Höring D72,058/48: The SSP-like manifestations which may occur during treatment of typhoid with Pyriter (a suspension of killed *E. coli*) can be avoided if the author's treatment schedule is strictly observed.

Reich D92,102/48: In typhoid patients treated with Pyriter, a fatal generalized hemorrhagic diathesis can occasionally result, presumably through the production of an SSP-G.

Geks G23,262/50: It is not possible to produce an SSP-L either in the guinea pig or in the rabbit by two injections of Pyriter under conditions in which *E. coli* filtrates are active. It is concluded that lysis of the organisms is necessary to liberate the active principle. The claim of Reich (D92,102/48) that Pyriter can produce an SSP when used for therapeutic purposes in patients with typhoid fever has been contested by Höring (D72,058/48) and is also rejected by the present author.

Scarlet Fever. *Biernacki & Dykes G27,364/13:* A case of fatal purpura following scarlet fever in which "the purpuric areas showed a definite inflammatory element."

Meleney G21,658/30: An eight-year-old girl received a small prophylactic dose of scarlet fever serum into the right buttock when an

older sister came down with the disease. Four days later she herself developed typical scarlet fever, and was given a large dose of scarlet fever antitoxin into the left buttock. The swelling caused by this second injection gradually progressed to hemorrhagic gangrene. The author considers specific hypersensitivity or the SSP as possible explanations of this complication.

Shwartzman et al. G24,322/36: In certain cases of scarlet fever, the pathologic changes are reminiscent of the SSP-G.

Koller et al. B56,576/50: Two cases of scarlet fever with purpura fulminans in which factor V was completely missing from the blood.

Storck G21,672/51: The cutaneous hemorrhagic responses in pneumococcal or meningococcal sepsis and purpura fulminans after scarlet fever are assumed to be manifestations of the SSP. As in the SSP of the rabbit, there is a drop in factor V with hemorrhages from maximally dilated vessels.

Rocky Mountain Spotted Fever. *McKay E4,788/65:* Rocky Mountain spotted fever provides an excellent illustration of the association of hemorrhagic phenomena with rickettsial disease. It is accompanied by thrombocytopenia, focal tissue necrosis and disseminated fibrin thrombosis of arterioles, capillaries and venules. Presumably, the clots are secondary to endothelial damage, but release of intrinsic prothrombin activator from damaged platelets may also play a role.

Epidemic Hemorrhagic Fever. *McKay E4,788/65:* Epidemic hemorrhagic fever is presumably an infectious disease, although no specific pathogen could be demonstrated. It "has a number of features suggestive of a participation of disseminated intravascular coagulation in its pathogenesis. These include thrombocytopenia, diminished prothrombin activity, prolonged coagulation time, multiple hemorrhages, shock, and the sequelae commonly associated with intravascular coagulation, i.e., infarct necrosis of the anterior hypophysis and acute renal failure (lower nephron nephrosis). Direct evidence of microscopic thrombosis has yet to be obtained."

Leishmaniosis. *Gatto G25,243/39:* An SSP-L can be produced in the rabbit by two injections of Leishmania donovani filtrate. The author concludes that "the hemorrhagic phenomena observed in visceral leishmaniosis may possess a mechanism similar to that of Sanarelli-Shwartzman's phenomenon."

Favre-Gilly et al. G26,877/51: In the hemorrhagic form of Leishmaniosis, thrombocytopenia may be associated with complete absence of megakaryocytes in the bone marrow,

fibrinogenopenia, hypoprothrombinemia, defective clot retraction, prolongation of the bleeding time, and vascular fragility.

McKay E4,788/65: Leishmaniosis, or Kala-azar may be associated with intravascular coagulation because "(1) The organisms could act as particulate objects and induce platelet agglutination and clotting when released from a host cell upon its death. (2) The histiocyte undergoing necrosis could release tissue thromboplastin and initiate clotting by this agent. (3) The extent of clotting initiated by both the parasite and tissue thromboplastin would be greatly increased if the parasitism of the reticuloendothelial system resulted in reticuloendothelial 'blockade.'"

Cholera. *Sanarelli B78,422/24:* In rabbits given a normally subthreshold dose of cholera vibrios i.v., an acute cholera-like condition can be produced by the i.v. injection 24 hrs. later of colitoxin. At the same time, the invasion of the gastrointestinal tract by live cholera vibrios is augmented. Apparently here, the cholera infection is revived and aggravated by the colitoxin.

De et al. E59,120/54: Partial or complete renal cortical necrosis with medullary congestion is frequently seen in patients who die of cholera. Thromboses were not observed and the lesions were ascribed to extreme cortical vasospasm, but proliferative glomerular nephritis may occur in chronic cases.

McKay E4,788/65: Although Sanarelli's first experiments were performed with cholera vibrios, disseminated intravascular coagulation seldom occurs in clinical cases of cholera.

Malaria. *McKay E4,788/65:* "Malarial infections, particularly with *P. falciparum*, are characterized by intravascular hemolysis, fever, shock, sudden death, acute renal failure, and focal necrosis in various organs, such as the liver, spleen, kidneys, brain, and adrenals. Hemolytic anemia and leukopenia are part of the acute paroxysm. Occasionally, a severe hemorrhagic diathesis may occur. Disseminated intravascular coagulation has been observed at autopsy in the form of thrombi in the capillaries and arterioles of the liver, kidney, adrenals, and brain."

Subacute Bacterial Endocarditis. *Pagel G27,013/49:* Cyanosis with necrosis of the "acra" (e.g., nose, ear, finger tips) commonly occurs in subacute bacterial endocarditis. The phenomenon is ascribed to microthromboses rather than embolisms because of its symmetrical distribution and histologic characteristics. The term "acronecrosis" is suggested to describe this phenomenon although similar thrombi may also develop in the smaller branches of the pulmonary arteries.

Varicella. *Montgomery & Olafsson D84,266/60:* A case of Waterhouse-Friderichsen syndrome due to varicella in an adult.

Charkes D3,749/61; McKay E4,788/65: Five major forms of purpuric chickenpox are described: Febrile purpura, malignant chickenpox with purpura, postinfectious purpura, purpura fulminans and anaphylactoid purpura. In general, purpuric chickenpox is associated with thrombocytopenia and widespread hemorrhages not only in the skin but also in internal organs. Sometimes, there is fibrinoid necrosis of vessels, thrombosis, hemorrhagic necrosis, gangrene, and occasionally bilateral adrenal cortical necrosis.

Vaccinia. *Kozlowska & Sztymela D33,377/62:* A 2½-year-old girl with acute leukemia died of generalized hemorrhagic vaccinia three months after vaccination against smallpox. Hemorrhages were noted not only at the site of vaccination and in the vaccinia pustules, but also in the mucosa of the jejunum and stomach.

Purpuric Smallpox. *Ikeda G24,333/27:* Purpuric smallpox is a rare and invariably fatal variant of variola in which hemorrhagic diathesis is the prominent feature. [Although no thromboses are mentioned in this report, the description of the pathologic lesions suggests the possibility of a relationship to other forms of the THP (H.S.).]

McKay E4,788/65: Attention is called to a severe form of smallpox with hemorrhagic diathesis, thrombocytopenia and disseminated intravascular thrombosis involving vessels of microscopic size in many organs.

Pseudomonas Septicemia. *Rapaport et al. F15,597/64:* In a patient with pseudomonas septicemia, there developed a coagulopathy with extensive intravascular blood clotting and widespread fibrin thrombi in the renal glomerular capillaries. "These findings clearly demonstrate that bacterial endotoxin may induce a generalized Shwartzman reaction in man."

Tuberculosis. *Gougerot G23,005/36:* The production of a THP by *E. coli* or its toxins in tuberculous animals is designated as the Sanarelli-Shwartzman-Bordet phenomenon. It probably plays a role in certain hemorrhagic manifestations of patients with tuberculosis.

Gougerot & Hamburger G22,527/37: In a syphilitic patient, tuberculin i.c. produced a topical necrosis of the tuberculin-reaction type but, at the same time, also a purpuric response in an old syphilitic scar at a distance from the injection site. This is interpreted as a Shwartzman-Sanarelli-Bordet type of response.

Gougerot & Degos G22,251/41: An SSP-like

reaction is elicited in tuberculous rabbits by the i.v. injection of *E. coli* endotoxin at a site prepared on the previous day by the i.c. injection of tuberculin. This is referred to as the Sanarelli-Shwartzman-Paul Bordet phenomenon. When given i.v., tuberculin can also act as a provocative factor, e.g., in tuberculous guinea pigs in which it elicits hemorrhagic responses at sites where talcum produced a sterile peritonitis. Several apparently quite comparable reactions have been observed in tuberculous patients.

Urbach & Goldburgh G21,529/42: In one patient extremely minute i.c. doses of a purified protein derivative (PPD) of tuberculin induced severe hemorrhagic necroses at the site of injection as well as fever and thrombocytopenia. "This is to be considered not as the type of severe tuberculin reaction occasionally seen in tuberculous patients, but an expression of hypersensitivity, which corresponds, both clinically and histologically, to the Shwartzman phenomenon."

Holzberger & Packalén G22,357/54: In guinea pigs infected with *M. tuberculosis*, old tuberculin i.v. is less effective than *E. coli* filtrate i.v. in producing focal injury at sites of dermal tuberculin inflammation. Direct injection of *E. coli* endotoxin into the sites of moderate tuberculin reactions causes hemorrhagic necrotic lesions in tuberculous guinea pigs, but sterile broth has a similar, though much less pronounced, effect. The mechanism of this type of THP "might well be analogous to the Shwartzman-like phenomenon which Black-Schaffer and associates (G22,334/50) produced in sensitized animals through a mixed single injection of homologous antigen and a Shwartzman-preparatory toxin."

Stetson G22,085/55: In hypersensitive animals, large doses of tuberculin i.c. produce hemorrhagic necrosis which appears several hours after the injection and resembles endotoxin-induced lesions.

Kiss E89,874/62: General review concerning the possible role of the SSP in the development of tuberculosis in man. [No new experimental findings (H.S.).]

Kiss G24,105/62: The fact that recurrences of tuberculous lesions in adults usually occur in the immediate vicinity of old foci, is ascribed to a mechanism homologous to that of the SSP.

Ascaridosis. *Vanni G22,353/38:* If the filtered coelomic fluid of ascaris (*Parascaris equorum*) is injected i.c. and 24 hrs. later i.v. in the rabbit, a typical SSP-L develops concurrently with visceral hemorrhages. It is assumed that certain symptoms of patients with ascaridiosis may be due to the same phenomenon.

Hog Cholera. Röhrer E59,724/32: Bilateral renal cortical necrosis with hyaline deposition in the renal vessels and multiple hemorrhagic necroses in various organs is observed in hog cholera. [The lesions resemble those of the SSP-G (H.S.).]

Shwartzman et al. G24,322/36: In hog cholera, hyaline thrombosis of the renal glomerular capillaries is frequently found and this may be indicative of an SSP-like mechanism.

McKay E4,788/65: Hog cholera is a virus disease affecting swine. It is often associated with hemorrhages in various organs including the kidneys and the mucosa of the renal pelvis. Bilateral cortical necrosis has been obtained by the i.v. injection of the pure virus. Here, the vasa afferentia and most of the glomerular loops showed hyaline degeneration or closure.

Swine Erysipelas. Shwartzman et al. G24,322/36: In swine erysipelas, renal cortical necrosis and hyaline thrombosis of the glomerular capillaries is common. This may be indicative of an SSP-like mechanism.

Mouse-pox. Fenner G25,096/49: Mouse-pox is a disease caused by the ectromelia virus which leads to ulcerating lesions of the feet, tail and snout, often conducive to spontaneous amputation of the extremities. It may be associated with hemorrhagic foci in the kidneys and occasionally in the bladder, as well as foci of hepatic necrosis. The acral distribution of the necroses is reminiscent of the anaphylactoid type of THP that can be produced in the rat, but there is no evidence of any wide-spread hemorrhagic thrombosis in mouse-pox.

RENAL DISEASES

Among the lesions most characteristic of the SSP-G are *hyaline thrombosis of the renal glomerular capillaries and bilateral renal cortical necrosis*. The occurrence of these changes in patients with generalized infections (particularly the Waterhouse-Friderichsen syndrome and septic abortion), as well as in eclampsia, amniotic-fluid embolism and abruptio placentae, are discussed in other sections of this chapter. Suffice it to point out here that bilateral cortical necrosis with hyaline thrombosis of the glomerular capillaries and afferent arterioles, first described by Juhel-Rénouy (1886), has subsequently been observed in patients who died of various systemic infections, intoxications and crush injuries. The condition is a particularly common accompaniment of various diseases of pregnancy, which occurs frequently in combination with thrombohemorrhagic lesions in the liver, spleen, lungs, adrenals, brain, and other tissues.

Allegedly, certain forms of toxic *nephritis*, particularly focal and embolic glomerular nephritis and diabetic glomerulosclerosis may also be related to the nephropathy of the SSP-G.

Renal Cortical Necrosis. Juhel-Rénouy G22,712/1886: First description of bilateral renal cortical necrosis in a girl who died from anuria following scarlet fever. The glomeruli and the afferent arterioles were filled with thrombi.

Bradford & Lawrence G25,408/1898: First description of renal cortical necrosis in a woman with eclampsia. There was hyaline deposition in the renal glomerular capillaries and thrombosis with inflammation in the interlobular arteries.

Jardine & Teacher 60,384/11: Two cases of bilateral renal cortical necrosis which developed during eclampsia.

Herzog E80,521/13: Bilateral renal cortical necrosis with hyaline fibrin thrombi in the glomeruli and afferent arterioles in a case of

fatal eclampsia. Similar hyaline thrombi were seen in a man with lobar pneumonia and a ten-year-old girl with purulent peritonitis.

Scriver & Oertel 63,237/30: Review of the literature and personal observations reveal that renal cortical necrosis occurs most commonly in eclampsia with retroplacental hemorrhage, but it is also seen after various infections outside of pregnancy. "The very high intravascular fat contents of some of these cases suggest an associated hyperlipaemia." Fibrin thrombi are found in the glomerular capillaries as well as in the afferent and efferent glomerular vessels.

von Zalka D7,009/33: Review of the literature on symmetrical renal cortical necrosis. It is thought that the primary lesion is a toxic necrosis, with fibrinous transformation of the

wall of the interlobular arteries, which secondarily leads to glomerular thrombosis and necrosis of the cortical parenchyma.

Navasquez G22,068/35: Bilateral renal cortical necrosis occurs most commonly in pregnancy, but it is also seen following various infections and intoxication with dioxane or bacterial toxins.

Duff & More E63,272/41: Extensive review of clinical and experimental conditions conducive to bilateral renal cortical necrosis with thrombosis of glomerular capillaries. The capillary thrombi may consist of fibrin or merely of "masses of packed, conglutinated red blood cells." Sometimes, there are thrombi also in larger vessels.

Dunn & Montgomery G22,069/41: A review of the literature and numerous personally observed cases indicate that bilateral renal cortical necrosis, with fibrin thrombi in the interlobular arteries and glomerular capillaries, occurs both in pregnant and in nonpregnant patients. "The ultimate determining factor in bilateral renal cortical necrosis is extreme glomerular capillary dilatation with loss of plasma leading to inspissation of the blood and complete circulatory blockage in the kidney at this level."

Zuelzer et al. E61,667/51: Bilateral renal cortical necrosis often occurs in infants and children with diarrhea, dehydration and shock-like states. It may be associated with thrombosis and arteritis in the small vessels of the mesentery and small intestine.

Burt & Kearns G22,070/53: Bilateral renal cortical necrosis is most commonly found in association with eclampsia, abruptio placentae and hemorrhage, but it also occurs after burns, crush injury, and severe infection.

Rostenberg G21,665/53: Numerous observations are quoted in support of the view that "bilateral renal cortical necrosis and the Waterhouse-Friderichsen syndrome, arise on the basis of a Shwartzman mechanism."

Lauler & Schreiner C51,421/58: Bilateral renal cortical necrosis in an elderly patient, following shock after an automobile accident.

Humair G28,328/60: Bilateral renal necrosis in a seventy-year-old man with erysipelas and streptococcus septicemia is ascribed to the SSP-G, especially since the glomerular capillaries contained fibrinoid thrombi.

Goranow & Jurukowa E43,692/61: In 4 cases of bilateral renal cortical necrosis (developing after abruptio placentae, bronchopneumonia, postoperative shock or brain tumor), hyaline thrombi were constantly present in the renal glomerular capillaries, as well as in other vessels of the kidney, lung, hypophysis and

liver. Thrombosis of the renal vessels is considered to be the cause of the cortical necrosis.

Tessler & Hotchkiss G22,082/61: In bilateral renal cortical necrosis "the thrombosis and fibrin deposits are believed to be secondary phenomena, and are the result, not a cause, of the ischemia."

Vassalli & Richez G24,706/61: Detailed review on renal cortical necrosis in clinical and experimental medicine.

Lindqvist et al. D9,552/63: In a woman, septic abortion was followed by bilateral renal cortical necrosis with hyalinization of the glomerular capillaries and necrotic areas in the liver, spleen, adrenals and brain. There was also leukopenia, a generalized hemorrhagic diathesis, thrombopenia, hypoprothrombinemia, decreased plasma fibrinogen and skin necrosis after noradrenaline infusion. The syndrome is considered an equivalent of the SSP-G in man.

Naddachina & Lvova G30,461/64: The renal cortical necrosis and focal necroses in other organs that develop after septic abortion, are ascribed to the SSP.

Skjörten G22,099/64: Detailed description of the morphologic characteristics of glomerular fibrin precipitations in cases of bilateral renal cortical necrosis. Small round bodies with the staining characteristics of fibrin have also been found in the pituitary and cerebral vessels. There is evidence of intravascular coagulation in various forms of shock even if unaccompanied by renal cortical necrosis "and the relationship to the generalized Shwartzman reaction is pointed out."

Skjörten G28,487/64: Several cases of renal cortical necrosis with thromboses of the glomerular capillaries in males and females are attributed to the SSP.

Lower Nephron Nephrosis, Crush Syndrome.
Hardaway & McKay D95,869/59: Acute hemorrhagic pancreatic necrosis is produced in dogs by the intra-aortic infusion of human blood. The reaction is associated with intravascular clotting in the pancreas and other organs. A review of the literature shows that hemorrhagic pancreatitis in man is also frequently associated with thrombosis in veins and capillaries, as well as with lower nephron nephrosis.

McKay & Hardaway G26,439/59: Following release of a crush to the muscles of the dog, there was prompt activation of fibrinolytic and fibrinogenolytic enzymes with elevation of circulating fibrinogen and gradual decrease of platelets. No thrombi were observed, wherein the response differs from incompatible blood-transfusion reactions.

Allen D43,123/62: The renal changes in the "crush-syndrome" (which develops following crushing injuries), hemoglobinuric nephrosis, lower nephron nephrosis and myohemoglobinuric nephrosis are often virtually indistinguishable. The relationship of these changes to the THP is questionable, but intensely congested vasa recta, sometimes with hemorrhages into the renal medulla, and renal cortical necrosis suggest possible connections between these clinical conditions and the SSP-G.

McKay E4,788/65: The crush syndrome is closely related to lower nephron nephrosis and like the latter may be associated with a shift of the intrarenal circulation from the cortex towards the medulla. "The evidence that the 'crush syndrome' alters the blood coagulation mechanism and is responsible for the acute renal failure comes from the observation of thrombi in the small renal veins next to areas of tubular necrosis, and from studies of the crush syndrome in experimental animals."

Diseases of the Urinary Passages. *Cataliotti*

G28,645/38: An SSP-L can be produced in the urinary bladder of the rabbit by topical preparation followed by i.v. provocation with *E. coli* endotoxin. It is assumed that certain forms of hemorrhagic cystitis in man depend upon the SSP-mechanism.

Nephritis. *Christian G22,338/42:* A variety of experimental infections, as well as uranium nephritis in the rabbit, can copy the diverse forms of proliferative hemorrhagic and hyalinizing changes seen in patients with renal disease. "What happens depends more on the degree than on the kind of the injury inflicted on the glomerulus." Hence, we can "find identical appearances in the glomeruli resulting from different injurious actions affecting the kidney."

Fehr & Brunson G21,900/57: In rabbits in which an SSP-G-like response was elicited by bovine globulin s.c., followed by Liquoid or *E. coli* endotoxin i.v., the renal lesions resembled "focal" or "embolic" glomerulonephritis and the lesions of diabetic glomerular sclerosis as they occur in man.

DISEASES OF PREGNANCY

A generalized thrombohemorrhagic tendency with hyaline thrombosis of the glomerular capillaries, renal cortical necrosis, afibrinogenemia, thrombocytopenia and an increase in fibrinolytic and antithrombin titers is characteristic of the *obstetrical hemorrhagic syndrome*. It occurs with particular frequency in *amniotic-fluid embolism*, *abruptio placentae*, *septic abortion*, *eclampsia*, *missed abortion*, *intra-uterine death of the fetus*, *hydatidiform mole*, and particularly *traumatic deliveries*.

Since similar changes could be produced in animals by the intravenous injection of amniotic fluid or placental extracts rich in thromboplastin, it is generally assumed that the liberation of excessive amounts of thromboplastic substances from the placenta is the causative factor in all these conditions.

Obstetrical Hemorrhagic Syndrome in General. *Käser G21,300/56:* Review of the early history of the "obstetrical hemorrhagic syndrome" which occurs in women with eclampsia, missed abortion, septic abortion, hydatidiform mole, etc. Also report of personally observed cases in which eclampsia was associated with multiple hemorrhages, afibrinogenemia, thrombocytopenia, a decrease in factor V and an increase in the fibrinolytic and antithrombin titers.

Beller G27,366/57: Review on the disturbances of blood coagulation that occur in abruptio placentae, intra-uterine fetal death and amniotic fluid embolism.

Junghans C80,452/58: Following a rather difficult forceps delivery of her second (still-

born) child, a young woman developed symmetrical bilateral hemorrhagic necrosis of both renal cortices and adrenals. Since no fibrin thrombi were found, these lesions are not considered to be explicable on the basis of the SSP-G mechanism.

Beischer D10,558/61: In two patients with uterine hemorrhage during the last trimester of pregnancy (one complicated by Clostridium septicemia and possibly amniotic fluid embolism) hypofibrinogenemia was associated with multiple fibrin thrombi in various organs including the capillaries of the lung and of the renal glomeruli. There developed bilateral renal cortical necroses and anterior pituitary infarcts. The lesions resembled those of the SSP-G.

Elsner G24,364/63: Review of the literature on the "hypofibrinogenemic hemorrhagic diathesis (HFG)" elicited by abruptio placentae, intra-uterine retention of the dead fetus, amniotic fluid embolism, septic abortion and related conditions.

Neff & McKay F33,329/65: The obstetric shock syndrome is thought to be a manifestation of the SSP-G on the basis of a literature review and personal observations.

Abruptio Placentae. *Magara et al. E83,073/41:* A water soluble extract of human placenta, given i.v., causes abruptio placentae and retroplacental hemorrhages in the guinea pig and rabbit. The serum of patients with abruptio placentae, abortion and eclampsia exerts a similar effect, while that of normal pregnant women is ineffective except during labor. It is assumed that a placental factor may play a role not only in the development of pregnancy toxicosis and abruptio placentae but even in the induction of normal delivery.

Schneider B56,544/50: In rabbits, thromboplastin-containing rabbit placenta extracts i.v. cause pulmonary thromboembolism, cerebral hemorrhages and liver necrosis, especially if the animals are pregnant. Similar results are obtained by trauma to the placenta. Perhaps "following placental damage, material from the placenta might gain access to the maternal blood circulation, and initiate clotting. Thromboplastin is considered to be the chief one of these activators." The changes thus produced may represent an experimental counterpart of obstetrical shock and eclampsia.

Page et al. G22,348/51: Intravenous infusion of thromboplastin containing human placental extract produces fibrin deposition in the renal glomerular capillaries and in the hepatic vessels with blood sludging in arterioles, particularly those of the lungs. Sometimes, there are scattered hepatic necroses. These changes are ascribed to a coagulation defect similar to that seen in abruptio placentae. [Possible relations to the SSP are not considered (H.S.).]

Schneider B58,259/51: Disseminated intravascular coagulation with defibrination of the blood appears to be the underlying process in abruptio placentae, obstetrical shock, hemorrhagic diathesis of pregnancy, and eclampsia. It may lead to pulmonary edema and cardiac failure during gestation. Several pertinent cases are described. [No mention is made of any possible relation to the SSP (H.S.).]

Käser G21,676/52: In eclampsia combined with abruptio placentae, the blood may become incoagulable, presumably as a consequence of thromboplastin and/or plasmin formation in the abnormal placenta.

Jackson et al. G21,656/55: Seven cases of hypofibrinogenemia with thrombocytopenia occurred as a complication of premature separation of the placenta. In three additional patients, hypofibrinogenemia occurred as a complication of fetal death in utero, amniotic fluid embolism, and septic abortion respectively. "It is felt that the most likely mechanism for the production of the fibrinogen deficiency in these cases is the entrance into the maternal circulation of thromboplastic agents from the uterine contents with resultant intravascular defibrination."

McKay et al. G33,280/55: A case of fatal renal capillary thrombosis in a patient with squamous cell carcinoma of the cervix who had just been delivered by cesarean section is tentatively ascribed to the SSP-G.

Johnstone & McCallum G21,668/56: "A case of hypofibrinogenaemia developing in abruptio placentae is described: many fibrin deposits were found in the renal glomerular capillaries as well as in the pulmonary vessels, and this unusual distribution of the deposits was reproduced in rabbits by intravenous thromboplastin injections."

Lauler & Schreiner C51,421/58: Bilateral renal cortical necrosis following abruptio placentae.

Schneider C69,273/59: General review on the coagulation defect induced by abruptio placentae. The bulk of evidence suggests that in abruptio placentae normally occurring in women or artificially induced by trauma in the rabbit, thromboplastin enters the maternal circulation and causes wide-spread intravascular clotting, with defibrination and generalized tissue changes not unlike those of eclampsia.

Wuketich C85,685/60: Symmetrical bilateral renal cortical necrosis with thrombotic occlusions of renal arteries, and necroses in suprarenals and hypophysis, occurred in a 27-year-old woman following abruptio placentae during the sixth month of pregnancy. The lesions are ascribed to an SSP-G caused by thromboplastin liberation from the placenta.

Moore D95,837/61: Periplacental hemorrhage and fetal death with renal cortical and/or liver necrosis occur in late-pregnant rats given progesterone. These changes are ascribed to vasoconstriction, and their resemblance to human abruptio placentae is noted.

Nilsen G33,247/63: Systematic study of the changes in blood clotting factors associated with hypofibrinogenemia in premature separation of the placenta.

McKay E4,788/65: Approximately 10% of patients with premature separation of a normally implanted placenta during the last trimester of gestation develop a severe hemorrhagic diathesis with petechiae or ecchymoses of the skin, hemorrhage from the mucous membranes of the mouth or rectum, and massive uncontrollable hemorrhage from the placenta. There is a depletion of circulating fibrinogen, prothrombin and Ac-globulin, sometimes with increased fibrinolytic activity in the blood and thrombocytopenia. Fibrin thrombi are frequently found in the lungs, liver, adrenals, kidneys, intestine, spleen, pituitary, brain and, more rarely in other organs. The renal lesions may result in lower nephron nephrosis or bilateral cortical necrosis.

Septic Abortion, Chorioamnionitis, Placentitis. Jeddelloh E42,127/32: Two cases of bilateral renal cortical necrosis following septic abortion, in which typical hyaline thrombi were found in the glomerular capillaries.

O'Sullivan & Spitzer D73,668/46: Review of the literature and report on some personally observed cases of bilateral renal cortical necrosis associated with thrombosis of renal vessels and/or hyaline thrombi in the glomerular capillaries following septic abortion.

Conley et al. G21,652/51: Afibrinogenemia in a patient with septic abortion, acute yellow atrophy of the liver and bacteremia due to *E. coli*.

Adebahr G22,084/55: In a woman who died from septic abortion, multiple cutaneous petechiae were associated with bilateral renal cortical necrosis. The disease is ascribed either to the SSP-G or to the Trueta shunt mechanism.

Studdiford & Douglas D8,983/56: Septic abortion may lead to adrenal hemorrhages and other changes similar to those of the Waterhouse-Friderichsen syndrome, owing to infection by coliform organisms (*E. coli* or *Aerobacter aerogenes*). [The patients received epinephrine for the relief of shock; hence, the combined action of this hormone and the bacterial toxins may have been of pathogenic importance (H.S.).]

Bohle & Krecke C94,892/59: SSP-G-like changes were observed in three patients with septic abortion.

McKay et al. C75,747/59: Organ lesions similar to those of the SSP-G are observed in women with septic abortion or premature rupture of the membranes associated with chorioamnionitis and placentitis. The most common infective organism is *E. coli*. There are disseminated intravascular clots with renal

cortical necrosis and thrombosis of the glomerular capillaries, and sometimes hemorrhages and thromboses with necrosis in the adrenals, pituitary, pancreas and heart. Hyaline thrombi may also be found in the choroid plexus.

Pfau et al. C95,349/60: In a case of septic abortion, an SSP-G developed with fibrin thromboses in the kidneys, lung, liver, spleen and uterus. *E. coli* could be cultured from the spleen and bone marrow. In a second, similar case, the probable diagnosis of an SSP-G was based on the clinical course with complete defibrination of the blood and with typical changes of the coagulation system as well as on a favorable response to heparin.

Pfau C94,038/60: In two women, an SSP-G developed as a consequence of septic abortion. In one case, the diagnosis was verified by the presence of fibrin coagula in various organs and in both cases there was a pronounced drop in blood fibrinogen.

Lasch et al. G25,137/61: A woman was in deep shock with a generalized hemorrhagic tendency and signs of "consumption coagulopathy" after abortion with *E. coli* sepsis. Heparin effected a dramatic recovery.

Dellenbach et al. D85,446/62: A woman in whom an SSP-G-like syndrome developed following an abortion complicated by septicemia caused by coliform organisms.

Fazekas & Jakabovits E72,488/62: In three patients with septic abortion, there were bilateral adrenal hemorrhages with capillary thromboses and renal changes described as "necrotizing nephrosis."

Jabłoński & Drabina E56,234/62: In several cases of septic abortion, an SSP-G-like syndrome developed. Biopsy specimens of the diffuse cutaneous hemorrhages showed no fibrin coagula, but this may be because 5 days had elapsed between the appearance of the lesions and the histologic study, during which time fibrinolysis may have set in.

McCally & Vasicka D16,097/62: A case of abortion with sepsis by *E. coli*, complicated by shock (unrelated to blood loss), acute thrombocytopenia and hypofibrinogenemia. "The clinical and autopsy findings are identical with those produced in the experimental animal by intravenous injections of bacterial endotoxin, i.e., the generalized Shwartzman reaction." (Hyaline thrombi in renal glomerular capillaries and placental sinuses, with thrombohemorrhagic necroses in the adrenals, liver and gastro-intestinal tract.)

McKay D14,183/62: In a woman with septic abortion there developed a typical SSP-G with hyaline thrombosis of the glomerular capil-

laries, disseminated intravascular coagulation with deposits of fibrin in other organs and defibrination of the blood.

Adebahr E48,703/63: In a series of 100 deaths following abortion, 10 cases combined with sepsis were associated with typical manifestations of the SSP-G. Massive treatment with antibiotics is thought to liberate bacterial endotoxins which then provoke the response. Numerous additional cases are collected from the literature.

Decenzo et al. D9,959/63: Septic abortion with bacteremia due to coliform organisms is frequently associated with endotoxin shock and microthromboses with hemorrhagic necrosis in different organs, which are ascribed to the SSP-G.

Josey & Szeiklies D64,820/63: Hypofibrinogenemia often follows septic abortion and the autopsy findings resemble those of the experimental SSP-G in the rabbit. After a review of the relevant literature, one non-fatal case of septic abortion, accompanied by moderate hypofibrinogenemia and thrombocytopenia is described in which the infective organisms isolated were *Proteus* and *Aerobacter aerogenes*. "The pattern of observed hemostatic alterations appears to be analogous to that exhibited by experimental animals subjected to the generalized Shwartzman reaction."

Lindqvist et al. D9,552/63: In a woman, septic abortion was followed by bilateral renal cortical necrosis with hyalinization of the glomerular capillaries and necrotic areas in the liver, spleen, adrenals and brain. There was also leukopenia, a generalized hemorrhagic diathesis, thrombocytopenia, hypoprothrombinemia, decreased plasma fibrinogen and skin necrosis after norepinephrine infusion. The syndrome is considered an equivalent of the SSP-G in man.

de Anta & Mateu-Aragonés G28,486/64: A case of septic abortion with hemorrhagic diathesis is ascribed to the SSP.

Coleman G21,831/64: Septic shock in pregnancy is viewed as a manifestation of the SSP-G.

Florek F12,519/64: Literature on the preparation by pregnancy for the elicitation of an SSP-G by bacterial toxins in animals and by infections in women. Hypofibrinogenemia and intravascular precipitation of fibrin in the capillaries of the lungs, liver and intestines are common in patients with septic abortion. This may be a modification of the SSP-G.

Niesert et al. G22,077/64: Case reports of SSP-G-like manifestations following septic abortion.

Hjort & Rapaport G32,971/65: Detailed re-

port on 21 patients with gram-negative septicemia following abortion strongly suggests participation of the SSP-G in the resulting coagulopathy.

Bohle G34,275/60: In two cases of presumably criminal abortion, manifestation of the SSP-G (fibrin precipitates in the renal glomerular capillaries as well as in the microcirculation of the adrenals, lung and liver) were observed both in the maternal and the fetal organism.

McKay E4,788/65: Literature on disseminated intravascular coagulation following infected abortion and premature rupture of the membranes with chorioamnionitis and placentalis. Here, the THP apparently results from hypo- or afibrinogenemia with platelet accumulation and fibrin thrombi in the lumens of small vessels, including those of the renal glomerular capillaries. The condition is frequently associated with renal cortical necrosis.

Kut F52,393/65: In a woman with septic abortion there was thrombosis of the sagittal sinus and other cerebral veins combined with adrenal hemorrhages, "crush kidney," a hemorrhagic infarct in the lung, cutaneous petechiae and thromboses of the utero-vaginal and femoral veins. The syndrome was interpreted as an SSP-G due to bacterial endotoxins.

Amniotic-Fluid Embolism. *Steiner & Lushbaugh B40,676/41:* First description of the syndrome of amniotic-fluid embolism. Clinically, it is characterized by shock during or soon after labor, and anatomically by widespread embolism of small pulmonary arteries, arterioles and capillaries with particulate matter such as is found in amniotic fluid, and by meconium. The disease can be duplicated in rabbits by the i.v. injection of human amniotic fluid and meconium.

Weiner et al. G26,133/49: Uncontaminated sterile amniotic fluid acts like thromboplastin or oxalated plasma in vitro. It also possesses anti-hemophilic properties.

Weiner & Reid G26,140/50: The hemorrhagic diathesis and the formation of microthromboses in amniotic-fluid embolism are ascribed to the coagulant activity of amniotic fluid and the resulting consumption of fibrinogen.

Bohle & Krecke C94,892/59: SSP-G-like changes in women with premature detachment of the placenta and amniotic fluid embolisation.

Brozman E99,641/61: In a woman who died of amniotic fluid embolism during delivery, the pulmonary vessels contained thrombi consisting predominantly of platelets with very little fibrin.

McKay E4,788/65: The THP consequent to amniotic fluid embolism is presumably due to the passage of particulate matter within the amniotic fluid into the venous channels of the uterus and thence into the general circulation. "Lacerations of the membranes or placenta, separation of the placenta, open uterine sinuses following placenta previa, and uterine rupture may be the portals of entry."

Hydatidiform Mole. *Talbert et al. D7,779/61:* Disseminated thromboses are rare in patients with hydatidiform moles. Yet they can occur as a consequence of an acquired coagulation defect and may lead to typical fibrin thromboses in renal glomerular capillaries, lungs and adrenals.

McKay E4,788/65: The occurrence of disseminated intravascular coagulation in connection with hydatidiform mole, though rare, has considerable theoretical interest; it represents the clinical counterpart of defibrination produced in animals by the i.v. injection of placental extracts. It may be associated with widespread thrombosis of the renal glomerular capillaries. Possibly, liberation of tissue thromboplastin from necrotic trophoblast or decidua is of pathogenic importance here.

Eclampsia. *Bradford & Lawrence G25,408/1898:* First description of renal cortical necrosis in a woman with eclampsia. There was hyalin deposition in the renal glomerular capillaries and thrombosis with inflammation in the interlobular arteries.

Jardine & Teacher 60,384/11: Two cases of bilateral renal cortical necrosis in eclampsia.

Herzog E73,475/13; E80,521/13: Three cases of widespread fibrin thrombosis in the renal glomerular capillaries following lobar pneumonia, purulent peritonitis and eclampsia respectively. In an eclamptic woman, there was also bilateral cortical necrosis of the kidneys. Earlier pertinent publications are reviewed.

Schüppel G22,079/14: In a case of eclampsia with bilateral renal cortical necrosis, the glomerular capillaries and afferent arterioles exhibited hyaline thrombi.

Shwartzman et al. G24,322/36: The pathologic changes, and especially the renal cortical necrosis of eclampsia, suggest an SSP-like pathogenetic mechanism.

Dill & Erickson 91,301/38: An eclampsia-like syndrome occurs in pregnant dogs and rabbits following renal artery constriction.

Greene G25,944/39: In rabbits subject to a spontaneous disease of pregnancy reminiscent of eclampsia, treatment with crude anterior pituitary extracts towards the end of pregnancy elicited this disease (characterized by

bilateral renal cortical necrosis and lesions in the liver and kidneys) with great frequency.

Magara et al. E83,073/41: A water soluble extract of human placenta, given i.v., causes abruptio placentae and retroplacental hemorrhages in the guinea pig and rabbit. The serum of patients with abruptio placentae, abortion and eclampsia exerts a similar effect, while that of normal pregnant women is ineffective, except during labor. A placental factor may play a role, not only in the development of pregnancy toxicosis and abruptio placentae, but even in the induction of normal delivery.

Schneider G24,554/47: The substance in placental extracts which causes thrombosis is thromboplastin, while the blood-borne inactivator of this material is antithromboplastin (as judged by in vivo and in vitro assays). Thromboplastin may be responsible for the development of eclampsia.

Symeonidis B32,969/49: An eclampsia-like syndrome is induced in rats by large doses of progesterone given during the last third of pregnancy. There is abortion or resorption of the embryos, albuminuria, azotemia, edema, and hypertension. "The lesions in other organs especially in the liver and the kidney, were similar to those of human eclampsia. These were peripheral lobular necrosis of the liver, with capillary dilatation, fibrin thrombi, and hemorrhages, fibrin thrombi in glomeruli, thickening of the glomerular basement membrane, and tubular degeneration and necrosis in the kidney."

Magara E83,075/50: An aqueous placental extract given i.v. to pregnant guinea pigs or rabbits produced retroplacental hemorrhage with abruptio placentae. The liver showed fibrin thrombi in the small portal veins with hemorrhage into the vessel wall and intense capillary dilatation, resulting in necrosis. Eclampsia-like changes were also found in the kidney, heart and lungs. The active factor is thought to play a role in the pathogenesis of eclampsia.

Schneider B58,008/50: Thromboplastin containing placental extracts i.v., or trauma to the placenta can produce a generalized THP with disseminated minute thrombi hemorrhages and necroses in the rabbit. Thromboplastin release from the placenta may play a role in the pathogenesis of eclampsia and abruptio placentae.

Masson et al. B70,138/52: In rats rendered hypertensive by desoxycorticosterone + unilateral nephrectomy + NaCl renin-containing renal extracts elicit an "eclampsia-like syndrome" associated with wide-spread thrombotic hemorrhagic lesions in various organs. Fibrin

thrombi occlude the renal glomerular capillaries as well as capillaries and arterioles in other parts of the body. Many of the arterioles show homogenization of their walls.

McKay et al. B88,756/53: "Toxic material suddenly released into the maternal blood stream is responsible for the deposition of fibrin, the hemorrhages and necroses, and the acute clinical symptoms of shock, anuria, and hemorrhage in toxemic patients with premature separation of the placenta and in eclamptic patients, and that these conditions are manifestations of the generalized Shwartzman phenomenon in human beings." This view is supported by the fact that in pregnant animals a single injection of bacterial toxin suffices to produce an SSP-G.

Käser G21,300/56: Review of cases in which eclampsia was associated with multiple hemorrhages, afibrinogenemia, thrombocytopenia, a decrease in factor V and increased fibrinolytic and antithrombin activity.

Komuro G24,699/61: Unlike the serum of normal pregnant women, that of patients with eclampsia or uterine cancer produces an "SSP-L" when given in two injections to rabbits.

McKay & Goldenberg G15,616/63: In pregnant rats kept on a diet low in vitamin E and supplemented by oxidized cod-liver oil, there

develops an SSP-G and a variety of pathologic changes in the placenta similar to those of human pregnancy toxicosis.

McKay & Corey G33,291/64: Brief review of the literature on cryofibrinogen (also referred to as "contractininogen"), heparin precipitable fraction or HPF indicating that the blood concentration of this material rises not only in toxemia of pregnancy but also in rheumatic fever, rheumatoid arthritis, acute bacterial infections, cancer and, to a lesser extent, even in normal pregnancy.

Kyank F37,252/65: Theoretic arguments in favor of the view that placental ischemia induced by "hysterotonin" can initiate an "SSP-G" which manifests itself as a pregnancy toxicosis.

McKay E4,788/65: The pathologic changes in eclampsia are very similar to those of the SSP-G. "The thrombi are of a special nature and consist of strands and homogeneous masses of fibrin, in most instances occluding the lumen of the vessel. In some larger arterioles, however, fibrin forms a coat lining the vessel wall and thins out toward the center. Only rarely can red cells, white cells, or platelets be found in the thrombi, which sets them apart from the usual antemortem thrombi of large vessels and from postmortem clots."

THE PURPURAS

Among the purpuras, Moschowitz's disease and anaphylactoid purpura have been considered to be closely related to the SSP.

Moschcowitz's disease (thrombotic thrombocytopenic purpura) is characterized by the triad of thrombocytopenic purpura, hemolytic anemia and bizarre neurologic and mental manifestations presumed to result from disseminated arteriolar occlusions. At autopsy, hemorrhages are found in many organs, particularly the heart, liver and kidney, with microthromboses in the arterioles and capillaries including those of the renal glomeruli.

There is some discussion about the composition of these thrombi; they consist of granular material, presumably degenerating thrombocytes, but in view of the well known difficulty of identifying damaged platelets on histologic sections, there is some doubt about this interpretation. In young lesions, fibrin has been demonstrated by histochemical and fluorescent-antibody techniques. In old lesions, the thrombi may assume a hyaline appearance suggesting transformation of fibrin into fibrinoid. Megakaryocytes are increased in the bone and may also be found occasionally in pulmonary capillaries. This presumably reflects an effort on the part of the organism to compensate for the thrombocytopenia that results from platelet aggregation in thrombi.

The associated hemolytic anemia is accompanied by the appearance of fragmented erythrocytes including "triangular," "helmet" and "burr" cells in the

peripheral blood; it has been suggested that damage to the erythrocytes may play a role in the formation of the thrombi.

Vascular factors also appear to be involved since aneurysmic dilations of small vessels are common in this disease. A relationship to the SSP-G has been suspected, mainly on the ground of morphologic resemblances.

Anaphylactoid purpura is a term applied to a variety of apparently related syndromes including Schönlein's purpura or peliosis rheumatica (in which articular symptoms are prominent), Henoch's purpura (associated with abdominal pain) and purpura simplex (with no particular localized sign). Although the mechanism of this disease is far from being clearly understood, it is assumed that allergic reactions play an important role in its development and that purpura fulminans, purpura hemorrhagica gangrenosa, and purpura necrotica merely represent particularly acute variants of the same condition. Here again, hyaline thrombi in the renal glomerular capillaries and multiple hemorrhages in the skin as well as in internal organs suggest that the SSP may play a pathogenic role. Anaphylactoid purpura sometimes tends to occur in combination with rheumatic fever, polyarteritis nodosa and glomerulonephritis, a fact which raised the question of some relationship to the collagen diseases.

Symptomatic afibrinogenemia is also associated with extensive thrombus formation and a "consumption coagulopathy"; hence, this disease has likewise been regarded as a special form of the SSP.

Hemorrhagic thrombocythemia is defined as a condition in which excessive hemorrhage occurs in the presence of a persistently high platelet count. Thromboembolic phenomena are inconstant but they can occur in association with alterations in the vascular wall. The disease is thought to be related to polycythemia vera and myelosclerosis.

The possible connection between the SSP and *purpura necrotica, dysproteinemic purpura* and *visceral thrombophlebitis migrans* has also been considered.

Moschcowitz's Disease. *Moschcowitz G22,715/25:* First publication on: "An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries—an undescribed disease." In a 16-year-old girl with petechiae of the skin, pallor and neurologic disturbances, the disease progressed to coma and death. Hyaline thrombi were found in the terminal arterioles and capillaries of the heart, liver and kidney. The lungs were edematous and congested.

Baehr et al. G23,057/36: In 4 cases of thrombotic, thrombocytopenic purpura with fever, the most striking hematologic changes were progressive anemia and marked thrombocytopenia. At autopsy, diffuse platelet thromboses of capillaries and arterioles were noted. "The enormous numbers of platelets caught in thrombosed capillaries in all the viscera were quite sufficient to have exhausted the available supply, and in this manner to have been responsible for the thrombocytopenia in the

peripheral blood." It is emphasized that the platelet thrombi here are chiefly located in precapillary arterioles and the arterial side of the capillary bed, while in the SSP they are predominantly found on the venous side of the capillary bed. Although Moschcowitz considered the thromboses as "hyaline" in his case, he based this conclusion merely on the eosinophilia of the occluding material.

Altschule G27,357/42: Detailed description of the platelet thrombi which occurred throughout the body in the capillaries of a patient with Moschcowitz's disease.

Fitzgerald et al. G27,012/47: The literature and several personally observed cases of Moschcowitz's disease are described and the name "thrombocytic acroangiothrombosis" is suggested for this malady. Histologically, the platelet thrombi in the capillaries, arterioles and venules are considered to be pathognomonic.

Gore G22,705/50: Moschcowitz's disease is characterized by an insidious onset, fever, purpura, anemia, thrombocytopenia, leukocytosis, reticulosis and a rapidly progressive fatal course in which severe nonlocalizing mental and neurologic signs are prominent. There is an increased bleeding time and defective clot retraction. The most striking features at autopsy are widespread petechiae and ecchymoses with disseminated thrombi in arterioles and capillaries, consisting predominantly of platelets. The disease is designated as a "disseminated arteriolar and capillary platelet thrombosis." Megakaryocytes are increased in the bone marrow and found occasionally in the capillaries of the lung. In the SSP, the thromboses are predominantly in venules and venous capillaries and the lesions are associated with inflammation: here, the thrombi are predominantly in arterioles and the lesions are bland.

Beigelman G27,352/51: Two cases of Moschcowitz's disease with multiple platelet thrombi in the capillaries of various organs including those of the renal glomeruli, heart, muscles, lung and skin were associated with signs of lupus erythematoses. "It is proposed that the platelet thrombosis syndrome be placed in the same category as the so-called collagen diseases, such as periarteritis nodosa, lupus erythematosus and dermatomyositis."

Orbison G23,268/52: In a case of thrombotic thrombocytopenic purpura, microaneurysms were found at the arteriolar-capillary junctions. Veins and venules were not affected. It is assumed that in this disease thrombocytopenia is associated with arterial damage.

Symmers B75,771/52: "Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy) is the name proposed for an unusual disease, possibly related to the so-called collagen diseases."

Fisher & Creed G22,073/55: In a case of thrombotic thrombocytopenic purpura, occlusion of many capillaries, arterioles and prearterioles by intraluminal masses of homogeneous and granular eosinophilic material was noted in the heart, spleen, kidneys, brain, pancreas, lymph nodes, bone marrow, stomach, lungs, and liver. Histochemical studies indicate that "the occlusive material is similar, if not identical, with fibrinoid rather than platelet or fibrin masses."

Muirhead C15,392/56: Following bilateral nephrectomy, occlusive vascular lesions develop in the dog with a syndrome reminiscent of Moschcowitz's disease. The small arteries and arterioles throughout the viscera exhibit hyaline thrombi which often appear to be continuous with similar substances within the

necrotic vascular wall and give the histologic reactions of fibrinoid. "It is suggested that several features of the experimental lesion support an origin of the occlusive masses via extrusion or herniation of the necrotic smooth muscle of the media into the lumen."

Stuart & MacGregor-Robertson G23,477/56: In a case of thrombotic thrombocytopenic purpura, staining reactions indicate "a close similarity of the 'thrombi' to fibrin rather than to platelets."

Craig & Gitlin G23,478/57: The thrombi in two cases of thrombotic thrombocytopenic purpura reacted specifically with fluorescein-labeled rabbit antihuman fibrin antibodies. It is concluded that these thrombi are composed of a saline-insoluble derivative of fibrinogen or fibrin.

Nussbaum & Dameshek G26,175/57: A transient form of Moschcowitz's disease was observed in a patient presumably as a consequence of meningococcemia.

Vazquez D80,507/58: By means of the fluorescent antibody technique, the "fibrinoid" was examined in various human and experimental diseases. Fibrinogen with little or no albumin or gamma globulin was found in the fibrinoid of the SSP-G (rabbit), thrombotic thrombocytopenic purpura and abruptio placentae. On the other hand, in the collagen diseases (lupus erythematosus or rheumatic fever in man, serum sickness in the rabbit), the fibrinoid contained much gamma globulin with little or no fibrinogen or albumin. "It is suggested that a different composition of the fibrinoid in the above studied diseases might indicate a different pathogenesis for the diseases of these 2 groups."

Cahalane & Horn G23,267/59: A case of thrombotic thrombocytopenic purpura of at least 3 years' duration, with 19 similar cases collected from the literature. Polypoid mural thrombi are seen in vessels with membranous and proliferative glomerulitis in the kidneys. The bone marrow contains numerous megakaryocytes. Fibrinogen contained in platelets may play a role in thrombus formation.

Frick & Hitzig G33,286/59: Among 5 patients with Moschcowitz's disease, one "had a congenital agammaglobulinemia; a second patient was found to have no γ -globulin and a third one no β_{2M} -globulin at the time of the disease. It appears very unlikely, therefore, that an antigen-antibody reaction is involved in the pathogenesis of this syndrome. It is suggested that thrombotic microangiopathy and the experimentally induced generalized Sanarelli-Shwartzman phenomenon may have a common pathogenetic mechanism which is independent of autosensitization."

Bechtelsheimer & Schallock G27,365/60: As judged by its histochemical behavior, the material deposited in the vessels of patients with Moschcowitz's disease is identified as a glycoprotein.

Bernstock & Hirson G27,355/60: In two cases of Moschcowitz's disease, remissions occurred under the influence of heparin treatment.

Moore & Schoenberg G23,269/60: Four cases of thrombotic thrombocytopenic purpura "consistently disclosed an accumulation of acidic polysaccharide similar to chondroitin sulfate or hyaluronic acid. This is presented as further evidence for a primary alteration of the vessel walls in this disease."

Brain et al. G23,832/62: In patients with thrombotic thrombocytopenic purpura and renal failure, there is frequently hemolytic anemia with the appearance of fragmented cells ("triangular," "helmet" and "burr" cells) in the peripheral blood. Similar changes were noted in malignant hypertension, renal cortical necrosis and microscopic polyarteritis nodosa. "It is suggested that an important factor in the pathogenesis of the haemolysis is direct contact between red cells and the diseased blood vessels." Such changes may also play a role in the SSP-G.

Bukowski & Koblenzer D21,423/62: A case of thrombotic thrombocytopenic purpura (with hypofibrinogenemia, leukopenia and the appearance of leuko-agglutinins) exhibited hyaline thrombi in the renal glomerular capillaries.

Masland & Barrows G33,259/62: Description of a woman with thrombotic thrombocytopenic purpura and hemorrhagic leukoencephalitis as a clinical form of the SSP-G.

Renaud G23,270/62: Rats kept for several months on a high-fat diet containing supplements of cholic acid develop multiple platelet and fibrin thrombi often located in aneurysmic dilatations of vessels in the heart, kidneys, lungs and adrenals. Only small vessels are affected but, occasionally, minute cardiac infarcts occur. The syndrome is associated with icterus, hemolytic anemia and thrombocytopenia. Although only minute petechiae are seen in the lungs and heart, the condition is thought to resemble thrombotic thrombocytopenic purpura.

Taub et al. G22,240/64: A review of the literature suggests that in Moschcowitz's disease "the thrombocytopenia may arise as the result of platelet injury during the intravascular coagulation process, and the hemolytic anemia may develop because of trauma to the red cells in their passage through abnormally narrowed and altered vascular channels, the result of fibrin deposits. As a working hypothe-

sis, the possibility that many aspects of TTP (thrombohemolytic thrombocytopenic purpura) are analogous to those of the generalized Shwartzman reaction must be considered."

McKay E4,788/65: Review of the literature on "thrombotic" or "thrombohemolytic thrombocytopenic purpura" shows its relationship to other forms of disseminated intravascular coagulation.

Rivera G33,834/65: In a patient with thrombocytopenic purpura, there were renal glomerular capillary thromboses and hyaline material beneath the intima with intravascular coagulation in the lungs, heart, pancreas and adrenals. The lesions are ascribed to an SSP-G resulting from bacterial infection.

Anaphylactoid Purpura. *Peck E65,257/31-32:* In the Schönlein-Henoch syndrome, as in the SSP of the rabbit, treatment with moccasin snake (*Ancistrodon piscivorus*) venom exerts a protective effect.

Glanzmann G25,143/37: In a 6-month-old infant, an anaphylactoid type of purpura fulminans affected mainly the face and the extremities; it was associated with edema of the feet. The hemorrhagic papules had a definitely urticaria-like character. Similar cases occur after various infections, especially pneumonia, measles and varicella. It is assumed that purpura fulminans is due to the SSP, the skin being sensitized by the initial exanthema of an infectious disease (e.g., measles, scarlet fever, varicella) and provoked during the post-infectious stage when massive amounts of microbes are absorbed.

Boncinelli G26,563/38: A case of intermittent chronic anaphylactoid purpura (with cutaneous hemorrhages, urticaria, edema, gastrointestinal disturbances and rheumatoid phenomena) is tentatively ascribed to the SSP.

Hamazaki et al. G27,522/40: In a case of Schönlein-Henoch's disease, the pathologic alterations are interpreted as manifestations of the SSP-G.

Malaguzzi-Valeri G28,853/40: A case of Schönlein-Henoch's disease precipitated by the ingestion of chicken meat is tentatively ascribed to the "SSP."

Sheldon D71,995/47: Purpura necrotica, also known as "purpura haemorrhagica gangrenosa," is a type of anaphylactoid purpura with bullous necrotizing hemorrhagic skin lesion of unknown origin, presumably induced by pressure under certain conditions of sensitization. "It is suggested that the disease may be connected with the Shwartzman phenomenon."

Gairdner B45,718/48: Detailed review of anaphylactoid purpura. "Purpura fulminans and post-scarlatinal gangrene are probably

variants of the Schönlein-Henoch syndrome." . . . "Clinically, pathologically, and aetiologically, the Schönlein-Henoch syndrome is linked with acute nephritis, rheumatic fever, and polyarteritis nodosa. A pathogenesis common to this group of conditions is suggested."

Dunn G25,121/51: Description of gangrenous purpura associated with meningococcal septicemia. "Sensitization as in the Shwartzman phenomenon may play a part in the pathogenesis of the vascular lesions which are responsible for the purpura in this disease."

Storck G21,672/51: Under the name of "hemorrhagic microbids," the author brings together purpura Schönlein-Henoch, anaphylactoid purpura, and purpura rheumatica. In all of these, as a rule, a focus of infection is found with microbes to which the skin is specifically sensitized, so that it reacts with hemorrhagic lesions upon i.c. injection of the corresponding bacterial filtrates. There is a temporary rise in blood heparin and thrombocytopenia. "Histologically, the massive perivascular leucocytic infiltrates with leucoplasia, swelling of the endothelial cells and fibrinoid degeneration are characteristic." Yet here, unlike in purpura fulminans after scarlet fever or meningococcal sepsis, a direct relationship to the SSP is not suspected.

Quick E4,524/57: An extensive review of anaphylactoid purpura suggests that "it is probable that both purpura fulminans and Schönlein-Henoch purpura are manifestations of the Sanarelli-Shwartzman reaction."

Vernier et al. C59,803/58: "Focal glomerular capillary occlusion by hyaline material" may occur in anaphylactoid purpura.

Little G25,131/59: "The pathological similarities between the lesions of purpura fulminans and those of the localized Shwartzman phenomenon support the hypothesis that purpura fulminans is fundamentally a thrombotic disease." Description of a case successfully treated with heparin.

Burke et al. C95,978/60: Of 88 children with anaphylactoid purpura, 39 had nephritis.

Norkin & Wiener D33,353/60: Detailed review of the pathologic changes in the kidney, skin, gastrointestinal tract, heart, lung, liver, adrenals and joints in anaphylactoid purpura.

Feldt & Stickler D29,209/62: Attention is called to the frequent occurrence of gastrointestinal manifestations, particularly melena, hematemesis and intussusception in anaphylactoid purpura. An association was noted between these changes and renal lesions.

Rio & Rozman D85,441/62: Review of the literature on the incidence of renal lesions in

anaphylactoid purpura. Twenty-one personally observed cases, all exhibited nephropathy with hematuria and one third had hypertension, another third renal insufficiency. Biopsy specimens of the kidney showed diffuse proliferative glomerular nephritis with PAS-positive membranes lining the glomerular capillaries.

Dean D18,545/64: A review of the literature suggests close relations between anaphylactoid purpura, purpura fulminans, glomerulonephritis and various collagen diseases. Streptococcal allergens and toxins are thought to be the possible common etiologic agents.

Hjort et al. G22,019/64: Fifty cases of purpura fulminans have been reviewed, and one personally observed case (responding dramatically to treatment with heparin and cortisol) has been added. The disease appears to occur only in children, usually a few weeks after an infection such as scarlet fever or varicella. All patients appear to have one or several episodes of intravascular clotting, resulting in secondary coagulation defects. A relationship between purpura fulminans and the SSP is suspected.

Symptomatic Afibrinogenemia. Deutsch & Zweymüller E28,392/63: Review of cases of "symptomatic afibrinogenemia" which develops as a consumption coagulopathy after extensive thrombus formation. In a personally observed child, recurrent thromboses in the cavernous sinus induced this syndrome which is regarded as a form of the SSP.

Hemorrhagic Thrombocythemia. Hardisty & Wolf G26,854/55: Hemorrhagic thrombocythemia is defined as a condition in which excessive hemorrhage occurs in the presence of a persistently high blood-platelet count. The 5-HT content of the platelets is low, although the total blood 5-HT is not reduced.

Arlotti & Ballerini G27,496/57: In various forms of thrombocythemia, there is a simultaneous thrombotic and hemorrhagic tendency associated with structural alterations in the vascular wall. [The lesions described resemble those of the THP (H.S.).]

Gunz G26,515/60: Hemorrhagic thrombocythemia is characterized by excessive bleeding and extremely high platelet counts, usually associated with other hematologic abnormalities. It is thought to be closely associated with polycythemia vera and myelosclerosis. Thromboembolic phenomena are inconstant, but splenic-vein thrombosis is rather common and other major vessels may also be involved. The hemorrhagic tendency is ascribed to abnormalities of the clotting mechanism which often accompany the thrombocytosis and the neutrophil polymorphonuclear leukocytosis of this disease.

Hall F41,442/65: Hemorrhagic thrombocytopenia is a hemopoietic disorder characterized by high numbers of circulating platelets, hemorrhages and thromboses of unknown origin.

McKay E4,788/65: Hemorrhagic thrombocytopenia is commonly associated with recurrent spontaneous hemorrhages in many tissues, often accompanied by thromboses in superficial and deep veins, polycythemia and a high platelet count.

Ohler et al. F39,819/65: Literature and personal observations on "hemorrhagic thrombocytopenia": a hemorrhagic diathesis resulting from increased thrombocyte formation. The pathogenesis of the disease could not be adequately explained.

Purpura Necrotica (cf. also "Anaphylactoid purpura"). *Jager E95,817/62:* In a man with lymphatic leukemia, there developed an acute illness that included ischemic necrosis of the nose, toes, petechial hemorrhages in the skin, hemorrhagic conjunctivitis and hemorrhage in the vitreous. "The only pertinent laboratory abnormality was a large amount of cold-precipitable fibrinogen in the plasma. Unlike the usual cryofibrinogen, which is demonstrable only upon cooling of heparinized plasma, this protein also appeared when plasma containing citrate, oxalate or edathamil calcium disodium was cooled. It seemed likely that cryofibrinogenemia was a significant factor in the production of thrombosis and hemorrhage." A cryofibrinogen-like substance was also detected in the blood of patients with acute or chronic illness using anticoagulant other than heparin.

Patterson et al. F50,894/65: In an eleven-year-old boy with Purpura fulminans (thought to be possibly related to the SSP-G), dextran

i.v. resulted in a remarkable recovery, after antibiotics, corticoids and heparin were shown to be ineffective.

Cremer F40,317/65: The absence of a coagulation defect and of fever, as well as the lack of correlation with an immediately preceding infection, differentiate purpura necrotica from the SSP.

Dysproteinemic Purpura. *Linke G26,040/50:* The syndrome of primary "dysproteinemic purpura" is described. A patient with hyper-γ-globulinemia developed generalized cutaneous purpura upon muscular exertion.

Visceral Thrombophlebitis Migrans. *Gerber & Mendlowitz G27,023/49:* A review of the literature and several personally observed cases show that visceral thrombophlebitis migrans is often associated with thromboangiitis obliterans and thrombocytopenic purpura. "It is possible that the purpura here was caused by a withdrawal of platelets into the thrombi, as has been postulated in so-called acute febrile anemia with purpura."

Nilsson et al. G27,029/61: In a 28-year-old man, repeated thromboses had occurred in various parts of the venous system since childhood. The blood fibrinogen and the inhibitory activity of the serum on plasminogen activation were increased, while fibrinolytic activity was absent. The patient died from cerebral hemorrhage with widespread atherosclerosis, multiple thromboses and necrotic changes in the skeleton. An almost identical syndrome was subsequently seen in a 44-year-old man. Similar changes had previously been described under the name of "visceral thrombophlebitis migrans" without associated skeletal lesions. The high inhibitor content of the serum is regarded as the decisive etiologic factor.

BLOOD DYSCRASIAS

Polycythemia vera is frequently associated with thrombosis and hemorrhage. Here, the initiation of thrombosis has been ascribed to destruction of the greatly increased number of platelets or to the release of clotting factors from decomposing blood corpuscles.

The common occurrence of thrombosis in myelogenous leukemia has also been ascribed to the increased platelet count. In *sickle cell disease*, multiple infarcts may occur as a consequence of capillary occlusions by rigid sickle-shaped erythrocytes and sometimes increased blood coagulability may lead to true thrombosis, but the relationship of this disease to the SSP is questionable.

Acquired hemolytic anemia is often associated with thrombocytopenia and probably due to autoantibodies against erythrocytes. The accompanying intravascular coagulation may be connected with the hemolysis, but a close relationship to the classical THPs is difficult to prove.

Polycythemia Vera. *Wasserman G27,344/54:* Thromboses occurred in one fourth of the patients with polycythemia vera, and hemorrhage in about 10%.

Whitelaw & Thomas G26,857/55: In polycythemia vera, massive hemorrhages may occur perhaps as a consequence of hypofibrinogenemia and inadequate clot retraction.

Baker & Castleman G26,139/62: Polycythemia vera is frequently associated with multiple thromboses. In a personally observed case, there were thrombi in the aorta, femoral arteries, the smaller coronary vessels and a small branch of the pulmonary artery. Hemorrhages from both adrenals resulted in extensive bilateral retroperitoneal hematomas.

McKay E4,788/65: In polycythemia vera, thromboses occur in a quarter of the patients and account for a quarter of the deaths. Cerebral, coronary, and mesentery arteries, as well as peripheral arteries and veins may be involved. The associated gastrointestinal ulcers are regarded as secondary to thromboses in the small vessels of the mucosa. The initiation of thromboses may be due to the destruction of the greatly increased numbers of platelets or to the release of clotting factors, particularly tissue thromboplastin from decomposing leukocytes and erythrocytes. The further progress of the hemorrhagic tendency is presumably due to a depletion of coagulation factors with a release of fibrinolysin.

Leukemia. *Alexander & Thompson G26,200/25:* In a case of chronic leukemia, autohemagglutination occurred when the blood was cooled below body temperature. The agglutinated cells dispersed again when the temperature was raised. The phenomenon may be accompanied by paroxysmal hemoglobinuria.

Kozlowska & Sztymela D33,377/62: A 2½-year-old girl with acute leukemia died of

generalized hemorrhagic vaccinia three months after vaccination against smallpox. Hemorrhages were noted not only at the site of vaccination and in the vaccinia pustules, but also in the mucosa of the jejunum and stomach.

McKay E4,788/65: The well-known association of thrombosis with myelogenous leukemia is ascribed to the abnormally high platelet levels, frequently seen in this disease.

Verstraete et al. G15,997/65: Acute promyelocytic leukemia may be associated with hypofibrinogenemia and a consumption coagulopathy.

Sickle Cell Disease. *Kimmelstiel G26,514/48:* Most investigators believe that the production of multiple infarcts in sickle cell disease is due to stasis in capillaries occluded by the rigid sickle-shaped erythrocytes. However, infarctions may occur without demonstrable thromboses, perhaps as a consequence of tissue anoxia because the abnormal erythrocytes do not carry enough oxygen.

McKay E4,788/65: Sickle cell anemia is a hereditary disease transmitted as a Mendelian dominant and is caused by the presence of abnormal hemoglobin in the erythrocytes. The crises of sickle cell anemia are associated with hemolysis, shock, increased blood coagulability, and thromboses in large or small vessels with consequent infarction.

Acquired Hemolytic Anemia. *McKay E4,788/65:* Acquired hemolytic anemia is often associated with thrombocytopenia and is probably due to autoantibodies against erythrocytes. Hemolysis is presumably the cause of the associated intravascular coagulation. Unlike in other forms of THPs, the large veins are predominantly involved, perhaps because the rate of hemolysis is slower in acquired hemolytic anemia than in most of the related conditions.

DERMATOSES (OTHER THAN PURPURAS)

The participation of the SSP has been suspected not only in the pathogenesis of Moschcowitz's disease, anaphylactoid purpura and related diseases, but also in the development of many other dermatoses such as: the hemorrhagic forms of pemphigus, herpes zoster, dermatitis nodularis necrotica, eczema, pyoderma and cutaneous gangrene.

Pemphigus. *Proppe G23,255/48-49:* In Pemphigus acutus febrilis gravis, the cutaneous bullae are hemorrhagic. This disease is considered to be a form of the SSP in which local preparation is due to cutaneous infection with various organisms, while an unknown systemic factor would act as the provocative agent.

Richter G23,069/50: On theoretic grounds, various hemorrhagic and necrotizing skin lesions, especially those of Pemphigus acutus febrilis gravi, Ekthyma gangraenosum, and those developing after acute infectious diseases or surgical interventions, are ascribed to the SSP-L.

Pfleger & Tappeiner G23,073/51: The authors ascribe the appearance of necrotizing skin ulcers in patients with Pemphigus vulgaris chronicus and salvarsan dermatitis to the SSP-L.

Herpes. *Hausner G19,190/49; Richter & Johne G23,888/50:* In a 44-year-old woman with chronic generalized lymphogranulomatosis and scabies with pyoderma, nitrogen-mustard therapy elicited multiple thrombophlebitic lesions in the skin which lasted for weeks. Immediately after a new attack of thrombophlebitis, there developed a generalized herpes zoster with hemorrhagic vesicles, and 6 days later the patient died. Apart from the lymphogranulomatosis, autopsy revealed hemorrhagic necrosis of the small intestine, pleura and lungs. The authors assume that a decrease in the antibody titer, induced by lymphogranulomatosis and nitrogen-mustard therapy, may have been responsible for the sudden multiplication of the zoster virus which perhaps in conjunction with the pyoderma microbes may have caused an SSP.

Dermatitis Nodularis Necrotica. *Binkley C33,713/57:* The macro- and microscopic appearance of the lesions in dermatitis nodularis necrotica are very similar to those of the SSP-L. "Dermatitis nodularis necrotica may be a continuous state of the Sanarelli-Shwartzman reaction. The preparatory bacterium in this case may have been the ubiquitous surface *S. pyogenes*, and the reacting factor may have been the coliform bacteria."

Eczema. *Gougerot & Meyer G22,257/51:* In a patient who suffered from eczema, hemorrhagic necrosis of the skin developed following topical treatment with a sulfonamide ointment. The lesion is interpreted as a "Sanarellide."

Pyoderma. *Gougerot & Vial E56,335/37:* In a patient with pyoderma (considered to be the preparatory factor), injection of a streptococcal vaccine (considered to be the provocative factor) produces a generalized morbilliform erythematous eruption which was regarded to be an SSP, although it was unaccompanied by purpura.

Richter E59,723/54: In a patient who, for many years, suffered from "Pyoderma chronica papillaris et exulcerans," penicillin therapy suddenly precipitated vesicular and hemorrhagic necroses of the skin. Toxins, liberated from bacteria under the influence of penicillin, are assumed to have acted as the preparatory factor, while invasion of the vessels by *Proteus vulgaris* is regarded as the provocative factor.

Kohlenbrener et al. G25,130/58: Pyoderma gangrenosum occurred in an infant in asso-

ciation with otitis media and *Pseudomonas*'s infections. "The Shwartzman phenomenon can produce necrotic skin lesions that are identical with the ones found in this case."

Grüneberg F14,329/64: Pyoderma gangrenosum is considered to be a clinical form of the SSP. It responds well to high doses of glucocorticoids.

McKay E4,788/65: Pyoderma gangrenosum or "chronic undermining burrowing ulcer" usually begins as a pustule which enlarges, dries into a scab in the center, and ulcerates with peripheral spread at the margins. There may be a striking parallel between the activity of the cutaneous lesions and an associated ulcerative colitis. The concurrent development of cutaneous and pulmonary damage with thrombi in both skin and lungs suggests that here again we are dealing with a form of disseminated intravascular coagulation similar to that of the SSP.

Acrodynia. *Ritzel et al. E96,978/62:* In a two-year-old child with acrodynia (pink disease), the urinary elimination of norepinephrine and 3-methoxy-4-hydroxymandelic acid was increased, and excess production of catecholamines is thought to be of pathogenic importance in this disease.

Pierson et al. G29,948/65: A six-year-old girl developed severe acrodynia with trophic disturbances in hands and feet after prolonged use of calomel. Urinary catecholamine is increased and the derangement in catecholamine metabolism is supposed to play a role in the pathogenesis of acrodynia.

Svenningsen F54,102/65: Two cases of thrombocytopenia after rubella complicated by purpura. Glucocorticoid + EACA treatment was allegedly effective.

Hamza & Meherzi G35,081/65: In a six-year-old boy with mutilating acrodynia (without evidence of mercurial intoxication), the urinary elimination of catecholamine metabolites was increased.

Various Other Dermatoses. *Kohn et al. G20,034/38:* In a patient sensitive to horse serum, repeated s.c. injections of horse serum resulted in extensive cutaneous hemorrhagic necrosis. The lesion is regarded as possibly an Arthus or a Shwartzman phenomenon.

Storck G21,672/51: The term "secondary hemorrhagic dermatoses" is applied to hemorrhagic eczema, Morbus Schamberg and purpura teleangiectodes annularis Majocchi "in which local haemorrhagic damage seems to occur without general participation of clotting factors, thrombocytes and capillary resistance and without special reactivity to bacterial filtrates." Unlike in meningococcal sepsis or

purpura fulminans after scarlet fever, there, a direct relationship to the SSP is improbable.

Rostenberg G21,665/53: Among the dermatoses, the following are suspected of developing on the basis of an SSP: Toxic-infectious purpuras, purpura fulminans, pyoderma gangrenosum, dermatitis gangrenosa infantum, dermatitis nodularis necrotica, Lazarine leprosy and butcher's pemphigus.

Anonymous B91,492/54: Brief review of various clinical conditions which may be due to an SSP-G. Among these are: infective purpas, hemorrhagic forms of the common fevers, tuberculides, bullous and necrotic forms of leprosy, the so-called "butcher's pemphigus," ulcerative colitis and certain thrombohemorrhagic drug reactions especially those elicited by antibiotics.

DISEASES OF THE DIGESTIVE TRACT

The SSP has been implicated in a number of gastrointestinal diseases of man particularly in peptic ulcer, gastroenteritis, intestinal gangrene, ulcerative colitis and appendicitis.

In rabbits in which the preparatory dose of endotoxin is injected directly into the wall of the gastric mucosa, a topical, often exulcerating, SSP-L results following i.v. provocation. Hence, it has been suspected that bacterial invaders of the gastric mucosa may similarly prepare the gut for blood-borne microbes or endotoxins in man and thus create a predisposition for *peptic ulcers*.

Following infiltration of the vagus and splanchnic nerves with herpes simplex, provocation with the same virus i.v. also produces exulcerating gastroduodenal hemorrhages and necroses in rabbits. Since herpes simplex is allegedly common in patients with gastroduodenal ulcers, it has been assumed that similar phenomena may be involved in the pathogenesis of peptic ulcers in man.

During an epidemic of *infantile diarrhea* and *gastroenteritis* caused by *E. coli*, multiple thrombohemorrhagic necroses occurred in the intestinal mucosa as well as in the kidney, brain, spleen and lung. The changes were ascribed to the SSP.

Certain cases of *intestinal gangrene* have been attributed to the SSP. For example, in 1946, there was an epidemic of necrotizing duodenitis and jejunitis in Northern Germany in which multiple thrombohemorrhagic lesions were associated with renal glomerular thromboses. Essentially similar lesions could be produced in rabbits by local preparation of the jejunal wall and subsequent i.v. provocation by *E. coli* endotoxin.

The thrombohemorrhagic lesions which induced perforation of the colon in a woman with shock and hypofibrinogenemia following a stillbirth, also exhibited the structural characteristics of the SSP.

The possible role of the SSP in the pathogenesis of *ulcerative colitis* has been the subject of particularly intensive study. Lesions resembling the SSP-L can be produced by local preparation of the colon followed by i.v. provocation with SSP-active substances. The histologic changes characteristic of ulcerative colitis in man and the frequent occurrence of thrombohemorrhagic cutaneous lesions in patients suffering from this disease suggest a relationship to the SSP.

Pseudomembranous enterocolitis can be produced in dogs by the intra-aortic injection of incompatible blood, thrombin or *E. coli* endotoxin. It is significant that these changes can be prevented by heparin.

Certain forms of hemorrhagic-necrotic *appendicitis* have been ascribed to the SSP-mechanism, partly because of their histologic aspect and partly because it was possible to produce similar changes in rabbits by removing the mucosa of the

appendix with a sharp spoon and then injecting endotoxin i.v. It is conceivable that trauma to the mucosa by foreign bodies which enter the appendix of man may permit access of intestinal microbes to the underlying tissue, thereby preparing the region for provocation by blood-borne SSP-active principles.

Oral Cavity. Rizzo & Mergenhagen G28,648/60: An SSP-L has been produced both in the skin and in the oral mucosa of the rabbit by topical preparation followed by i.v. provocation with an extract of Veillonella organisms. It is suggested "that a similar mechanism may operate in oral disease. Periodontal conditions which should be considered in the light of the Shwartzman phenomenon include acute Vincent's necrotizing gingivitis and the acute exacerbations of chronic gingivitis frequently associated with an episode of generalized illness."

Peptic Ulcer, Hemorrhagic Duodenitis. Crohn & Shwartzman E51,541/37-38: A patient who had previously received prophylactic injections of typhoid vaccine, was reinfected ten years later (by mistake) with triple the usual dose. Thereupon he developed an acute, bleeding duodenal ulcer with petechial hemorrhages over the lower extremities. The response was attributed to the SSP-G. The phenomenon may also explain the pathogenesis of certain gastric ulcers. "Whatever the primary etiologic factor of gastric ulcer may be, secondary bacterial invaders are commonly found in the bed of gastric ulcers. These bacterial invaders may be, then, responsible for a lasting state of reactivity in the tissues of the gastric ulcer."

Niosi G22,351/39: In rabbits in which a preparatory dose of *E. coli* endotoxin is injected into the wall of the stomach, a topical SSP-L (often with exulceration of the mucosa) occurs, following the i.v. administration of the same material 24 hrs. later. Similar reactions may explain the pathogenesis of certain peptic ulcers in man.

Gonçalves G22,359/50: Following preparation by infiltration of the vagus or splanchnic nerves with live herpes simplex virus, the i.v. injection of the same material 24 hrs. later produces gastroduodenal ulcers with local hemorrhages and necrosis. These are interpreted as an SSP-L. Herpes simplex is allegedly common in patients with gastroduodenal ulcers. Perhaps localization of a virus in the autonomic nerves with a subsequent SSP-L is involved in the pathogenesis of gastroduodenal ulcers in man.

Katz D87,740/59: Hemorrhagic duodenitis associated with intense dilatation of the duodenal microcirculation is frequently seen in patients under severe stress and particularly after myocardial infarction. "It is certainly

plausible that hemorrhagic duodenitis represents one part of the shock phase of the alarm reaction."

Gastroenteritis and Infantile Diarrhea. McKay & Wahle D6,653/54; G21,644/55: In an epidemic of often fatal infantile diarrhea due to *E. coli*, the clinical and pathologic features closely resembled the SSP-G as it occurs in the rabbit. "The outstanding pathological change, in most of the cases, was intravascular fibrin thrombosis of capillaries and precapillary arterioles in the lungs, liver, brain, spleen, adrenals and kidneys. Perivascular infiltrations with polymorphs and macrophages as well as intravascular accumulations of these cells were prominent in the brain, spleen and lung. The amount of thrombosis varied from case to case, but in the more severely affected kidneys every glomerular tuft was completely occluded by fibrin thrombus." It is concluded that the pathogenic agent "attacks the mucosa of the small intestine and allows Shwartzman active materials—whether from a specific micro-organism, from the bacteria of the intestinal flora, or from products of cellular necrosis—to gain access repeatedly to the blood-stream and thus to prepare and to provoke the local and generalized Shwartzman phenomena in these infants."

Belnap & O'Donnell G22,053/55: During an epidemic of infantile diarrhea and gastroenteritis due to *E. coli*, several patients were observed with "clinical findings and post-mortem changes resembling those of the generalized Shwartzman reaction."

McKay E4,788/65: A syndrome reminiscent of the SSP-G can develop during epidemics of infantile diarrhea due to *E. coli* 0-111:B₄.

Intestinal Gangrene. Schoen B44,153/48: Since 1946, many cases of thrombohemorrhagic necrosis in the duodenum and jejunum have been observed in Northern Germany. The changes resemble the SSP-G in their histologic structure but are usually unaccompanied by characteristic renal glomerular thrombosis.

Jansen G23,254/54: A necrotizing jejunitis took on almost epidemic proportions in Northern Germany in 1946. It was characterized by hemorrhages in the submucosa with arteritic, periarteritic and phlebitic lesions but no ulcer formation. The disease was usually fatal although no characteristic pathogen could be demonstrated in the lesions. The response is attributed to an SSP-L in which intestinal

microbes are thought to induce local preparation, some accidental infection at a distance acting as the provocative factor. This theory is supported by experiments showing that in rabbits local preparation of the jejunal wall by *E. coli* endotoxin results in topical hemorrhagic lesions upon subsequent i.v. administration of the same material.

Various authors D20,144/59: Account of a young woman who developed bloody diarrhea with shock and hypofibrinogenemia following a stillbirth. The colon was resected for perforation. The entire bowel wall was infarcted by thrombosis of veins and small arteries, and there were large intramural hematomas with numerous ulcerations. The pathologist emphasized the striking similarity between the histopathology of the colon and the lesions of the Shwartzman phenomenon.

Hermann G31,511/65: In a new-born with perforation of the colon from necrotizing colitis, the circumstances of uncertain cause of the disease as well as "the pathologic findings in the resected colon, have led to the suggestion that the cause of necrotizing colitis and perforation of the colon in this patient may have been a localized Shwartzman reaction."

Ming G32,853/65: "Hemorrhagic necrosis of the gastrointestinal tract probably represents a conglomeration of microinfarcts of the mucosa secondary to markedly decreased local blood flow." The disease occurs most frequently in association with shock and various forms of cardiac disease.

Ulcerative Colitis. *Shwartzman & Winkelstein G24,143/34:* "There is described a method of treatment of non-specific, ulcerative colitis in which is employed antitoxic, anti-*coli* horse serum of a high neutralizing titer, as determined by means of the phenomenon of local skin reactivity to *B. coli*."

Baggio G21,837/37: Certain phlegmonous types of appendicitis, which accompanied by similar changes in the cecum and colon, are ascribed to local preparation by microorganisms, followed by subsequent provocation through SSP-active substances absorbed into the blood.

Winkelstein & Shwartzman G21,664/42: A concentrated horse serum preparation, strongly antitoxic to *E. coli*, was beneficial in certain cases of ulcerative colitis.

Rostenberg G21,665/53: Ulcerative colitis appears to be a special form of the SSP. "The sequence of events postulated is somewhat as follows: in the intestinal wall an infection develops which serves as the Shwartzman preparatory factor, then circulating toxins from

the same or an unrelated infection act as the eliciting factor."

Warren & Berk D15,452/57: The histologic changes in ulcerative colitis resemble those of the SSP-G. It is proposed that microorganisms or their toxins may sensitize the blood vessels of the bowel mucosa and exacerbations might occur whenever bacterial toxins are present in the systemic circulation. It is concluded that "the Shwartzman phenomenon has certain features making it an attractive explanation for the pathogenesis of ulcerative colitis."

Goldgraber & Kirsner G24,332/60: In a patient with ulcerative colitis and thrombohemorrhagic cutaneous lesions conducive to gangrene, "the histologic features and the rapid changes in the skin suggest a Shwartzman phenomenon as the basis of the cutaneous manifestations."

Kirsner & Goldgraber D8,610/60: In a pregnant woman with upper respiratory infection and bronchopneumonia, acute ulcerative colitis developed. The phenomenon is interpreted as an SSP "with the respiratory infection as the reaction factor and the pregnancy as the potentiating mechanism." Attention is called to observations of others who found that ulcerative colitis may have dermatologic complications resembling the SSP. In another fatal case of ulcerative colitis, histologic examination of the kidneys demonstrated lesions of the SSP-G type.

Patterson et al. D14,188/62: An SSP-L in the colon of the rabbit can be elicited by *E. coli* injected first into the submucosa of the colon and then i.v. However, the authors doubt "that this phenomenon is of importance in the production of chronic ulcerative colitis in man."

Patterson et al. D58,647/63: A review of the literature on possible relationships between colitis and the SSP. In rabbits prepared by *E. coli* toxin injected into the rectal mucosa, subsequent i.v. injections of the same toxin elicited acute thrombohemorrhagic lesions in the intestine, but these did not become chronic and failed to reproduce the picture of ulcerative colitis.

Kirsner F32,654/65: A review of the literature suggests that neither the SSP nor experimental immune lesions of the colon "reproduce human ulcerative colitis and their occurrence does not necessarily relate colitis to such mechanisms."

Pseudomembranous Enterocolitis. *Wilson & Qualheim G33,249/54:* Description of 20 cases of acute hemorrhagic enterocolitis observed at the Cincinnati General Hospital among approximately 3,400 autopsies. The condition

resembles pseudomembranous enterocolitis occurring postoperatively or following broad-spectrum antibiotic therapy. It "has occurred for the most part in elderly individuals suffering from chronic cardiac disease or other debilitating illness and has frequently simulated mesenteric thrombosis in its clinical manifestations."

McKay et al. G33,264/55: Pseudomembranous enterocolitis with intravascular clotting in the microcirculation of the bowel can be produced in dogs by the administration of incompatible blood into the aorta with concomitant surgical trauma in the abdomen. "It is suggested that the pathogenesis of the lesion in man depends on the same two factors, i.e., intravascular coagulation and stasis of blood in the intestinal mucosal capillaries."

Hardaway & McKay G33,251/59: A type of pseudomembranous enterocolitis with multiple thromboses in the microcirculation of the bowel can be produced in dogs by transfusion of incompatible blood. Heparin prevents this phenomenon. It is concluded that pseudomembranous enterocolitis can result at least from two causes: "(a) Formation of intracapillary fibrin thrombi in the submucosa and mucosa of the intestine, leading to infarct necrosis and pseudomembrane formation of the mucosa, and (b) staphylococcal infection, usually in the absence of normal intestinal flora and associated with antibiotic therapy."

Hardaway et al. D18,362/61: Intra-aortic injection of incompatible blood, thrombin, or *E. coli* endotoxin, produces hemorrhagic necrosis with intravascular fibrin-clot formation in the dog. The changes resemble pseudomembranous enterocolitis in man and can be largely prevented by heparin pretreatment.

Freiman G32,852/65: Hemorrhagic necrosis of the gastrointestinal tract (also known as hemorrhagic enteropathy, enteritis necroticans and pseudomembranous enterocolitis with hemorrhagic necrosis) is probably a clinical variant of the SSP.

Appendicitis. *Baggio* G21,837/37: Certain phlegmonous types of appendicitis, which are

sometimes accompanied by similar changes in the cecum and colon, are ascribed to the SSP. It is assumed that local preparation by microorganisms, followed by subsequent provocation through SSP-active substances absorbed into the blood, are thought to elicit these phenomena. "Thus we have a uniform cause of the various acute and chronic forms of appendicitis and the accompanying colitis which still remains following the appendicectomy."

Basile G23,055/41: Review of earlier work on the production of an SSP-L in the appendix by the local administration of a preparatory endotoxin injection. The following experiment was performed: Under anesthesia, a small oculist's spoon was introduced into the appendix from its base and a piece of mucosa and submucosa removed; the following day, *E. coli* endotoxin was injected i.v. Of 16 rabbits so treated, 5 showed a definite SSP-L at the traumatized region, while the remainder exhibited only minor lesions such as were found also in controls not provoked by i.v. endotoxin. One of the positively reacting rabbits likewise showed SSP-G-like changes. It is concluded that topical trauma to the mucosa of the appendix can act as a preparatory treatment. In man, foreign bodies in the appendix may produce such trauma, and certain types of fulminating hemorrhagic appendicitis could represent manifestations of the SSP-L.

Heilmann G22,332/52: On theoretic ground the author assumes that appendicitis may result from an SSP-L in which bacteria within the appendix act as preparatory factors, while a subsequent systemic infection corresponds to the provocative factor.

Savino G22,092/52: Two cases of appendicitis are interpreted as manifestations of an SSP, mainly because of the hemorrhagic-necrotic character of the inflammatory lesions. Several similar cases are compiled from the literature.

Schöngut & Liszkai G28,867/64: Clinical observations suggest that certain forms of "allergic appendicitis" in man may be related to the SSP.

IMMUNOLOGICAL DISEASES

The participation of various immune reactions in the production of THPs has been discussed at length in Chapter III. Suffice it to mention here that transfusion with *incompatible blood* and, in particularly susceptible patients, even with compatible plasma, can produce a hemorrhagic diathesis with thrombocytopenia and hemolysis not unlike the changes of the classic SSP-G. Similar changes have occasionally been seen after *vaccination* and *in paroxysmal hemoglobinuria*.

Blood Transfusion. Samtsov G22,347/40: The i.v. injection of human, guinea pig, or canine blood produces an SSP-L in rabbits which 24 hrs. earlier have received *E. coli* endotoxin i.c. Sheep, cat, rabbit, chicken, duck and turtle blood is ineffective.

Ackerman 57,770/42: In a patient with acute thrombohemorrhagic pancreatitis following incompatible blood transfusion, thromboses and hemorrhages were also noted in other organs.

Crosby & Stefanini D9,062/52: The plasma-transfusion reaction (PTR) occurs when susceptible patients are transfused with compatible blood. The reaction is encountered in hemolytic diseases, terminal cancer, and in paroxysmal nocturnal hemoglobinuria when the reaction is always followed by a hemolytic crisis. "During the preliminary phase of the reaction, the majority of leukocytes and platelets are swept out of the circulation and about half of the fibrinogen disappears. The white cells are probably removed by the lungs. Emboli composed of platelets or fibrin may be responsible for the various clinical symptoms such as diarrhea, headache, and abdominal pain." The PTR is nonspecific since similar changes have been found during anaphylactic and peptone shock, incompatible blood transfusions, i.v. administration of foreign proteins, tuberculin and typhoid bacilli or ferric oxy-saccharate, to susceptible people. The reaction also occurs during the hemolytic paroxysms of cold hemoglobinuria, favism and blackwater fever. This pattern of response has been described as "colloidoclastic" or "hemoclastic" reaction. [Although the authors do not mention the SSP-G, a relationship between the latter and the PTR is obvious from their description (H.S.).]

Hardaway et al. G26,830/54: Following incompatible blood transfusion, lower nephron nephrosis developed in four patients. This was accompanied by a generalized hemorrhagic diathesis. "Depletion of all blood-clotting elements is probably indicative of intravascular clotting with resultant using up of clotting elements. Activation of fibrinolysin may occur in the body's attempt to stop this process."

McKay et al. D9,845/55: Following an incompatible blood transfusion reaction, hemorrhagic diathesis developed with thrombocytopenia, prolongation of the coagulation time and prothrombin time, a decrease in circu-

lating white blood cells and the appearance of fibrinolytic activity. The authors do not suggest any relationship, however, between this response and the SSP-G.

Vaccination. Bernard et al. D69,624/63: A 22-year-old man suddenly fell ill following revaccination with TABDT vaccine. He developed high fever and an extensive erythematous papular non-pruriginous skin eruption. Eventually, profound shock ensued and the patient died on the sixth day. Autopsy revealed hemorrhagic fluid in the peritoneum, bilateral renal cortical necrosis with fibrinoid thrombi in the glomeruli as well as hemorrhagic necroses (without fibrin thrombi) in the adrenals, small intestine and other organs. The authors state that "there is no doubt that this case represents an instance of the Sancarilli-Shwartzman phenomenon" but it is also related to anaphylaxis and Reilly's "syndrome of neuro-vegetative irritation."

Paroxysmal Hemoglobinuria. Mackenzie G27,022/29: Review of the early literature on paroxysmal hemoglobinuria.

McKay E4,788/65: From a review of the literature, the author concludes that "in paroxysmal nocturnal hemoglobinuria it has been shown that there is: (1) intravascular hemolysis, (2) anemia, leukopenia, and thrombocytopenia, (3) multiple venous thromboses which often are the cause of death, and (4) an intimate relationship between the coagulation system and the hemolytic system, in vitro and in vivo."

Paroxysmal cold hemoglobinuria or the "hemoclasic reaction" of Widal "is characterized by intravascular hemolysis, hypotension, leukopenia, development of fibrinolytic activity, increased blood viscosity, shortening of whole blood coagulation time, thrombocytopenia, and pathologic evidence of intravascular coagulation, including venous and arterial thrombi with gangrene and non-bacterial thrombotic endocarditis." Apparently, there are two types of paroxysmal cold hemoglobinuria, one of which does, while the other does not, depend on a marked increase in the cold agglutinin titer of the blood. The former type is frequently associated with Raynaud's phenomenon presumably because the cold agglutinins cause clumping of erythrocytes in skin capillaries and thereby bring about cessation of blood flow.

COLLAGEN DISEASES

The histologic lesions seen in the early stages of carditis in patients with acute rheumatic fever resemble those of the SSP-G. Furthermore, extracts prepared from

skin lesions provoked in rabbits by type 28 group A streptococci followed by i.v. provocation with *S. typhosa* toxin, produce a myocarditis with multinucleated giant cells not unlike that of rheumatic fever.

In rabbits in which an SSP-L was elicited with streptococcal skin lesions and streptolysin O, intranasal infection with β -hemolytic streptococci produced a polyarthritis reminiscent of that seen in rheumatic fever.

Finally, the procryofibrin level of the blood is increased in rabbits during the SSP as well as in patients with rheumatic fever and it diminishes under the influence of salicylate and cortisone therapy.

All these facts suggested some relationship between the SSP and rheumatic fever.

There is also reason to suspect some relationship between the SSP and *lupus erythematosus*. The "L. E. phenomenon" can be reproduced in vitro by adding Liquoid to human blood. The THP-G induced by Liquoid i.v. in rabbits is associated with "wire loop" lesions in the renal glomerular capillaries such as are found in patients with lupus erythematosus.

Periarteritis nodosa is common in anaphylactoid purpura which undoubtedly belongs to the clinical equivalents of THPs. Furthermore, coronary lesions resembling periarteritis nodosa accompany certain forms of the classic SSP-G.

The concept of the "systemic fibrinoid disease" postulates that acute rheumatic fever, scleroderma, lupus erythematosus, Moschcowitz's disease, malignant hypertension, periarteritis nodosa and subacute glomerular nephritis belong to one nosologic group in which the formation of fibrinoid from altered fibrinogen plays a prominent part. The same mechanism is activated by bacterial endotoxins during the SSP.

Rheumatic Fever. Chini B69,573/34: It is postulated, on purely theoretic grounds, that an SSP-G elicited by streptococci may be the cause of rheumatic lesions.

Stetson C11,252/51: A review of the literature suggests that "the tissue damage of both the Arthus and the Shwartzman phenomenon has been found to be due to a characteristic vascular lesion, consisting of occlusion of the capillaries and small veins by masses of leukocytes and platelets, followed by necrosis and hemorrhage." . . . "Similar vascular lesions have been found in the hearts of patients showing evidence of early active rheumatic carditis, and it is suggested that these lesions may be involved in the pathogenesis of the disease."

Stetson D88,174/51: "Leucocyte-platelet thrombi, involving the smaller branches of the coronary blood vessels, have been found in the hearts of patients with active rheumatic fever and rheumatic carditis. A consistent correlation has been observed between the existence of these vascular lesions and the presence of typical Aschoff bodies." It is suggested that close relationships may exist between the

SSP and the pathogenesis of rheumatic carditis.

Thomas et al. G25,140/53: Rabbits, infected by i.v. injection of type 1 streptococci and two days later given meningococcal endotoxin i.v., developed "infiltration of the walls of the coronary arteries by homogeneous eosinophilic material resembling fibrinoid, accompanied by varying degrees of necrosis of the arterial walls." . . . "The possibility that rheumatic fever may be a special manifestation of a continuing systemic infection by streptococci has been discussed."

Thomas et al. G21,293/53: Cutaneous and systemic infections with Group A streptococci prepare the rabbit for the SSP-L and SSP-G respectively by subsequent i.v. injection of meningococcal or *S. marcescens* toxin. Under optimal conditions of dosage and timing, fibrinoid deposits appear in the coronary arteries in approximately 50% of the animals. "These are obvious points of resemblance between the vascular lesions of fibrinoid necrosis produced in rabbits and the changes in blood vessels which occur in certain human disease states, characterized by fibrinoid deposition,

such as rheumatic fever, periarteritis nodosa, thrombotic thrombocytopenia and disseminated lupus erythematosus."

Schwab et al. B83,779/53; Watson C29,780/54: Rabbits given a small quantity of an extract prepared from the tissues of other rabbits infected with streptococci (group A, type 28) i.c. and 16 hrs. later injected with sublethal quantities of typhoid toxin i.v., usually died within 24 hrs.; controls, receiving only typhoid toxin without preparation, survived. "This was the first indication that a soluble product derived from group A streptococci could prepare rabbits for the generalized Shwartzman reaction. We were surprised, however, that the intradermal injection of lesion extract or 'preparative factor' did not prepare the animals for the local Shwartzman reaction." . . . "This failure, however, may be explained on the basis of the high content of hyaluronidase in the lesion extract which might permit a rapid diffusion of the factor into the circulation." The existence of an SSP-G was documented by the presence of hemorrhagic cardiac necrosis, but the characteristic renal lesions were absent. In rabbits prepared by the i.v. injection of streptococcal-lesion extract and challenged with Streptolysin-O, i.v., myocardial necrosis occurred in conjunction with bilateral renal cortical necrosis and hyaline thrombosis of the glomerular capillaries. The possibility of producing, with products derived entirely from group A streptococci, an SSP-G and cardiovascular lesions reminiscent of those seen in rheumatic fever, is taken as an indication that the SSP-G may play a part in the pathogenesis of rheumatic diseases.

Thomas et al. C241/54: The fibrin-like fraction of the plasma, which can be precipitated by heparin in the cold and is increased in rabbits during the SSP, was found to be also considerably raised in a patient with rheumatic fever; it diminished under the influence of salicylate and cortisone therapy.

Raška et al. G23,259/56: In rabbits in which an SSP-L is elicited by means of an extract from streptococcal skin lesions and Streptolysin-O, intranasal infection with β -hemolytic streptococci, 3-4 weeks later, produced a polyarthritis. "The clinical and histological aspects of these lesions exhibited a close similarity to the findings in acute rheumatic fever and in the postrheumatic myocardium."

Minervin & Yaroshik G27,942/63: When streptococcus allergen is added to *E. coli* filtrate, the ability of the latter to produce an SSP-L in the rabbit is greatly increased. The authors assume that, in rheumatic patients, the intestinal microflora intensifies the sensitization caused by the streptococcus.

Lupus Erythematosus. Inderbitzin G21,895/51; B76,311/52; B99,377/53: Upon prevention of blood coagulation by Liquoid or PVAS (polyvinyl alcohol polysulfonic acid ester) the phagocytic power of leukocytes is greatly increased and LE-cell-like phenomena appear. No such effect is obtained by other anticoagulants such as citrate, oxalate or heparin. "We assume that Liquoid Roche so alters the serum proteins that phagocytic phenomena occur in the leukocytes, especially the polymorphonuclear neutrophils whereby the LE phenomenon is made possible." Perhaps "the genuine LE phenomenon is based on the action of pathologic heparinoids in combination with the gamma-globulin fraction in the patients serum."

Hausman & Dreyfus C99,073/53: A single i.v. dose of Liquoid causes hyaline thrombosis of the renal glomerular capillaries, lungs and adrenals of the rabbit. In the kidney, "they often lined the walls of the capillaries and formed casts which resembled to some extent the 'wire-loop' lesions seen in disseminated lupus erythematosus." The finding of Inderbitzin (G21,895/51, B76,311/52, B99,377/53) that Liquoid reproduces the "L. E. phenomenon" in normal human blood in vitro and in rabbit blood in vivo has been confirmed. "During the course of this work a rabbit died suddenly some hours after receiving a single injection of Liquoid i.v. Postmortem examination disclosed intracapillary precipitates in the glomeruli which resembled to some extent the 'wire-loop' lesions frequently seen in the kidneys of patients with disseminated lupus erythematosus, with similar precipitates also in the capillaries of the lungs and in those of other organs."

Periarteritis Nodoso. Gairdner B45,718/48: Detailed review of anaphylactoid purpura. "Purpura fulminans and post-scarlatinal gangrene are probably variants of the Schönlein-Henoch syndrome." . . . "Clinically, pathologically, and etiologically, the Schönlein-Henoch syndrome is linked with acute nephritis, rheumatic fever, and polyarteritis nodosa. A pathogenesis common to this group of conditions is suggested."

Fehr & Brunson G21,900/57: In rabbits in which an SSP-G-like syndrome was produced by combined treatment with bovine gamma globulin and *E. coli* endotoxin or Liquoid, "the coronary arterial lesions were associated with an inflammatory reaction which resembled the changes of polyarteritis."

Thiers et al. D31,774/58: In a patient with the clinical manifestations of periarteritis nodosa, a large hemorrhagic cutaneous necrosis occurs which terminates in exulceration. Exudates from this ulcer, injected i.c., elicit

a hemorrhagic necrosis interpreted as an SSP-L. [No conclusive evidence against an anaphylactic origin is presented (H.S.).]

Raynaud's Disease. *Marcus G23,205/21:* First demonstration of the fact that following infection with streptococci, s.c. injection of epinephrine into the rabbit ear produces local hemorrhagic necrosis. Since gangrene frequently develops in patients with latent Raynaud's disease under the influence of infection, it is assumed that here adrenergic mechanisms may also play a role.

Iwai & Meisai G17,420/26: Attacks of Raynaud's disease are due to mechanical occlusion of the vessels by erythrocytes agglutinated through the effect of autohemagglutinins at low temperatures.

Wintrobe & Buell G26,423/33: In a patient with myelomatosis and hyperproteinemia, symptoms suggesting Raynaud's disease were combined with thromboses of the retinal veins.

Benians & Feasby D13,160/41: In two middle-aged women, Raynaud's syndrome was associated with spontaneous cold hemagglutination.

Helwig & Freis G26,421/43: Demonstration of cold autohemagglutinins in a patient who developed acrocyanosis after atypical pneumonia. Unlike in most previously published cases of this type, there was no paroxysmal hemoglobinuria. The symptoms resembled Raynaud's syndrome.

Stats & Bullowa G26,422/43: Cold hemagglutination with symmetric gangrene of the tips of the extremities was seen in a patient with paroxysmal hemoglobinuria. Detailed review of the literature on cold hemagglutination.

Hansen & Faber C89,337/47: In a patient with aleukemic plasma-cell leukemia, "Raynaud attacks were not vascularly dependent, but caused by the presence of an abnormal euglobulin which upon cooling was precipitated in the vessels with a reversible embolism as the result. The attacks ceased upon heating, the precipitated protein being again dissolved." Apparently, Raynaud's syndrome is not necessarily dependent upon vascular spasms alone.

Baumgartner B40,110/48: Following what appears to have been a virus pneumonia, a patient developed special sensitivity to cold, in that the ears, nose and fingers became intensely cyanotic upon exposure to low temperature. The erythrocytes in a drop of citrated blood, agglutinated upon exposure to cold in vitro in a manner detectable by naked eye inspection and dispersed again upon raising the temperature. Erythrocyte agglutination could also be demonstrated by the capillary

microscope in vivo. Blood taken from a finger, immediately after immersing it into cold water, contained "cold hemo-opsonins" demonstrated by the fact that the monocytes phagocytosed erythrocytes. It is assumed that, in patients of this type, exposure to cold in vivo produces erythrocyte agglutination thrombi which interfere with the microcirculation.

Linke B53,875/49: Various forms of Raynaud's syndrome are described: 1. Cryoglobulinemia with spells of cyanosis which are elicited by cold, presumably because the labile blood globulins precipitate in the capillaries and produce thromboses when the external temperature falls below a certain level. 2. Raynaud's syndrome with cold-auto-agglutination of erythrocytes which produces erythrocyte thrombosis in the microcirculation.

Linke G26,040/50: In some patients, Raynaud's syndrome develops upon exposure to cold, because of cold agglutination of erythrocytes.

Ferriman et al. G27,045/51: In three cases with Raynaud's phenomenon, cold agglutinins, cold hemolysins and incomplete cold antibodies were abundantly present in the serum. The patients suffered from hemolytic anemia with hemoglobinuric attacks in cold weather. Nine similar cases were found in the literature. "The Raynaud's phenomena are almost certainly due to obstruction of the peripheral circulation caused by auto-haemagglutination in vivo."

Valva & Morandini E23,956/63: In patients with Raynaud's disease, the digital vessels are hypersensitive to adrenergic substances and particularly to norepinephrine.

Buerger's Disease. *Schmidt-Weyland G24,461/32:* Following infection with live streptococci or tubercle bacilli, as well as after inoculation with killed *E. coli*, rabbits become hypersensitive to epinephrine injected s.c. into the ear. Unlike control rabbits, they develop hemorrhagic necrosis with leukocytic and hyaline thrombi in the capillaries and veins (less frequently in the arteries). These changes are compared to those of Thromboangiitis obliterans and it is suspected that some adrenergic mechanism may play a role not only in this disease, but also in the thromboembolic phenomena frequently observed in the course of severe infections (e.g., cholera, dysentery).

Tingaud D19,725/64: In many patients with Buerger's disease, long-lasting remissions are obtained after total or even partial adrenalectomy. It is assumed that adrenal hormones (corticoids, catecholamines?) play an important part in the pathogenesis of this malady.

Collagenoses in General, "Systemic Fibrinoid Disease" (Including Malignant Hyperten-

sion). *Becker* G28,260/48: Benzol, nitrogen mustard and x-irradiation inhibit the SSP-L in the rabbit. "It is postulated that the mechanism of suppression by these agents is exerted through their specific but common suppressive action on the reticulo-endothelial system, primarily the vascular endothelium. These endothelial cells being rendered anergic are not able to react to the active principles in a way that otherwise would be self-destructive." . . . "This concept would be directed toward suppressing the ability of the vascular endothelium to react adversely to whatever circulating toxin might be the inciting agent. A group of these diseases would include active rheumatic fever, acute, subacute, and chronic disseminated lupus erythematosus, periarteritis nodosa, generalized vascular diseases due to hypersensitivity reactions to drugs, sera or vaccines, and probably dermatomyositis, rheumatoid arthritis, and acute and subacute glomerulonephritis."

Beigelman G27,352/51: Two cases of Moschcowitz's disease with multiple platelet thrombi in the capillaries of various organs including those of the renal glomeruli, heart, muscles, lung and skin were associated with signs of Lupus erythematoses. "It is proposed that the platelet thrombosis syndrome be placed in the same category as the so-called collagen diseases, such as periarteritis nodosa, lupus erythematosus and dermatomyositis."

Booth et al. G28,649/55: In rabbits in which an SSP-G was produced by two injections of *E. coli* endotoxin, the hyaline material deposited in various vessels (and especially in the renal glomerular capillaries) was identified as fibrinoid by a variety of histochemical tests. It is indistinguishable from the fibrinoid accumulating in the necrotic arterioles of malignant hypertension in man.

Brunson & Davis G23,480/55: On the basis of histologic studies, it is assumed that acute rheumatic fever, scleroderma, lupus erythematosus, thrombotic thrombocytopenic purpura, malignant hypertension, periarteritis nodosa and subacute glomerulonephritis have many features in common, especially the formation of fibrinoid presumably from altered fibrinogen which is also a prominent feature of the SSP elicited in rabbits by bacterial endotoxins. "Factors important in the experimental production and localization of fibrinoid lesions appear to be an alteration in or production of abnormal serum proteins and structural or functional alterations in the endothelium of the cardiovascular system. It is suggested that similar mechanisms may operate in the patho-

genesis of the human diseases which have been discussed."

Craig & Gitlin G26,196/55: Tissues of patients suffering from various collagenoses, glomerulonephritis, and thrombotic thrombocytopenic purpura were stained by Coons' technique for the fixation of labeled antihuman fibrin serum detectable under ultraviolet light. "The evidence here was highly suggestive that fibrin was deposited intimately among the collagen bundles but often the collagen appeared intact and coated with fibrin."

Pagel & Treip G24,219/55: Dermatomyositis and scleroderma are considered to be "stages of the same disease" and Lupus erythematosus is likewise closely related. In lupus and dermatomyositis, extravascular fibrinoid necrosis associated with capillary thrombosis in the nail folds is characteristic. Glomerular capillary thrombosis may accompany "wire-loop" formation in lupus and all these diseases may be associated with visceral changes. For intermediate forms, the name of "viscero-cutaneous collagenosis" is proposed.

Booth et al. G12,832/56: Histochemical analysis shows that the fibrinoid, accumulating in the glomerular capillaries and afferent arterioles of the rabbit kidney during an SSP-G induced by two i.v. injections of *E. coli* endotoxin, resembles that seen in human malignant hypertension.

Bechtelsheimer & Shallock G27,365/60: On the basis of histochemical studies the following collagen diseases are considered to be related to the SSP-G and described as "thrombotic microangiopathies": Moschcowitz's disease, Lupus erythematosus, scleroderma, dermatomyositis, rheumatic endarteritis and the acronecrosis of Pagel.

McKay G30,936/65: Disseminated intravascular clotting occurs in certain types of hypersensitivity including disseminated Lupus erythematosus, glomerulonephritis, periarteritis nodosa, rheumatoid arthritis, rheumatic fever, dermatomyositis and scleroderma. The chronic form is associated with thrombocytopenia, cryofibrinogenemia, granular deposits of macromolecules of fibrin on the basement membrane of the renal glomeruli, and Raynaud's phenomenon. In the acute form, there is disseminated thrombosis of arterioles, capillaries and venules often associated with shock, a hemorrhagic tendency, decrease in circulating clotting factors and focal necrosis in various organs including lungs, heart, kidney, adrenals, pancreas, etc. All these reactions are closely related to the SSP.

HYPERPARATHYROIDISM

Hyperparathyroidism tends to be associated with a "thromboembolic diathesis" affecting predominantly the small vessels of the kidneys and pancreas. The duodenal ulcers and the acute hemorrhagic pancreatitis of hyperparathyroidism may also find their explanation in the formation of microthrombi. Although calcium plays a cardinal role in the blood clotting process, it remains to be seen whether the thrombotic tendency in hyperparathyroidism is mediated through this electrolyte.

Mellgren 76,911/36: In a woman with acute hyperparathyroidism, multiple thrombi developed in the principal renal vein and the interlobular and arcuate veins, as well as on the surface of the endocardium and the lung.

Arnold G27,026/40: In a 40-year-old man, a cystic parathyroid adenoma was associated with numerous thromboses and embolisms in the tumor itself as well as in the portal vein and the vessels of the pancreas, kidney, pelvic organs and gastrointestinal tract. The associated pancreatic necrosis, duodenal ulcers, and glomerular nephritis may have been related to the generalized thromboembolic diathesis.

Smith & Cooke A35,233/40: In a woman who died during a crisis in the course of chronic hyperparathyroidism, there were recent thromboses in the kidneys and the pancreas, in addition to the usual soft-tissue calcification.

Mellgren 91,165/43: "The multiple thromboses, which are plainly the expression of an intensive thrombo-diathesis, constitute a spe-

cific element in the pathology of acute hyperparathyroidism and are assuredly of great importance to the lethal issue." Their pathogenesis is obscure but they may be the result of hemoconcentration or an increased blood calcium, both of which facilitate blood coagulation.

Henriksson C92,586/60: A case of acute hyperparathyroidism with pancreatitis and multiple thrombi including hyaline thrombosis of the renal glomerular capillaries. Review of earlier literature on thrombohemorrhagic lesions in hyperparathyroidism as seen in animals and man.

McKay E4,788/65: Acute fatal hyperparathyroidism is frequently associated with disseminated intravascular coagulation. There may be necrotizing pancreatitis, multiple thrombi in the kidneys and a parathyroid tumor itself, as well as thrombi in the renal arterioles and glomerular capillaries reminiscent of the SSP-G.

PANCREATITIS

Thrombosis and hemorrhage is a common feature of acute pancreatitis in man; it may be associated with renal cortical necrosis and glomerular capillary thromboses. In animals, hemorrhagic inflammation has been produced experimentally in the pancreatic tissue by topical preparation followed by i.v. provocation with bacterial endotoxins; it may also occur after heterologous blood transfusion. In view of these facts, several investigators suspect a close relationship between acute pancreatitis and the SSP.

Bezza G28,396/38: An SSP-L can be elicited in the pancreas of the dog by the injection of *E. coli* endotoxin into the pancreatic duct, followed 24 hrs. later by the i.v. administration of the same material. It is assumed that the SSP may play a role in the development of certain types of hemorrhagic pancreatitis in man.

Smyth B33,682/40: Among 40 cases of acute hemorrhagic pancreatic necrosis, thrombosis was the most common vascular lesion, veins

being more frequently occluded than arteries. In several cases, extrapancreatic thrombi were also found, e.g., in the heart, lungs, and kidneys.

Ackerman 57,770/42: In a patient with acute thrombohemorrhagic pancreatitis following incompatible blood transfusion, thromboses and hemorrhages were also noted in other organs.

Heilmann B88,956/52: It is assumed on theoretic grounds that certain cases of acute pancreatic necrosis are due to the SSP.

Thal & Brackney B93,944/54: Fulminating hemorrhagic pancreatitis can be produced both in the rabbit and in the goat if *E. coli* endotoxin is first introduced into the pancreatic duct and later injected i.v. No lesion occurs if the provocative i.v. injection is omitted. Histologic studies uniformly showed capillary and venular hyaline thromboses such as also occur in clinical cases of hemorrhagic pancreatitis.

Hardaway & McKay D95,869/59: Acute hemorrhagic pancreatic necrosis is produced in dogs by the intra-aortic infusion of human blood. The reaction is associated with intravascular clotting in the pancreas and other organs. A review of the literature shows that hemorrhagic pancreatitis in man is also frequently associated with thrombosis in veins and capillaries, as well as with lower nephron nephrosis.

Henriksson C92,586/60: A case of acute hypoparathyroidism with pancreatitis and multiple thrombi including hyaline thrombosis of the renal glomerular capillaries.

Richez et al. E91,184/60: Acute pancreatitis in man is frequently associated with renal cortical necrosis, thrombosis of the afferent arterioles and dilatation of the glomerular capillaries which are packed with erythrocytes. It remains to be shown whether the renal changes (which are quite similar to those of the SSP-G) are secondary to the pancreatitis or whether both the pancreatic and the renal lesions are the consequence of a common pathogenic derangement.

McKay E4,788/65: In acute hemorrhagic pancreatitis, intravascular coagulation is not confined to the pancreas. The renal glomerular capillaries may be filled with fibrin thrombi and, occasionally, ureteral mucosal hemorrhages and subendothelial hemorrhages occur.

Seifert F30,647/65: General review of the evidence suggesting that hemorrhagic pancreatitis in man may be related to the SSP.

TUMORS

An association between malignant neoplasms and a thrombotic diathesis has long been suspected. The phenomenon sometimes referred to as "thrombophlebitis migrans" can develop in conjunction with various types of tumors but is particularly common in patients with prostatic carcinoma. The pathogenesis of this phenomenon is not known, but the liberation of tissue thromboplastin by the neoplasm or the mere flooding of the circulation with necrotic tumor particles, which block the RES, may be involved.

The hemorrhagic diathesis associated with giant hemangiomas is presumably a consumption coagulopathy in which eddying of blood and stasis initiate clotting which secondarily leads to thrombocytopenia and a depletion of blood-clotting factors. Here, a causal relationship to the neoplasm has been definitely established by the cure of the coagulation defect that follows excision of the hemangioma.

Smith G27,028/32: Thrombophlebitis migrans affecting both superficial and deep veins developed in a patient as a consequence of generalized carcinomatosis, probably originating in a primary tumor of the pancreas or gut.

Sprout G26,512/38: Disseminated venous thrombosis is unusually common in patients with various types of carcinomas, particularly when these originate in the pancreas.

Hausner G19,190/49; Richter & Johne G23,888/50: In a 44-year-old woman with chronic generalized lymphogranulomatosis and scabies with pyoderma, nitrogen-mustard therapy elicited multiple thrombophlebitic lesions in the

skin which lasted for weeks. Immediately after a new attack of thrombophlebitis, there developed a generalized Herpes zoster with hemorrhagic vesicles, and 6 days later the patient died. Apart from the lymphogranulomatosis, autopsy revealed hemorrhagic necrosis of the small intestine, pleura and lungs. The authors assume that a decrease in the antibody titer, induced by lymphogranulomatosis and nitrogen-mustard therapy, may have been responsible for the sudden multiplication of the zoster virus which perhaps in conjunction with the pyoderma microbes may have caused an SSP.

Cosgriff & Leifer B70,958/52: Pronounced hemorrhagic diathesis (parahemophilia) owing to factor-V-deficiency developed, following orchiectomy in a patient with metastasizing prostatic carcinoma.

Soulier et al. G21,655/52: Eight cases of fatal hemorrhage among patients who underwent pneumonectomy for cancer or tuberculosis of the lungs. It is assumed that the blood becomes incoagulable because of intravascular clot formation as a result of thromboplastin liberation from damaged lung tissue. There is afibrinogenemia and greatly accelerated fibrinolysis.

Tagnon et al. E58,975/52; E54,961/53: Prostatic carcinoma is frequently associated with fibrinolysis and fibrinogenopenia, a prolongation of the prothrombin time and generalized hemorrhagic manifestations. It is suggested that fibrinolytic enzyme originates in the prostatic cancer itself.

McKay & Wahle G26,855/55: In a patient with carcinoma of the colon, fibrin deposits were formed in the capillaries of the heart, lungs, spleen and liver, as well as on the heart valves. Many additional cases of disseminated thrombosis in cancer patients are quoted.

McKay et al. G33,280/55: A case of fatal renal capillary thrombosis in a patient with squamous cell carcinoma of the cervix who had just been delivered by cesarean section is tentatively ascribed to the SSP-G.

Rapaport & Chapman G33,245/59: In a patient with metastatic prostatic carcinoma, hypofibrinogenemia was associated first with bleeding and then with hypercoagulability. "This case is thought to link the rare syndrome of acute hypofibrinogenemia with the common observation of venous thrombosis in malignancy."

Naeye E94,374/62: In an 81-year-old man with disseminated prostatic carcinoma, a hemorrhagic state with afibrinogenemia developed. EACA treatment produced widespread intravascular thrombosis, presumably because, by inhibiting fibrinolysis, it unmasked a process of intravascular coagulation that had initiated the hemorrhagic diathesis.

McKay E4,788/65: Review of the literature on the association of carcinoma with microscopic thrombi of major veins. This phenomenon, sometimes referred to as "thrombophlebitis migrans" has been known since the nineteenth century. It may be associated with fibrin thrombi in the renal glomerular capillaries, fibrinous vegetations on the cardiac valves and hemorrhagic diathesis. In these instances, the mechanism of the THP is not clear, but it may depend upon some clotting agent originating in the neoplasm, for example, the discharge into the blood of some tissue thromboplastin, a proteolytic enzyme (especially in the case of pancreatic and prostatic carcinomas) or merely particulate matter such as necrotic tumor particles which, having gained access to the blood, could act somewhat like RES-blocking agents. Metastatic prostatic carcinoma may represent a special case, because it is sometimes associated with hemorrhagic diathesis and fibrinogenopenia. It has long been known that giant hemangioma may be associated with a generalized hemorrhagic diathesis. There is good evidence that the hemangioma plays a causal role since its spontaneous regression or surgical excision results in the subsidence of the thrombocytopenia and hemorrhagic diathesis. It is reasonable to assume that eddying of blood and stasis, as well as damage to the abnormal endothelium, are responsible for the initiation of clotting within the tumor. "Agglutination of platelets in the tumor results in thrombocytopenia. Viscous metamorphosis allows release of clotting factors from the platelets and fibrinogen depletion along with prothrombin, Factor V, and VII, occurs. Fibrinolytic enzyme is activated causing a further depletion of clotting factors. Bleeding at a distance from the tumor might then result from the thrombocytopenia, and fibrinogenopenia with increased fibrinolytic enzyme activity."

Verstraete et al. G15,997/65: The Kasabach-Merritt syndrome (association of congenital hemangioma with marked thrombocytopenia and bleeding) is ascribed to a consumption coagulopathy.

VARIOUS OTHER DISEASES

The possible pathogenetic role of the SSP has also been considered in connection with a variety of other spontaneous maladies of man. On theoretic grounds, it would seem highly probable that thrombosis and embolism in *large vessels*—such as occur in coronary and pulmonary infarction and in many types of thrombophlebitis—are somehow related to the THP. In both types of disease, the principal derangement is a predisposition to the formation of intravascular clots,

although in one case, these tend to develop in large vessels, while in the other, they affect the microcirculation predominantly.

There is some evidence that decreased destruction of endotoxins derived from the intestinal flora may play a part in the development of the *shock syndrome*. Since shock can produce intravascular blood coagulation and even renal cortical necrosis, the SSP may play a role in its pathogenesis.

The frequent association of *intussusception* and anaphylactoid purpura has led to the assumption that an allergic disease may be responsible for both these phenomena. It would appear more probable, however, that the ischemic damage to the mesenteric vessels induced by intussusception is responsible for initiating a consumption coagulopathy by causing local thrombus formation. This could secondarily lead to thrombocytopenia and purpura.

The concept that *menstruation* may represent a naturally re-occurring SSP is not based on any solid experimental foundation.

Attention has been called to the structural similarity between the renal lesions of the THP-G and those of *diabetic glomerulosclerosis*. The retinal changes in the SSP-G resemble diabetic retinopathy.

Finally, the participation of the THP has been suspected on more or less speculative grounds in a number of other diseases such as *lipid embolism*, *liver cirrhosis*, *favism*, certain hemorrhagic diseases of the eye and *hypertonia labyrinthi*, etc.

Thrombosis of Large Vessels. *Vincke B24-, 876/47:* According to the method of Dietrich (E55,223/41), jugular vein thrombosis is produced in rabbits by partially constricting the vessel and then giving *E. coli* bacilli into the ipsilateral ear vein followed 24-48 hrs. later by the i.v. administration of *E. coli* filtrate into the contralateral ear vein. [This observation suggests some relationship between the SSP and the thrombosis of large vessels (H.S.).]

Rodriguez-Erdmann F4,492/64: Brief note cautioning against the use of fibrinogen in the treatment of clinical cases of SSP-G, because thrombus formation may be enhanced.

Shock. *Fine et al. D98,173/59:* Extensive animal experiments suggest that hemorrhagic and presumably other types of shock are largely dependent upon the increased absorption or decreased destruction of endotoxins derived from the intestinal flora.

Hardaway & Johnson E48,596/63: In dogs, *E. coli* endotoxin causes a decrease in blood fibrinogen, factor V and factor VII, as well as thrombocytopenia and endogenous activation of heparin. Heparinization prevents the fall in fibrinogen and maintains blood pressure. "All these findings are further evidence that endotoxin shock is produced at least in part by intravascular coagulation."

Skjörten G22,099/64: Detailed description of the morphologic characteristics of glomerular

fibrin precipitations in cases of bilateral renal cortical necrosis. Small round bodies with the staining characteristics of fibrin have also been found in the pituitary and cerebral vessels. There is evidence of intravascular coagulation in various forms of shock even if unaccompanied by renal cortical necrosis, "and the relationship to the generalized Shwartzman reaction is pointed out."

Intussusception. *McKay E4,788/65:* A review of the literature suggests that intussusception often occurs in combination with "anaphylactoid purpura" and that some allergic disease may be responsible both for the purpura and the intussusception. "In actual fact, the reverse is true; in most cases, the ischemic vascular damage to the mesenteric veins and arteries associated with intussusception is responsible for the hemorrhagic diathesis." It appears that the severity of the condition is proportional to the extent of the blood vessel compression and damage in the intussuscepted intestinal segment. The pathogenesis of the resulting syndrome is visualized as follows: "with the slowing or cessation of blood flow in this variable portion of the vascular system, ischemic damage to the endothelium occurs with agglutination and adherence of platelets. Thrombosis of large and small vessels may follow. When the intussusception is reduced, blood recirculates through this segment and

clumped platelets, platelet products, and fibrin are swept into the general circulation. The thromboplastin released from these damaged platelets generates thrombin, which causes further agglutination and destruction of platelets. The thrombocytopenia which develops is then responsible for the purpuric manifestations."

Menstrual Bleeding, Metrorrhagia. *Guarna G28,395/35:* An SSP-L can be elicited in the ovary, uterus or vagina of the rabbit by topical preparation and subsequent i.v. provocation with typhoid endotoxin. It is assumed that similar phenomena may play a role in certain metrorrhagias that develop in women in the course of infections and intoxications.

Freud & Vedder A38,416/40: Since it was impossible to reproduce an SSP in the rabbit by gonadotrophic pituitary extracts, menstruation is not considered to be a "natural reoccurring phenomenon of Shwartzman." [Neither the experimental techniques nor the rationale of these experiments are quite clear from the brief description given (H.S.).]

Diabetes Mellitus. *Fehr & Brunson G21,900/57:* In rabbits in which an SSP-G-like response was elicited by bovine globulin s.c., followed by Liquoid or *E. coli* endotoxin i.v., the renal lesions resembled "focal" or "embolic" glomerulonephritis and the lesions of diabetic glomerular sclerosis as they occur in man.

Berken D21,841/62: In rabbits in which an SSP-G was produced by two i.v. injections of *E. coli* endotoxin, retinal changes developed which resembled those characteristic of diabetic retinopathy. There was deposition of PAS-positive material within the dilated veins, thickening of small vessel walls and often aneurysmal capillary dilatation. "It is suggested that this reaction may be an etiological factor in the pathogenesis of retinal capillary aneurysms in the diabetic."

Lipid Embolism. *Bouvier G28,393/65:* Review of the literature on the production of an SSP by lipid embolisms through the production of a consumption coagulopathy.

Liver Cirrhosis. *Verstraete et al. G15,997/65:* In certain cases of chronic liver cirrhosis, a consumption coagulopathy results.

Favism. *Casper & Shulman C19,533/56:* Bilateral renal cortical necrosis with thromboses in the interlobular arteries, the afferent arterioles and the glomerular capillaries occurs in infants with favism. This condition is seen especially in individuals of Mediterranean origin following ingestion of fava beans, or even upon merely approaching a field of fava beans. It is associated with hemolytic anemia and ascribed either to allergy or to some plant agglutinin which acts specifically on erythrocytes in racially predisposed individuals.

McKay E4,788/65: Favism (caused by *Vicia faba*, commonly known as the broad bean) is particularly common in Sardinia and Sicily. Spells of favism are characterized by sudden intravascular hemolysis associated with shock, anuria, fever, hemorrhagic diathesis, thrombocytopenia and disseminated intravascular thrombosis, sometimes with bilateral cortical necrosis.

Diseases of the Eye. *Shwartzman G22,086/44:* Theoretic considerations regarding the possible role of the SSP-L in the production of various diseases of the eye.

Diseases of the Ear. *Tsuiki & Kamioka G22,252/52:* Following topical application of *B. typhosus* endotoxin to the internal ear, a provocative injection of the same material i.v. elicits an SSP-L in the labyrinth. [Species not stated, probably rabbit (H.S.).] It is claimed that this "experiment has offered thus some suggestion as to the etiology of the disease called hydrops or hypertonia labyrinthi."

Hemorrhagic Leukoencephalitis. *Masland & Barrows G33,259/62:* Description of a woman with thrombotic thrombocytopenic purpura and hemorrhagic leukoencephalitis as a clinical form of the SSP-G.

Agammaglobulinemia. *Hitzig & Gautier G33,-255/59:* In two children who died from agammaglobulinemia with renal disease and neurologic complications, necropsy "revealed the typical findings of the generalized Sano-relli-Shwartzman phenomenon, i.e., bilateral renal cortical necrosis and extensive vascular changes with subendothelial and intracapillary deposition of fibrinoid. The occurrence of this peculiar reaction of the body in the presence of a deficiency of antibody formation is stressed. An interaction of autoantibodies seems therefore very improbable."

CHAPTER VIII

THEORIES

ALLERGIC-IMMUNOLOGIC REACTIONS

SINCE the SSP resembles allergic-immunologic reactions in many respects, the earliest and perhaps the most widely discussed theory of its pathogenesis attempted to relate it to various types of serologic hypersensitivity responses and in particular to anaphylaxis.

Allergic-immunologic Phenomena in General with Special Reference to Anaphylaxis. In the SSP as in anaphylaxis, the blood becomes incoagulable and there is thrombocytopenia. Furthermore, the production of an SSP-L by endotoxin protects the guinea pig against anaphylaxis induced by some other antigen such as horse serum. However, thrombocytopenia with coagulation defects, and transient resistance to anaphylaxis are both comparatively nonspecific changes that can be induced by many agents (including anaphylactoid shock) which do not depend upon the formation of antibodies.

The SSP is certainly not an anaphylactic reaction in the ordinary sense of the term because: 1. one endotoxin can prepare for provocation by another endotoxin or even by a nonmicrobial product, 2. SSP-reactivity develops within hours after preparation, and is of short duration, 3. all attempts to demonstrate SSP-specific antibodies in the blood or tissues have been unsuccessful.

It is true that anaphylactic sensitization can so modify responsiveness that a classic anaphylactic response becomes thrombohemorrhagic under the influence of an endotoxin. In this event, immunization against the anaphylactogenic agent prevents the SSP-like response, but here, serologic immunity is induced only against the anaphylactic component of the complex pathogenic situation, not against the SSP itself.

Shwartzman E41,370/28: The SSP-L differs from known bacterial hypersensitivity phenomena by the following features: "Local reactivity; the short incubation period necessary to induce the local reactivity; the short duration of the state of reactivity; the ability to induce local reactivity by a single skin injection; the severity of the reaction; and the necessity to make the second injection of the toxic agent by the intravenous route."

Burnet E42,707/31: The SSP-L "is certainly not anaphylactic in any ordinary sense of the term, but it has some suggestive similarities to the classical anaphylactic phenomena."

Gratia & Linz E64,450/31: An SSP-L elicited by *E. coli* endotoxin injected first into the ear and next day i.v. in the rabbit, causes the blood to become incoagulable. The platelet

count drops from 700,000 to 70,000 and the red cell count also diminishes. The incoagulable blood can be made to clot by bubbling CO₂ through it. All these phenomena resemble classical anaphylaxis. Furthermore, the production of an SSP-L by *E. coli* in the guinea pig desensitizes the animal to classical anaphylaxis by repeated injections of horse serum. "These observations speak in favor of the anaphylactic nature of the phenomenon."

Gratia & Linz E68,985/31: "It appears that the Shwartzman phenomenon is a complex of anaphylactic and nonanaphylactic manifestations," because: 1. A strong anaphylactic response, produced in the sensitized guinea pig by horse serum, cannot protect the animal against the production of an SSP-L by *E. coli* endotoxin; 2. an SSP-L can protect the guinea

pig against anaphylactic shock as well as against the usual manifestations of intoxication with anaphylatoxin.

Klein E65,246/31-32: The SSP-L normally produced in rabbits by two injections of meningococcal or *B. dysenteriae* toxin can be prevented if, just prior to the i.v. provocative injection, these same toxins are injected into the prepared skin site. It has previously been thought that this local inhibition might be due to some immunological phenomenon, however, the author found that many substances (adrenalin, pituitrin, normal saline, phenolized saline, formalinized saline, sterile egg-white solution, immune rabbit serum, normal human serum) injected i.c. just prior to the provocative i.v. injection, exhibit the same inhibitory effect. Indeed, even compression of the skin site with padded clamps can protect it. Hence "it is believed that these agents produce their effects by creating a local ischemia which shields the prepared skin tissue from the injurious agents circulating in the blood stream."

Gratia & Linz D6,544/32; G23,092/33: The SSP is considered to be a manifestation of anaphylaxis because: 1. Like anaphylaxis, it is accompanied by capillary stasis, hypotension, thrombopenia and incoagulability of the blood; 2. the rabbit and guinea pig, which are highly sensitive to anaphylaxis, are also most susceptible to the SSP; 3. the SSP desensitizes against serum shock and that in proportion to the intensity of its manifestations. Hence, it is suggested to designate the SSP as a "hemorrhagic allergy" and, when it is elicited by nonspecific means, as a "hemorrhagic hetero-allergy." In this sense, the SSP "could be only a variant of the Arthus phenomenon and indeed identical with the latter as regards its manifestations."

Amantea 43,781/33: In rabbits deprived of their complement by hirudin or arsenobenzol, an SSP-L can still be produced by bacterial endotoxins; hence, the response differs from anaphylaxis.

Apitz D10,355/33: Topical re-injection of the prepared skin site with typhosus, coli or cuniculi septicum filtrates can produce intense local edema with leukocytic infiltration but no hemorrhage. "Thus, the resulting change in reactivity can also be demonstrated by this technique; only the hemorrhage is apparently dependent upon the intravascular administration of the antigen. Therefore, the morphologic specificity of the Shwartzman reaction depends upon the manner in which the filtrates are administered. The response is changed in the case of local re-injection and then becomes identical with local anaphylaxis."

Cassuto G26,876/33: On the basis of an extensive literature survey, the SSP is interpreted as an "allergic phenomenon."

Michelazzi D92,869/33: Intestinal loops, removed from rabbits 24 hrs. after *E. coli* endotoxin i.v. and exposed to the same endotoxin 24 hrs. after preparation, showed no change in their contractility suggestive of an anaphylactic phenomenon.

Michelazzi G26,872/35; G26,871/35: An extract of the skin of a rabbit previously given an i.c. injection of *E. coli* endotoxin, is incubated with the same endotoxin and then injected i.c. into another rabbit. Often, though not always, this mixture produces an "SSP-L" without subsequent provocation. [It remains to be seen whether this phenomenon is related to passive transfer, adjuviation, or—as the author believes—the formation of an antibody in the prepared skin site (H.S.).]

Michelazzi G26,190/36: "On the basis of various in vivo and in vitro experiments, the author concludes that the SSP-L is an immunological allergic reaction probably associated with the production of an antibody distinct from all those known up to date."

Shwartzman G24,342/36: Recapitulation of the principal differences between the SSP-L and true immune reactions.

Schmidt G28,194/37: A survey of the literature leads to the conclusion that the SSP is "closely related" to allergic phenomena.

Stetson G22,085/55: Systematic investigations have shown that the cutaneous ophthalmic and systemic reactions of normal rabbits to Gram-negative bacterial endotoxins are very similar to classical bacterial hypersensitivity reactions. Yet, it is concluded that "if bacterial hypersensitivity is involved in the reactions of rabbits to endotoxins, this hypersensitivity is probably not acquired. It is possible that there exists in normal rabbits a 'natural hypersensitivity,' analogous to the 'natural antibodies,' to gram-negative bacterial somatic antigens."

Hugues et al. G27,058/58: *S. typhimurium*, given i.p. and 24 hrs. later i.v. in rabbits, produces a peritoneal SSP-L in which the vascular changes can be observed in vivo on the exteriorized mesentery. The initial changes are detectable after about 6 min. and consist of ruptures of the veins with hemorrhages, but are unaccompanied by platelet embolisms or leukocyte agglutination. In these respects, they differ from the initial changes of anaphylaxis.

Kováts E99,030/61: Guinea pigs and rats sensitized 3-4 weeks previously with *S. typhosa* or *E. coli*, develop hemorrhagic skin lesions at sites prepared with endotoxin, on i.v. injec-

tion of endotoxin 24 hrs. later. Animals not pretreated with the bacteria do not develop hemorrhagic lesions. The endotoxin must not necessarily be derived from the bacteria used for sensitization. Rabbit antiserum, obtained by hyperimmunization with typhoid endotoxin, injected i.c. in guinea pigs or rats also causes hemorrhage, if followed 24 hrs. later by endotoxin i.v. Mixtures of typhoid endotoxin and colloidal silver i.c. followed by i.v. injection of the same material, likewise induce skin hemorrhages in guinea pigs. Normal rabbit, guinea pig or rat mononuclear peritoneal exudate cells injected i.c., and 24 hrs. later followed by endotoxin i.v. provoke similar skin hemorrhages. The author believes to have "succeeded in demonstrating that the first phase of the Shwartzman phenomenon, that is, preparation of the skin by endotoxin, is a specific reaction depending on a well-characterizable immunological mechanism, namely the phenomenon of local endotoxin hypersensitivity."

Enoki D60,740/62: Serological studies suggest that the SSP depends upon the interaction of a "Shwartzman antibody" and a "Shwartzman antigen." [Earlier Japanese literature on this subject is here reviewed in English, but the wording of the text is somewhat ambiguous (H.S.).]

Bernard et al. D69,624/63: A 22-year-old man suddenly fell ill following revaccination with TABDT vaccine. He developed high fever and an extensive erythematous papular non-pruriginous skin eruption. Eventually, profound shock ensued and the patient died on the sixth day. Autopsy revealed hemorrhagic fluid in the peritoneum, bilateral renal cortical necrosis with fibrinoid thrombi in the glomeruli as well as hemorrhagic necroses (without fibrin thrombi) in the adrenals, small intestine and other organs. The authors state that "there is no doubt that this case represents an instance of the Sanarelli-Shwartzman

phenomenon" but it is also related to anaphylaxis and Reilly's "syndrome of neuro-vegetative irritation."

Kováts et al. D85,430/63: Following i.c. injection of the serum of rabbits, hyperimmunized with typhoid endotoxin or vaccine (passive cutaneous anaphylaxis), *E. coli* or *E. typhosa* endotoxin i.v. produces an SSP-L at the site of preparation, both in guinea pigs and in rats. Essentially similar results are obtained if a mononuclear cell suspension, collected from the peritoneum of normal rabbits, guinea pigs or rats, is used for cutaneous preparation. The first experiment is interpreted as a cutaneous anaphylaxis due to endotoxin and the second as a cellular transfer of a delayed sensitivity to endotoxin. [It is not clear why the response induced by the mononuclears of the SSP-insensitive rat should be ascribed specifically to the transfer of hypersensitivity (H.S.).] "The phenomenon of endotoxin hypersensitivity is probably a natural hypersensitivity which exists in every mammal living in symbiosis with endotoxin producing microorganisms."

Lee G26,187/63: After RES-blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the appearance of "heparin precipitable fibrinogen" in the circulation. Apparently, antigen "antibody reactions in vivo can activate the blood-clotting system and endotoxins may act here on an immunologic basis."

Lee & Stetson E5,337/65: On the basis of an extensive literature survey the authors conclude "that bacterial endotoxins possess biologic activity by virtue of their antigenicity, and that in particular the tissue damage of the Shwartzman phenomena has an immunologic basis."

THE ARTHUS PHENOMENON

There are certain structural similarities between the SSP-L and the Arthus phenomenon, especially in that the latter may also exhibit a thrombohemorrhagic component. Furthermore, rabbits particularly sensitive to the SSP-L are also especially susceptible to anaphylactic shock and the Arthus phenomenon. However, not every THP can be equated with the SSP, and the same constitutional factors that make an animal sensitive to one kind of THP may also render it more susceptible to another, essentially unrelated type of this morphologic reaction form.

In rabbits sensitized with horse serum and prepared by an i.c. injection of the same antigen, provocation with *E. coli* filtrate i.v. can elicit a particularly throm-

bohemorrhagic response at the prepared skin site. However, this is merely another demonstration of the interaction between the SSP and the Arthus phenomenon; it does not prove the identity of these two reactions.

The Arthus response is obtained by repeated subcutaneous injection of specific antigens given at intervals of several days, and it is associated with the development of true immunologic antibodies. Thereby it differs essentially from the SSP.

Gratia & Linz G23,285/32: The SSP is regarded as essentially identical with the Arthus phenomenon, although it is elicited by different procedures, because: 1. A severe SSP is associated with capillary stasis, hypotension, thrombopenia and incoagulability of the blood, all characteristic manifestations of anaphylaxis; 2. an SSP can desensitize to the subsequent production of anaphylactic shock; 3. the rat and the mouse are refractory both to the SSP and to anaphylaxis; 4. hemorrhagic aseptic necrosis can be produced both by the SSP-L and by the Arthus phenomenon.

Apitz G24,112/33: Depending upon the technique of its elicitation, the Arthus phenomenon induced by repeated injections of horse serum in the rabbit may assume a strongly hemorrhagic character.

Gratia & Linz G23,076/33: The SSP-L is identical with the Arthus phenomenon and was correspondingly named "hemorrhagic allergy." The objection to this concept was the nonspecificity of the SSP-L but the Arthus phenomenon is likewise largely nonspecific since, in rabbits, pretreatment with horse serum facilitates the subsequent induction of an Arthus phenomenon with sheep serum, and vice versa.

Gratia & Linz G23,092/33: Earlier observers had noted that the Arthus phenomenon is often hemorrhagic. The authors show that rabbits especially sensitive to the SSP-L are also particularly susceptible to anaphylactic shock and to the Arthus phenomenon.

Polettini G25,136/35: In rabbits sensitized by an i.v. injection of horse serum, 8 days later *E. coli* endotoxin is injected i.c. Next day, the same site is injected with horse serum and simultaneously two new skin sites are injected respectively with horse serum or *E. coli* endotoxin. Without i.v. provocation, hemorrhagic reactions occurred at the site where either horse serum alone or horse serum and endotoxin was injected. Repeated s.c. injections of horse serum may also result in hemorrhagic necrotic types of the Arthus phenomenon which are indistinguishable from the SSP-L. Repetition of these experiments in dogs only rarely gave positive results.

Shwartzman G23,096/35: The SSP-L "should be clearly differentiated from the Arthus phe-

nomenon which may take place in the same animals after a considerably longer period of time of sensitization, and upon which the bacterial filtrates seemingly have no influence."

Gerber B78,161/36: "Although certain morphologic similarities exist between the phenomenon of Arthus and that of Shwartzman, they can be accurately differentiated immunologically and, to a certain degree, morphologically."

Fabiani G23,075/38: Those rabbits which respond most rapidly and intensely with an Arthus phenomenon upon repeated s.c. injection of horse serum, are also particularly sensitive to the production of an SSP-L by typhoid endotoxin. Conversely, rabbits which first proved to be particularly sensitive to the SSP-L react most rapidly and intensely with Arthus phenomena to subsequent treatment with horse serum. Presumably, in the first experiment, it was not the induction of an Arthus phenomenon that induced sensitivity to the SSP, but that the same constitutional factors are necessary to render the rabbit susceptible to either of these reactions.

Stetson B88,948/51: "The form of vascular damage determining the Arthus phenomenon is similar to that already observed in the case of the Shwartzman phenomenon, and the results of various metabolic, hematologic, and histologic studies indicate that the mechanisms resulting in both phenomena are closely related."

Stetson C11,252/51: A review of the literature suggests that "the tissue damage of both the Arthus and the Shwartzman phenomenon has been found to be due to a characteristic vascular lesion, consisting of occlusion of the capillaries and small veins by masses of leukocytes and platelets, followed by necrosis and hemorrhage." . . . "Similar vascular lesions have been found in the hearts of patients showing evidence of early active rheumatic carditis, and it is suggested that these lesions may be involved in the pathogenesis of this disease."

Rostenberg G21,665/53: Careful comparison of the characteristics of the SSP-L and the Arthus phenomenon suggests that the two "are essentially different though there are points of similarity in their mechanisms."

Rempt G23,511/54; Rempt & Julius G23,512/54; Rempt G23,068/56: A rabbit is sensitized with horse serum and injected parenterally with *E. coli* filtrate. Upon i.c. injection of horse serum, it develops an Arthus phenomenon with a central hemorrhage, indistinguishable from the SSP-L. "The result is a combined phenomenon of Arthus-Shwartzman. Without previous contact with *coli* filtrate only the Arthus phenomenon is induced."

Utshitel & Krymski C35,541/56: Both the Shwartzman and the Arthus phenomenon can be inhibited in rabbits by artificially induced hypothermia. It is assumed that these phenomena are allergic and that the protective effect of cold may be mediated through the alarm reaction with its stimulating effect upon corticoid production.

Gatling C58,378/58: In rabbits, hypersensitized to horse serum, 100 µg. of epinephrine i.c. given soon after an additional dose of horse serum i.v. produce a THP-L at the site of catecholamine treatment. A similar response is obtained by norepinephrine but not by ephedrine. The response shows individual variations but its intensity parallels that of an Arthus reaction elicited in the same rabbit. Epinephrine, injected into an Arthus lesion so alters the latter that it becomes similar to an epinephrine lesion. Epinephrine i.c. given to sensitized rabbits which have not received a simultaneous i.v. injection of horse serum is ineffective. Apparently, the "epinephrine lesion does not occur in the skin of the hypersensitive rabbit in the absence of circulating antigen, residual or injected."

Lee & Stetson G21,653/60: Single i.c. injections of *E. coli* or *S. typhosa* endotoxin produce delayed inflammatory reactions in the rabbit. Moderate erythema and leukocytic infiltration appear after 6-12 hrs., reaching a maximum at 20-24 hrs. By contrast, in rabbits which first received a single i.v. injection of *E. coli* endotoxin, the subsequent i.c. administration of *E. coli* or *S. typhosa* endotoxin produced a greatly accelerated and intensified cutaneous response. Within 1 hr., there was bleb formation with pronounced edema, erythema and leukocytic infiltration although extravasation of erythrocytes and necrosis were rarely conspicuous. The response resembled the Arthus reaction both

in general appearance and in being visible within an hour. This accelerated reactivity is detectable 6 hrs. after the i.v. injection and, in some animals, weak but definite, accelerated reactivity was demonstrable for as long as a month. Although the reaction was specific for endotoxins as a group, rabbits pretreated with one endotoxin i.v., responded with accelerated reactions to skin testing with other endotoxins. The capacity for accelerated reactivity can be transferred from a rabbit given *E. coli* endotoxin i.v. to another, unpretreated, rabbit in which the skin test is performed. These findings suggested that accelerated reactivity might be an Arthus phenomenon, due to interactions between antigen and precipitating antibody. However, in various experimental arrangements, no parallelism was found between the appearance of precipitating antibodies and accelerated skin reactivity. Besides, the precipitating antibodies found were highly antigen-specific. On the other hand, a cross-reacting nonprecipitating antibody appeared within 3 days after the i.v. injection of endotoxin concurrently with the accelerated skin reactivity. "The possibility that such antibodies may be involved in the non-specific immunity elicited by endotoxin would seem to deserve investigation." These cross-reacting antibodies may play a role in the production of the SSP-G and SSP-L.

Harkavy E4,625/63: "While it is evident that the underlying immunologic process in the Arthus and Shwartzman phenomena is decidedly different, the final tissue changes, that is, hemorrhagic necrosis, are associated with a peculiar form of vascular injury characterized in each instance by leukocytic thrombosis."

Cochrane E5,332/65: A survey of the literature shows many similarities between the SSP and the Arthus phenomenon. "Both reactions develop in the several hours following challenge, both are marked by an influx of polymorphs, and in at least the severe Arthus reactions in which large quantities of immune reactants are employed, leucocyte-platelet thrombi occur in both. However, at least one difference apparently exists, and that is the dependence of the Shwartzman phenomenon on thrombosis, for the reaction is preventable with heparin."

The Auer Phenomenon. The Auer phenomenon manifests itself by hemorrhagic blister formation at sites where xylol is gently rubbed into the ears of rabbits sensitized to horse serum and then challenged with the same antigen. It apparently depends upon the fact that the sensitized animal localizes the sensitizing antigen in inflamed tissues, so that particularly violent, topical anaphylactic responses

result. Although these may exhibit structural similarities to the SSP-L, they merely represent another form of THP-L which cannot be equated with the "phenomenon of local sensitivity to bacterial filtrates."

Auer G22,074/20: Xylol applied to the ears of rabbits sensitized with horse serum i.m. or i.p., and then challenged with the same antigen i.m. or i.p., respond with hemorrhagic blister formations at sites where xylol is gently rubbed into the ears. "The ear lesions of the sensitized reinjected rabbits which develop after the application of xylol are interpreted as a primary anaphylactic reaction. This primary anaphylactic reaction is con-

sidered the result of a local autoinoculation of the ear tissues with circulating antigen."

Kirsner & Elchlepp D72,475/57: According to Auer, a sensitized animal can localize the sensitizing antigen in inflamed tissues and thereby produces the state necessary for a local hypersensitivity or anaphylactic response. A survey of the literature on this phenomenon suggests some relationship to the SSP-L.

Forssman Antigen and Antibody, Anaphylatoxin. There are some indications that complexes of *Forssman antigen and antibody* may possess provocative potency in the production of an SSP-L and there has been speculation concerning the possible participation of *anaphylatoxin* in the production of the endotoxin-induced thrombohemorrhagic lesions. However, up to date we have no convincing evidence that any blood-borne immune body plays an indispensable role in the production of the SSP.

Gratia & Linz E67,648/32: An *anaphylatoxin-like "angeiotoxin"* is thought to be responsible for the production of the SSP. The testis of a rabbit was inoculated with "testicular vaccine," the rabbit was bled and its serum mixed with *E. coli* filtrate and the mush of the treated testicle. After incubation, this mixture was injected into two rabbits i.c. and produced a topical hemorrhagic response. [A very inconclusive preliminary report (H.S.).]

Shwartzman G18,862/37: Review of the literature and personal observations suggest that "there are some indications that the complexes of *Forssman antigen and antibody* may be endowed with provocative potency" in the production of the SSP-L. However, the phenomena conducive to the SSP-L "bear no relationship to anaphylatoxins."

BLOOD COAGULATION

There can hardly be any doubt about the fact that disturbances in blood coagulation play an important part in the production of all forms of THPs; however, there is some uncertainty concerning the relative importance of various blood-borne coagulation factors, the erythrocytes, and changes in the vascular wall itself.

The earliest relevant observations were made by Flexner (1902) who first described "agglutinative thrombi" composed of closely packed, and usually damaged erythrocytes in dilated small vessels of animals and man following infections and intoxications. As these thrombi aged, they became hyaline and, in the renal glomeruli, they often occluded the capillaries. These findings suggested that damaged, agglutinated erythrocytes may participate in the initiation of thrombus formation.

Various forms of THPs (including the SSP) are accompanied by a pronounced drop in the blood platelet count, but a comparable degree of thrombocytopenia induced by an antiplatelet serum, fails to cause a THP. It is reasonable to assume, therefore, that the thrombohemorrhagic lesions are not the consequence

but more probably the cause of thrombocytopenia. The latter probably develops because large numbers of platelets are withdrawn from the blood by precipitation in microthrombi.

Early investigators claimed that factors affecting blood coagulation (vitamin K, heparin, sodium oxalate, dicoumarol, antiplatelet serum) fail to alter the course of a typical SSP, and that consequently, blood coagulation could not play a part in the development of the structural lesions characteristic of this phenomenon. However, this view is no longer tenable since it has been convincingly demonstrated by numerous subsequent investigators that anticoagulants, and particularly heparin and warfarin, prevent not only the SSP but also other forms of THPs.

Conversely, i.v. infusion of thrombin induces the formation of multiple capillary fibrin thrombi, especially in the renal glomerular capillaries, the liver and the lung, in combination with thrombocytopenia and hyperfibrinogenemia. Similar results are obtained under suitable conditions by the i.v. administration of heparinoids such as Liquoid, presumably because all these agents cause intravascular precipitation of fibrinogen. This reaction is likewise inhibited by heparin. Finally, extensive observations with histochemical, fluorescent antibody and electron-microscopic techniques confirmed that the microthrombi in the THP do, in fact, contain fibrin and fibrinoid.

It has been claimed that, in order to become subject to phagocytosis by the RES, blood-borne particles must first be coated by fibrinogen. Such coating of RES-blocking agents and bacterial endotoxins may also be important for the development of the THP.

It appears that the coagulation defect characteristic of the THP (including the SSP), is primarily due to increased thrombin formation which initiates intravascular coagulation and depletes the blood of various coagulation factors. It has been postulated that thrombin forms a particularly labile form of fibrinogen ("cryoprecipitin") which is deposited in the small vessels and transformed into fibrin and fibrinoid. This massive fibrin precipitation is accompanied by the depletion of coagulation factors and allegedly thus elicits a "consumption coagulopathy" which makes the blood incoagulable. However, we have observed recently that, after death, the blood of rats sensitized for the THP (e.g., with ScCl_3) clots in the vessels much more rapidly than that of normal controls, although *in vitro* blood coagulation is greatly delayed. This observation is not readily compatible with the concept of a consumption coagulopathy and suggests that coagulation *in vitro* is not necessarily a reliable indicator of the clotting ability of the blood within the vascular tree.

In connection with the clotting defect of the THP, it may be significant also that 5-HT, bradykinin and certain 5-HT-blocking agents inhibit plasmin fibrinolysis *in vitro*.

The fact that prevention of thrombus formation (e.g., by heparin) also inhibits vascular damage and hemorrhage under conditions normally conducive to THP formation, suggests that the vasculitis and hemorrhage are secondary to thrombosis.

Flexner E76,861/02: Agglutination of erythrocytes in vivo can occur in various infectious diseases of man and animals, in eclampsia, and after i.v. injection of ricin, ether, or dog's serum in rabbits. Such "agglutinative thrombi" were first observed in a vessel of the ileum of a patient who died of typhoid fever. "The vessel was quite occluded by a conglutinated mass made up of globules of different sizes showing different degrees of refraction and varying staining properties. Careful study readily supplied the conviction that the mass was composed of red corpuscles, altered in form, adhesiveness, and staining properties." . . . "When such thrombi are old, or when the agglutination is compact, they may present appearances to which the name of 'hyaline thrombi' has been applied." The "hyaline glomerular thrombi occurring in the kidney in infectious diseases" as well as microthrombi in glaucoma and pulmonary infarction may have a similar origin.

Roskam E71,739/31: Injection of an anti-platelet serum s.c. or into the marginal vein of the ear, whose circulation is temporarily stopped by a clamp, causes large local ecchymoses. Since thrombocytopenia in itself does not produce hemorrhage, the phenomenon is ascribed to a combined platelet destroying and vasotoxic effect of the serum. [The author does not mention the SSP (H.S.).]

Boquet G20,920/43: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit is not inhibited either by vitamin K or by potent antihistaminics (929 F, 2339 R.P.). "The local hemorrhagic manifestations do not appear to be due exclusively to derangements in blood coagulability or the liberation of histamine by the provocative injection."

Shimkin & Zon E41,798/43: Hemorrhage can be produced in sarcoma-37 transplants in mice by single i.v. injections of *S. marcescens* endotoxin or moccasin venom. Both of these agents elicit marked thrombocytopenia, but this cannot be the cause of the hemorrhage because, if the platelet count drops to the same level as a consequence of anti-mouse-platelet serum, hemorrhagic necrosis of the neoplasms does not occur. It is concluded that "the action of the bacterial filtrate and of the snake venom on the transplanted sarcoma 37 is primarily that of an endothelial toxin."

Jürgens & Studer D38,953/48: Following slow i.v. infusion of thrombin in the rabbit, the blood becomes incoagulable and there is leukopenia, thrombocytopenia and hypofibrinogenemia. Multiple capillary fibrin thrombi develop, especially in the renal glomerular capillaries, the liver and the lung. Polymorphon-

clear leukocytes tend to accumulate in these same organs. [The possible implications of this observation in the pathogenesis of the SSP are not discussed (H.S.).]

Shwartzman et al. D71,760/50: "The possibility that a disturbance in the coagulation system is necessary for the elicitation of the reaction (SSP) is not supported by the fact that agents capable of altering blood coagulation, namely, distilled water, heparin, dicumarol, vitamin K, calcium salts, sodium oxalate, pyridine, and anti-platelet serum fail to produce any effect on the phenomenon."

Thomas & Good B79,249/52; Good & Thomas B86,937/53: Stetson found that platelet-leukocyte thrombi were a conspicuous histological feature of the developing Shwartzman reaction in the skin, and suggested that occlusion of small vessels may be an initiating event in the production of hemorrhage and necrosis." The fact that heparin prevents the SSP-G and SSP-L produced by various means strongly suggests that the phenomenon depends on vascular occlusion due to clot formation.

Brunson et al. C14,439/55: Histologic and histochemical studies of the microthrombi in the SSP-G (elicited by two i.v. injections of meningococcal toxin) suggest that "the occlusive material has the morphologic and tinctorial features of fibrinoid, and these features of the lesions suggest that fibrinoid may be derived from the circulating blood."

Gamble & Brunson G21,645/55: The blood of donor rabbits in which an SSP-G was elicited by two injections of meningococcal endotoxin or by one injection of meningococcal endotoxin plus Liquoid, was perfused 2-4 hrs. after the last injection into unprepared recipients by carotid-jugular cross transfusion. This resulted in the development of a typical SSP-G in the recipients. Since normally endotoxin is rapidly cleared from the blood, it is unlikely that residual endotoxin in the blood of donor animals could be responsible for the observed changes. "The presence of fibrinoid following transfusion in unprepared recipient animals offers considerable evidence for its transfer by way of the blood stream."

Rall et al. C2,777/55: Pretreatment with heparin or Tromexan (ethyldicoumarol acetate) prevents the SSP-L normally produced by two injections of *S. marcescens* endotoxin. "These observations are consistent with the thesis that thrombosis may be one important factor in the development of the local Shwartzman reaction."

Spanoudis et al. G21,524/55: The SSP-L normally produced by two injections of *S. mar-*

cescens endotoxin in the rabbit can be inhibited by pretreatment with Dicumarol. "Temporary thrombocytopenia occurs in Dicumarol-inhibited Shwartzman-negative rabbits, in Shwartzman-positive animals, and also after a single intravenous injection of *Serratia marcescens* toxins, without previous dermal preparation." . . . "This indicates that the thrombocytopenia, following the toxin injections, depends on the direct action of the toxin without any relation at all to the positivity or negativity of the Shwartzman reaction." Yet, *Bier & Amaral* (G22,098/44-45) suggested a possible correlation between the thrombocytopenic effect of glycogen and its ability to produce an SSP-L.

Thomas et al. E52,778/55: In the rabbit, Liquoid, given i.v. 2 hrs. before an i.v. injection of bacterial endotoxins (*meningococcus*, *S. marcescens*, *Shigella paradyenteriae*), produces an "SSP-G" with disappearance of blood fibrinogen. The response can be prevented by heparin (but not by nitrogen mustard or cortisone) and is attributed to intravascular precipitation of fibrinogen by the polymer. A qualitative change in fibrinogen, characterized by its precipitability by heparin in the cold, is regularly demonstrable in plasma 1-4 hrs. after the i.v. injection of endotoxin.

Eichbaum G27,048/57: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit can be prevented by dicoumarol or heparin. However, since in the SSP-L hemorrhage occurs before thrombosis, the effect of the anticoagulants cannot be ascribed to the prevention of blood clotting but is presumably due to some of their other pharmacologic properties such as antienzymatic activity or inhibition of platelet agglutination.

Thomas D1,020/57: Earlier work suggested that one important step in the process of phagocytosis by the RES may be the coating of the material to be ingested by proteins derived from the blood. Possibly, coating of RES-blocking agents and bacterial endotoxins by fibrinogen may participate in the development of the SSP.

Kliman & McKay G21,280/58: The SSP-G, normally induced by two injections of Shear's polysaccharide in the rabbit, is inhibited if streptokinase is administered conjointly with the second endotoxin injection but only slightly diminished if the enzyme is given with the first injection. Administration of the enzyme after the thrombi have been formed, does not cause their dissolution. Apparently, "fibrinolytic activity must be present during the period when the thrombi are forming in order to exert its lytic effect."

Pappas et al. G21,286/58: In rabbits, an SSP-G was produced by two i.v. injections of *E. coli* endotoxin or a single dose of endotoxin followed one hr. later by Liquoid i.v. As judged by electron-microscopic studies, the fibrinoid deposited in the renal glomeruli was the same in both types of experiment. The endothelial cells became swollen and exhibited balloon-like vesicles. Subsequently, fibrinoid, having a diameter of 200-300 Å and an axial repeating structure of 120 Å, was deposited within the capillary loops. These observations "are compatible with the hypothesis, proposed earlier, that intravascular fibrinoid, in the generalized Shwartzman reaction, is derived from fibrinogen."

Shapiro & McKay D15,422/58: In rabbits made hypoprothrombinemic by i.v. injection of warfarin, two i.v. injections of Shear's polysaccharide no longer produce the usual SSP-G. "It is concluded that the prothrombin complex is necessary for the production of the generalized Shwartzman reaction by bacterial endotoxins and that this phenomenon is essentially a process of disseminated intravascular coagulation." . . . "Perhaps in the Shwartzman reaction the primary event actually is fibrinogen precipitation by a circulating 'acidic polysaccharide,' as Thomas suggests; this, of itself, is not enough, apparently, to produce the characteristic pathologic lesions, were it not for the subsequent recruitment of the 'classical' clotting mechanism."

Kleinmaier et al. C81,035/59: An SSP-G elicited by two injections of various bacterial endotoxins produces a rapid increase in blood thrombin and thrombocytes associated with "viscous metamorphosis" of the latter and transformation of fibrinogen into fibrin. The acute consumption of coagulation factors results in loss of blood coagulability. The latter is regarded as the cause of the hemorrhagic diathesis in the SSP-G.

McKay et al. D15,431/59: Using the fluorescent antibody technique, it has been demonstrated that fibrin, or an insoluble derivative of fibrinogen, is a constituent in the thrombi found in the lungs, spleen, liver and kidney of rabbits in which an SSP-G was produced by two i.v. injections of *S. marcescens* endotoxin.

Rodriguez-Erdmann et al. G22,083/60: A single i.v. injection of Liquoid suffices to produce a typical SSP-G in the rabbit. This syndrome (like that elicited by two i.v. injections of endotoxin) is associated with a decrease in the activity of the prothrombin factors V (accelerator globulin), VII and the IX/X-complex, as well as severe acute thrombocytopenia. However, the pronounced loss of antihemo-

philia globulin characteristic of the SSP was not demonstrable. Protamine sulfate largely prevents these changes, including the pathologic lesions. "The similarity between the classical Sanarelli-Shwartzman phenomenon and the coagulopathy induced by Liquoid suggests that in both cases, an analogous mechanism induces intravascular precipitation of fibrin in various organs."

Robbins & Collins E85,082/61: The SSP-G elicited by two i.v. injections of bacterial endotoxin (kind not stated) is prevented or reduced by the injection of thrombin into the renal arteries. "These results are additional evidence that the initiation of blood coagulation by endotoxin has a basic role in the pathogenesis of the Shwartzman reaction."

Rodriguez-Erdmann & Lasch E63,756/61: A survey of earlier literature suggests that a derangement in the blood coagulation mechanism plays an important role in the development of the SSP. Fibrin thrombi appear in the vessels of various organs and there is an acute exhaustion of various components of the blood-clotting process: A diminution of blood fibrinogen and of the factors participating in the first phase of coagulation including prothrombin, factor VII and Acc globulin. The factors of thrombokinase formation are also deranged. The thrombocytes are not only diminished in number but also altered with regard to their function. The associated derangements in the antithrombin and antithrombokinase systems suggest an acute exhaustion as a consequence of intravasal clotting. The present experiments show that, during the first 2-6 hrs. of an SSP (method of production not given) in the rabbit, thrombin activity in the circulating blood increases considerably as tested by its effect upon a fibrinogen solution in vitro, and blood coagulability rises. This is the time when intravasal thrombi are formed. Earlier investigators ascribed clot formation during the SSP to a direct damaging effect of endotoxin upon the fibrinogen molecule; present observations suggest that, during the first phase of the SSP, hypercoagulability of the blood, induced through the enzymatic action of thrombin, is the cause of microthrombus formation. The concept is strengthened by the observations of Jürgens and Studer (D38,953/48), who noted that thrombin i.v. causes the formation of fibrin thrombi in the rabbit and simultaneously renders the blood incoagulable. These changes were prevented by heparin pretreatment. Since antithrombin can be inactivated by a thrombin, the diminution of antithrombin activity during the SSP could be due to increased thrombin formation. The secondary drop in blood thrombin during later phases of the

SSP is ascribed to the exhaustion of prothrombin, whose blood concentration does, in fact, drop considerably. Thus, the intravasal appearance of thrombin and the consequent increased utilization and exhaustion of coagulation factors are regarded as the cause of the hemorrhagic tendency. It remains to be seen, however, what causes increased thrombin formation, since endotoxin has no significant thrombokinase-like activity.

Lee E41,395/62: Heparin-precipitable fibrinogen (HPF or "cryoprecipitated") appears more rapidly in the blood of rabbits given thrombin i.v. than after *E. coli* endotoxin i.v. "The prompt appearance of HPF following thrombin infusion in contrast to the delayed onset after endotoxin injection may well explain the finding of recognizable fibrin deposits as early as 30 minutes after the start of thrombin administration as opposed to the consistent failure to detect fibrin deposits during the first two hours after the challenging injection of endotoxin." The release of endogenous thrombin may be a mediator in the production of HPF by endotoxins.

Lee & McCluskey G33,240/62: Following i.v. injection of thrombin or endotoxin, intracytoplasmic deposition of fibrin can be demonstrated in the hepatic and splenic RES-cells of the rabbit by immunohistochemical methods. Heparin prevents this fibrin storage. "The findings of this study substantiate the hypothesis that fibrin aggregates formed in the circulating blood during low grade intravascular coagulation are largely removed by the reticuloendothelial system."

Shore & Alpers G5,157/63: "Addition of small quantities of stearic, arachidic, or behenic acids, as the sodium salts, to heparinized platelet-rich rabbit plasma in vitro causes platelet clumping and other damage as reflected by marked release of platelet serotonin and histamine." . . . "The results suggest that certain pathologic changes in blood and vascular system, some already associated with altered fat metabolism, may be mediated in part through the actions of certain platelet damaging free fatty acids."

Hardaway & Johnson E48,596/63: In dogs, *E. coli* endotoxin causes a decrease in blood fibrinogen, factor V and factor VII, as well as thrombocytopenia and endogenous activation of heparin. Heparinization prevents the fall in fibrinogen and maintains blood pressure. "All these findings are further evidence that endotoxin shock is produced at least in part by intravascular coagulation."

Müller-Berghaus D60,636/63: Thromboelastographic studies revealed that, during the classical SSP-G (produced in rabbits by two

i.v. injections of *coli* endotoxin), there is no evidence of increased fibrinolysis. The disturbance in blood coagulation is due to excessive fibrin consumption ("Verbrauchskoagulopathie") consequent upon intravascular clotting.

Chryssanthou & Antopol F3,858/64: In connection with the clotting defect during the SSP, it is of interest that endotoxin, 5-HT, bradykinin, as well as certain 5-HT-blocking agents inhibit plasmin fibrinolysis in vitro.

Jókay et al. G28,485/64: Earlier experiments had shown that in vitro cysteine prevents platelet aggregation as well as the release of histamine and 5-HT which normally occurs under the influence of endotoxin in rabbit blood. It is now found that simultaneous administration of the provoking dose of *E. coli* endotoxin and cysteine i.v., in rabbits prepared for the SSP-L, inhibits thrombopenia and enhances leukopenia. At the same time, the resulting SSP-L is aggravated. Apparently platelet aggregation is less important than leukopenia in the production of an SSP.

Müller-Berghaus D13,794/64: An SSP-G elicited by two i.v. injections of *E. coli* lipopolysaccharide in the rabbit results in a rise in blood lipids, particularly cholesterol, β -lipoproteins and the cholesterol/phospholipid ratio. Administration of "essential" phospholipids at the proper time restores the cholesterol/phospholipid ratio to normal and renders the second dose of endotoxin ineffective in eliciting the SSP-G. The authors believe that the increased blood lipids not only accelerate intravascular coagulation but also block the RES and thus prevent the effective removal of fibrin and fibrin polymers.

Oyvin F27,793/64: Intravascular fibrin deposition is considered to be the most important factor in the SSP. [Theoretic considerations without new experimental data (H.S.).]

Rodriguez-Erdmann G31,454/64: Up-to-date summary of the evidence in support of the "consumption coagulopathy" concept of the SSP. Endotoxin does not activate purified prothrombin nor does it influence the conversion of prothrombin when it is activated in the presence of purified platelet factor 3 (cephalin) or purified factor V and Ca-ions. Apparently, the triggering for the SSP-G occurs in the "prephase of the clotting mechanism." The Hageman factor can be activated by endotoxin in vitro.

Scott & Blaszcynski G30,733/65: Plasminogen activator was readily demonstrated in various tissues of guinea pigs but only with difficulty in those of rabbits. On the other hand, an SSP-G was elicited by two i.v. injections of

E. coli endotoxin in rabbits, but not in guinea pigs. "This suggested a possible inverse relationship between the production of the generalized Schwartzman reaction and the formation of plasminogen activator in the tissues."

Levin & Cluff G25,182/65: The SSP-L produced by two injections of *E. coli* endotoxin in the rabbit was not prevented by repeated i.v. injections of antiplatelet serum, although the latter elicited a severe thrombocytopenia.

McKay E4,788/65: A review of the somewhat contradictory literature on the mechanism through which endotoxins produce an SSP-G leads to the conclusion that "endotoxin acts independently of leukocytes and red blood cells, and does not act as preformed thromboplastin or thrombin." The mechanism of the SSP-G is assumed to be as outlined in the adjacent schema.

Rodriguez-Erdmann G34,859/65: In rabbits pretreated with Thorotrast, i.v. injection of phospholipids, containing platelet factor 3 or Inosithin (soya bean phospholipid) there developed an SSP-G associated with the typical alterations of the clotting mechanism.

Hansson G35,342/65: In cats, perfusion of the kidney with cooled blood, homologous blood (ADP) or crushed connective tissue as well as transient mechanical interruption of the renal blood flow "induced a significant drop in the thrombocyte counts and when a complete renal blood flow obstruction ensued, the small renal vessels were occluded by aggregated thrombocytes. This was especially easily demonstrated in the glomerular capillaries." Subsequently, the kidneys became edematous and studded with patchy hemorrhages. Apparently, "the renal vascular bed is especially vulnerable to thrombocyte aggregation in the blood, presumably due to the special characteristics of this vascular circuit."

Solum & Stormorken F56,817/65: In experiments on washed human blood platelets, it was found that thrombin and collagen, unlike ADP and epinephrine, require externally added fibrinogen for the induction of platelet aggregation. The participation of these phenomena in the production of thromboses is discussed.

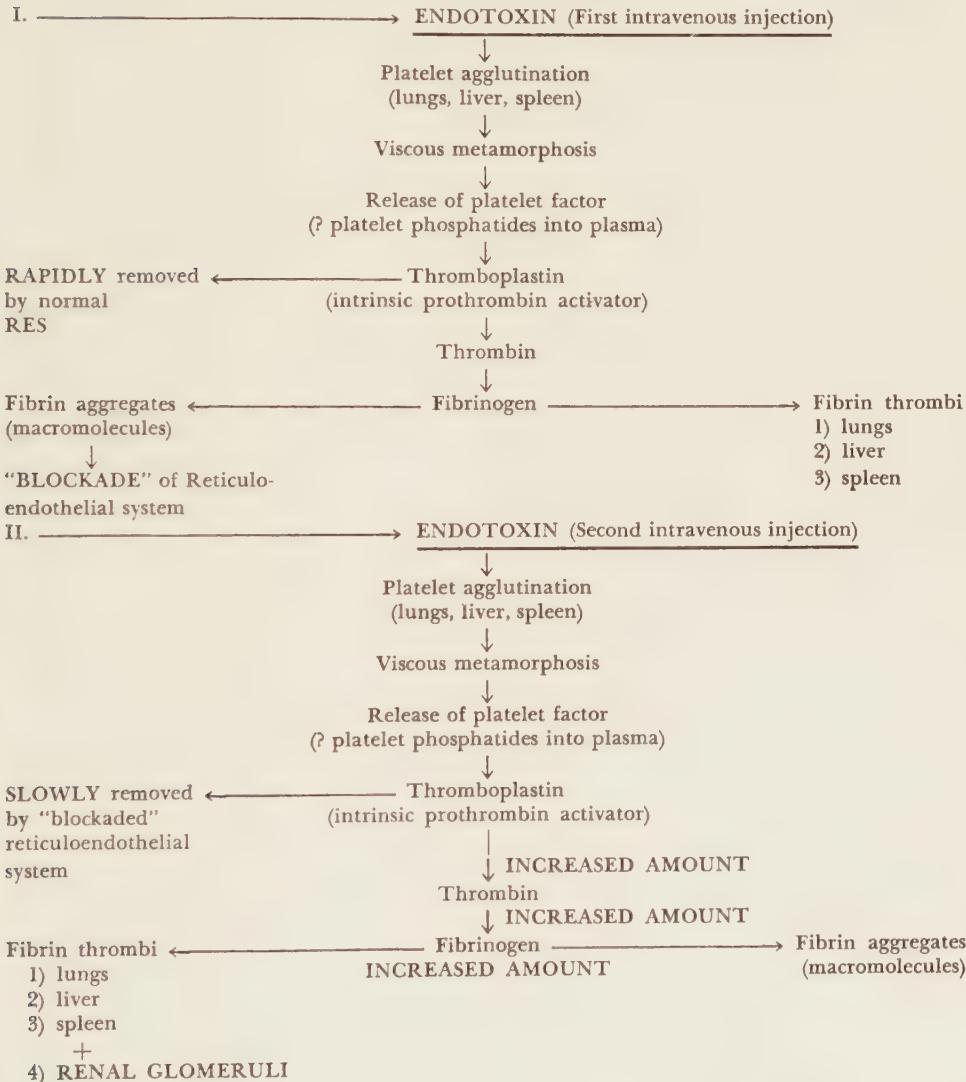
Prose et al. G31,934/65: Following a single i.v. administration of thrombin or *E. coli* endotoxin, fibrin uptake by hypertrophied Kupffer cells can readily be demonstrated with the electron microscope in the rabbit.

Selye et al. G32,007/65: In rats sensitized with $ScCl_3$ i.v., injection of epinephrine, norepinephrine or 5-HT into the musculature adjacent to large veins produces voluminous mixed thrombi in the neighboring vessels.

Although the blood of animals thus sensitized shows delayed clotting in vitro, it clots in the vessels much more rapidly after death than that of normal controls. This finding is not easily compatible with the assumption that the hemorrhages that occurred upon

challenge in animals sensitized for the pluricausal THP with metals result from a consumption coagulopathy. [Apparently, in vitro, blood clotting does not always furnish a reliable indication of the clotting ability of the blood within the vascular system (H.S.).]

MECHANISMS OF THE CLASSIC GENERALIZED SHWARTZMAN REACTION
(After McKay E4,788/65 p. 241)



THE VASCULAR FACTOR

It is obvious that, in addition to changes in blood coagulability, or any other derangement in the circulating blood, there must also be a local vascular factor to

account for the selective localization of THP-lesions in one or the other organ. Early investigators assumed the formation of an *anaphylatoxin-like "angiotoxin"* or some other factor specifically damaging to the endothelial cells of certain vascular regions. No convincing evidence supports this concept, yet there is good reason to believe that topical preparation by endotoxin or epinephrine so alters the local blood vessels that they become eminently susceptible to damage by certain blood-borne agents.

Using the rat mesoappendix, or the perfused rabbit ear preparation, it could be demonstrated that endotoxin induces the terminal arterioles and venules to become completely refractory to epinephrine, while the larger arteries and veins remain very reactive. Thus, the blood is pooled and becomes stagnant in the distended capillaries and venules, so that petechiae appear. Topical application of epinephrine at this stage increases the local hemorrhage. Possibly, *abnormal vascular reactions to catecholamines* or related substances may represent a basic phenomenon in the production of THPs. This view gained further support from the observation that adrenergic blocking agents can protect against several forms of THPs.

Topical treatment with substances that increase *capillary permeability*, offers some protection against the production of the SSP-L. It has been assumed that the entry of an inhibitory substance from the blood into the prepared area, or the exit of a damaging substance from the prepared skin, could be responsible for this protection. In any event, according to some (though not all) authors, i.v. injected dyes (e.g., Evans Blue) leak into the skin at sites pretreated with ordinary inflammatory irritants, but not at sites prepared by the i.c. injection of endotoxin. Allegedly, SSP-active agents, unlike other tissue irritants, do not increase capillary permeability or if they do they somehow compensate for its dye localizing effects (e.g., by topical vasoconstriction).

The renal cortical necrosis of the SSP-G has been ascribed to the "*Trueta shunt*" induced by constriction of the interlobular arteries, which results in a deviation of most of the blood away from the cortex to the medulla.

The influence of the aortic wall upon blood clotting has been examined in vitro and found to change considerably during successive stages of the SSP-G. Allegedly, some "*vasculokinase*" in the aortic wall can transform fibrinogen to fibrin and thereby play a key role in the pathogenesis of the SSP.

Gratia & Linz E67,648/32: An anaphylatoxin-like "angiotoxin" is thought to be responsible for the production of the SSP. The testis of a rabbit was inoculated with "testicular vaccine," the rabbit was bled and its serum mixed with *E. coli* filtrate and the mush of the treated testicle. After incubation, this mixture was injected into two rabbits i.c. and produced a topical hemorrhagic response. [A very inconclusive preliminary report (H.S.).]

Renaux & Alechinsky G18,585/36: It is assumed that the preparatory injection causes transient damage to the endothelial cells. If a second injection is made at the height of

this "endothelial disease," the lining becomes permeable to the blood.

Witebsky G24,001/36: It is postulated that "the bacterial toxin, injected locally, is first absorbed in the endothelial cells of blood vessels." . . . "If a second injection is given intravenously, the introduced material is conducted to the place where antibodies are accumulated." [No experimental data are given in support of this concept (H.S.).]

Horster G22,366/38: If, following preparation with bacterial endotoxin (kind not stated) into the rabbit ear i.c., the root of the ear is compressed to produce venous stasis, the site of

preparation responds with hemorrhagic necrosis. It is assumed that vascular factors may be decisive in eliciting the SSP.

Shimkin & Zon E41,798/43: Hemorrhage can be produced in sarcoma-37 transplants in mice by single i.v. injections of *S. marcescens* endotoxin or moccasin venom. Both these agents elicit marked thrombocytopenia, but this cannot be the cause of the hemorrhage because, if the platelet count drops to the same level as a consequence of anti-mouse-platelet serum, hemorrhagic necrosis of the neoplasms does not occur. It is concluded that "the action of the bacterial filtrate and of the snake venom on the transplanted sarcoma-37 is primarily that of an endothelial toxin."

Thomas & Stetson B28,612/48: The production of an SSP-L by two injections of *E. coli*, *S. marcescens* or meningococcal toxin in the rabbit can be prevented by a single application of bromobenzene to the surface of the prepared skin areas at any time during the 20 hrs. after the i.c. injection of endotoxin. Similar results were obtained with chlorobenzene, iodobenzene and benzene. Chloroform and methyl salicylate gave less constant results. Possibly, increased capillary permeability may have resulted either in the entry of an inhibitory substance from the blood into the prepared area or the exit of a damaging substance from the prepared skin. However, Evans Blue i.v. was shown to appear at the site of a single application of bromobenzene to normal skin but not at that prepared by endotoxin.

Shwartzman et al. D71,760/50: The "assumption receiving most support is that the damage to vascular endothelium necessary for the production of the reaction (SSP) can be elicited only when the provocative agent is brought in contact with the endothelium intravascularly."

Shwartzman G23,251/52: The renal cortical necrosis in the SSP-G is explained on the basis of the "Trueta shunt" induced by constriction of the interlobular arteries which results in a deviation of most of the blood to the medulla and away from the cortex.

Thomas C27,073/56: The fact that epinephrine i.c. produces a local THP in rabbits given various endotoxins i.v., leads to the conclusion "that endotoxin has the property of altering the reactivity of blood vessels to epinephrine in such a way that the hormone becomes a potent necrotizing agent."

Zweifach et al. D15,450/56: Unlike in the rabbit, "repeated attempts to produce skin lesions in the rat with combinations of endotoxin and epinephrine have been uniformly unsuccessful." In the rat mesoappendix prep-

aration, a lethal dose of endotoxin induced the terminal arterioles and venules to become completely refractory to epinephrine, while heightened reactivity persisted in the larger arteries and veins. "The end result was pooling of stagnant blood in distended capillaries and venules, accompanied by the appearance of petechiae. Topical applications of epinephrine during this stage were followed promptly by an increase in petechial hemorrhage at the site of testing." Analogous results were obtained in perfusion studies of the rabbit ear. Perfusion with small amounts of endotoxin was followed within minutes by potentiation of the epinephrine reactivity; larger doses caused complete reversal of this effect, so that epinephrine induced vasodilatation. "It is suggested that abnormal reactions to epinephrine or norepinephrine in the tissues of intact animals may represent a basic mechanism in the intoxicating and tissue-damaging properties of endotoxin."

Rall & Kelly C36,395/57: A single i.c. injection of *S. marcescens* endotoxin suffices to produce an SSP-L if followed by epinephrine or norepinephrine given i.v. or into the prepared skin site. Adrenergic blocking agents prevent this response. Hence, vasoconstriction appears to play an important part in the genesis of the SSP.

Thomas et al. G31,355/57: "Endothelial stickiness" (not only stickiness of leukocytes and platelets) plays an important part in the development of the SSP.

Spink E53,953/57-58: Review of the literature suggests that endotoxins do not act directly upon blood vessels but through the intermediary of changes which they produce in the blood. Thus, various endotoxins inhibited the activity of the calf adrenal in vitro only when the perfusate consisted of homologous whole blood and not when artificial perfusates were employed. Furthermore, pulmonary vascular responses were obtained in lungs perfused with heparinized blood, but not when defibrinated blood or dextran was used as a perfusion fluid.

Merriam & McKay C66,400/59: In rabbits pretreated for three days with 25 mg of cortisone per day, a single i.v. injection produces renal lesions with marked dilatation of the renal glomerular capillaries which become replete with carbon particles if India ink is injected i.v. This observation is "compatible with the theory that glomerular capillary dilation is in part responsible for lodgement of fibrin in these vessels in the Shwartzman reaction."

Schulhof & Richter G23,266/59: Neither Evans Blue nor bromsulphalein i.v. is con-

centrated in the affected cutaneous territory in rabbits in which an SSP-L is elicited by two injections of typhoid endotoxin.

Galton et al. D14,237/60; McKay & Merriam C85,593/60: In pregnant rabbits, a single injection of bacterial endotoxin (kind not stated) suffices to produce an SSP-G. The state of capillary dilatation was checked by intra-aortal administration of India ink. "Two to 4 hrs. after endotoxin the glomerular capillaries were grossly dilated and packed with ink. The lungs contained large 'ischemic' areas devoid of ink alternating with blackened areas containing markedly dilated ink-filled capillaries. The liver showed ink confined to dilated periportal sinusoids. The sinusoids of the adrenal and splenic pulp were dilated and filled with ink." . . . "It is concluded that capillary dilatation precedes the deposition of fibrin thrombi in all the organs characteristically affected in the Shwartzman reaction in pregnant rabbits and thus plays an important part in 'preparation' for the reaction."

Moore D95,837/61: Periplacental hemorrhage and fetal death with renal cortical and/or liver necrosis occur in late-pregnant rats given progesterone. These changes are ascribed to vasoconstriction, and their resemblance to human abruptio placentae is noted.

Stetson D7,247/61: A review of the vascular

effects of endotoxins suggests that these may play an important role in the pathogenesis of the SSP. Special emphasis is laid upon the induction by endotoxins of: vasomotion, increased vascular permeability and stickiness with intravascular agglutination of leukocytes and platelets, hyper or hyporeactivity to epinephrine, leukopenia and thrombocytopenia, thrombosis, the appearance of heparin-precipitable fibrinogen, altered histidine decarboxylase activity and fibrinolysis.

Wong et al. D10,406/61: Glomerular capillary dilatation occurs after one dose of Shear's polysaccharide in rabbits prepared with Thorotrast i.v. The same is true after preparation with endotoxin, cortisone, or in pregnancy. Glomerular capillary dilatation is not the result of fibrin deposition since it precedes the latter. "It is suggested that glomerular capillary dilatation is the factor responsible for localizing fibrin thrombi in the kidney during the generalized Shwartzman reaction."

Müller-Berghaus & Lasch G15,504/63: The influence of the aortic wall upon blood clotting (measured *in vitro*) changes considerably during successive stages of an SSP-G induced by two injections of *E. coli* endotoxin in rabbits. Some "vasculokinase" in the aortic wall, which transforms fibrinogen into fibrin, may play a key role in the development of the SSP.

THE NERVOUS FACTOR

(cf. also "The Reilly Phenomenon," p. 96, 250)

Despite much work on the subject, very little is known about the participation of the nervous system in the production of THPs.

Following topical preparation of the splanchnic and vagus nerves with live Herpes virus, i.v. provocation with the same material produces gastroduodenal ulcers with hemorrhages and necrosis. These changes were regarded as manifestations of an SSP-L induced by nervous stimulation, but this interpretation is questionable.

If one leg of a rabbit is completely denervated, topical preparation of the skin of both legs, followed by i.v. provocation, produces an SSP-L of equal intensity on both sides. Indeed, unilateral cervical sympathectomy increases the intensity of the SSP-L if preparatory endotoxin injections are given in both ears followed by i.v. provocation. Hence, it was concluded that the peripheral nervous system is not necessary for the development of an SSP-L.

The literature on the possible effect of general and local anesthetics on the development of the SSP is contradictory. The fact that various ganglionic blocking agents can inhibit the SSP-L suggests some nervous participation, but it does not necessarily prove it, since these drugs may protect through some other specific action independently of the nervous system.

Following treatment of one animal with agents conducive to a THP-G, transfusion of its blood to a recipient can elicit a THP-G in the latter. However, this is not a strong argument against the indispensability of the nervous system in the mediation of the THP, since the recipient's nervous system was not excluded.

Despite the many observations which showed that, following appropriate sensitization, catecholamines are highly effective challengers in the production of experimental THPs, there is still no convincing evidence that endogenous discharge of epinephrine or norepinephrine can also participate in the production of such lesions. In this connection it is interesting, however, that endotoxins are particularly efficacious in producing epinephrine discharge from the adrenal and that thromboplastic activity is released from the perfused rabbit aorta under the influence of epinephrine *in vitro*.

Kolpakow E63,708/36: In the rabbit, an SSP-L was produced by provocation with *E. coli* endotoxin after preparing the skin of both legs. The response was of equal intensity in both legs when one leg was completely denervated by severing all structures except the femoral artery and vein. The author concludes that the peripheral nervous system is not necessary for the development of an SSP-L.

Trueta et al. 99,193/47: Renal cortical necrosis in man is ascribed to a short-circuiting of the blood flow in the kidney, causing it to bypass the cortex and use only the medullary route, as a consequence of nervous reflexes. Attention is called to the similarity between this change and that seen in the SSP-G.

Gonçalves G22,359/50: Following preparation by infiltration of the vagus or splanchnic nerves with live Herpes simplex virus the i.v. injection of the same material 24 hrs. later produces gastroduodenal ulcers with local hemorrhages and necrosis. These are interpreted as an SSP-L. Herpes simplex is allegedly common in patients with gastroduodenal ulcers. Perhaps localization of a virus in the autonomic nerves, with a subsequent SSP-L, is involved in the pathogenesis of gastroduodenal ulcers in man.

Shwartzman et al. D71,760/50: "The role of the peripheral and central nervous system in the provocation of the phenomenon (SSP) is excluded by lack of effect of general anesthesia and a variety of local anesthetics, atropine, acetylcholine, physostigmine, curare and pilocarpine."

Penner & Klein G21,287/52: The toxin of *Bacillus shigae* produces edema and hemorrhage in the gallbladder, duodenum, and adrenal glands of the dog. These lesions, as well as the associated hemoconcentration and hyperglycemia, are assumed to be mediated through the central nervous system, because

they can be prevented by pretreatment with drugs causing paralysis of the myoneural junctions or the ganglia. Furthermore, in cross-circulation in which the blood of one dog treated with Shiga toxin is circulated through the head of a second dog, the characteristic organ lesions, together with hyperglycemia and hemoconcentration occur in this second dog, whose systemic blood contained no Shiga toxin.

Štork & Kovaříková C11,611/54: The SSP-L elicited by two injections of *E. coli* endotoxin is inhibited in the rabbit by anesthesia induced with urethan or dial. Presumably, the central nervous system plays an important part in the development of this response.

Kesztyüs & Csernyánszky C10,849/54; Kesztyüs et al. C12,656/55: The SSP-L elicited by two injections of *E. coli* endotoxin in the rabbit is not influenced by partial denervation (transection of the sciatic nerve with challenge in the corresponding leg skin, denervation of the challenged dorsal skin region). The SSP-L is prevented, however, by Sevonal anesthesia applied before both the preparatory and the provocative injection. Sevonal anesthesia, given only before the preparatory injection, results in partial inhibition, while similar anesthesia, given only before the provocative injection, is inactive.

Fowler C20,165/55: Unilateral cervical sympathectomy increases the intensity of an SSP-L if preparatory injections with *S. typhosa* endotoxin are given in both ears and followed by an i.v. injection of the same agent. Apparently, the SSP-L is subject to Cannon's "law of denervation."

Mignani & Graev C16,652/55: An SSP-L produced by two injections of *E. coli* endotoxin is not inhibited by pretreatment with the ganglionic blocking agent Pendiomid, but the structure of the cutaneous lesions is

changed. It is concluded that the autonomic nervous system plays a part in this response. [In view of the small number of animals used and the comparatively moderate change in response, the interpretation of these findings is difficult (H.S.).]

Kesztyüs et al. G22,097/58: Following pretreatment with sympatholytic agents such as ergotamine (and to a lesser extent chlorpromazine), the sensitivity of the rabbit to the production of an SSP-L by two injections of *E. coli* endotoxin, far from being blocked, actually rises. This observation makes it unlikely that the adrenergic action of endotoxins is of primary importance in the production of an SSP.

Egdahl G33,275/59: Extensive experimental work on dogs suggests that "epinephrine release is not necessary for the febrile and adrenocortical stimulating effects of endotoxin." [The role of epinephrine in the production of an SSP by endotoxin is not discussed (H.S.).]

Nykiel & Glaviano D52,546/61: In the dog, *E. coli* "endotoxin causes adrenal stimulation from reflexes initiated by the hypothalamus or peripheral baroreceptors," as judged by experiments in which the epinephrine content of the adrenal vein was directly determined after different interventions during endotoxin shock.

Schayer et al. D58,948/63: *S. enteritidis* en-

dotoxin suppresses histidine decarboxylase activity in the rabbit kidney. "The findings are consistent with the view that suppression of induced histamine synthesis, at a time of markedly increased catecholamine release, might potentiate the actions of these vasoconstrictors on the kidney. This event may be a factor in the early endotoxin-induced changes in the glomerular capillaries which prepares them for the subsequent events of the generalized Shwartzman reaction."

Shimamoto & Ishioka D57,197/63: In preparations of the rabbit aorta perfused in vitro, addition of small doses of epinephrine to the perfusion fluid causes a release of thromboplastin activity from the vessel wall. Norepinephrine and large doses of epinephrine are ineffective. The release of thromboplastin activity by epinephrine can be blocked by a MAO inhibitor such as nialamide.

Kóvats et al. D9,550/64: Autonomic drugs exert an important influence upon cardiovascular actions of bacterial endotoxins, as well as upon the SSP-L and the "Thomas reaction." Hence, it is assumed that the autonomic nervous system plays an important role in endotoxin-induced phenomena.

Szilágyi & Damjanovich D18,970/64: Ganglionic blocking agents such as hexamethonium and TEAB inhibit the SSP-L produced by two injections of *E. coli* endotoxin in the rabbit.

THE REILLY PHENOMENON

It will be recalled that the Reilly phenomenon (characterized by swelling and hemorrhage of the mesenteric lymph nodes and Peyer's plaques, and other lesions reminiscent of the THP) was obtained by the direct application of endotoxins to the splanchnic nerves and ganglia. Similar, though less constant results were elicited upon local irritation of sympathetic nerves by a variety of drugs, mechanical trauma or electrical stimulation. These lesions were ascribed to "neurovegetative irritation," but Reilly's work has not been adequately confirmed in other laboratories, and its relationship to THPs is doubtful.

Reilly et al. G21,897/35; G26,816/36: The application of typhoid, paratyphoid and diphtheria bacilli or their endotoxins, by direct injection into the mesenteric lymph nodes or the vicinity of sympathetic nerves (splanchnics, semilunar ganglion, adrenal medulla), produces changes similar to those of spontaneous typhoid fever in man. There is swelling and hemorrhage in the mesenteric lymph nodes and Peyer's plaques with exulceration of the latter in a great variety of animal species, including those that are quite insensitive to the same microbial products when

administered through other routes. Even intracardiac injection of paratyphoid endotoxin, causes intense perineuritis around the splanchnic nerves of the guinea pig, owing to the neurotropic effect of this toxin. The response is largely nonspecific, since certain metals (cobalt, nickel, lead, arsenic, as well as nicotine, snake venoms, etc.) applied directly to the splanchnics of the guinea pig, produce similar gastrointestinal hemorrhagic responses. The same is true of mechanical trauma (by ligatures placed around the splanchnics) or prolonged faradic stimulation of these nerves.

Sympathetic stimulation is held largely responsible for the gastrointestinal hemorrhagic syndrome characteristic of typhoid fever. The close anatomical connections between the mesenteric lymph nodes and the splanchnic nerves account for the fact that application of the irritants to either of these structures is effective. This form of hemorrhagic necrosis became known as "Reilly's syndrome of neuro-vegetative irritation."

Reilly et al. 99,381/42: Monographic description of the authors' experiments on the production of glomerulonephritis with hemorrhages associated with gastrointestinal hemorrhages in various animals in which the sympathetic nerves were stimulated by topical application of drugs, bacterial toxins or faradic current.

Decourt B72,103/52: The general adaptation syndrome is considered to be identical with the Reilly phenomenon [! (H.S.).]

Reilly G27,050/54: Faradic stimulation of the splanchnic nerves produces multiple hemorrhages and thromboses in the gastrointestinal tract, spleen, adrenals and kidneys of the guinea pig. In pregnant animals, retroplacental bleeding occurs. The rabbit, cat, dog and rat are decreasingly less sensitive in the order listed. Various poisons, especially certain metals and alkaloids, applied to the sympathetic nervous system produce the same results. This "syndrome of neurovegetative irritation" presumably plays an important role in many diseases, especially in hemorrhagic pancreatitis, nephritis, intestinal intussusception, acute dilatation of the stomach, and the "malignant syndrome" that develops in acute hemorrhagic forms of typhoid, influenza, scarlet fever, rubeola, etc. The fact that chlorpromazine is particularly effective in preventing the syndrome of neurovegetative irritation further

supports the view that nervous mechanisms play an important part in its pathogenesis.

Coste et al. E50,611/57: In a case of severe staphylococcal septicemia, there developed diffuse hemorrhages characteristic of Reilly's syndrome of "generalized sympathetic irritation," but at the same time there were fibrinoid thromboses in the glomerular capillaries and adrenal hemorrhages more characteristic of the SSP-G and of the Waterhouse-Friderichsen syndrome. A relationship between these conditions is suspected.

Bernard et al. D69,624/63: A 22-year-old man suddenly fell ill following revaccination with TABDT vaccine. He developed high fever and an extensive erythematous papular non-pruriginous skin eruption. Eventually, profound shock ensued and the patient died on the sixth day. Autopsy revealed hemorrhagic fluid in the peritoneum, bilateral renal cortical necrosis within fibrinoid thrombi in the glomeruli as well as hemorrhagic necroses (without fibrin thrombi) in the adrenals, small intestine and other organs. The authors state that "there is no doubt that this case represents an instance of the Sanarelli-Shwartzman phenomenon" but it is also related to anaphylaxis and Reilly's "syndrome of neuro-vegetative irritation."

Rapin G27,052/63: Detailed description of the hemorrhagic malignant syndrome which can occur in the course of various infectious diseases, particularly scarlet fever, typhoid, various other septicemias due to Gram-negative organisms, but also in viral infections such as influenza, rubeola, poliomyelitis and varicella. It can even occur in parasitic infestations with *Plasmodium falciparum*. This condition is possibly related to the general adaptation syndrome, Reilly's syndrome and the Shwartzman phenomenon, but a definite interpretation of its pathogenesis is not yet possible.

THE RES

RES-blocking agents (India ink, silicic acid, etc.) possess no provocative potency when given i.v., following i.c. preparation with potent endotoxins. Also, topical treatment of the prepared site with RES-blocking agents does not influence the production of an SSP-L. However, in rabbits which became resistant to the pyrogenic response of endotoxins because of repeated pretreatment, sensitivity is reestablished by blockade of the RES with trypan blue or Thorotrast. In rabbits in which resistance to the SSP-L was induced by repeated preparatory and provocative endotoxin injections, the same RES-blocking agents likewise restore reactivity.

Thorotrast or trypan blue i.v. sensitizes the rabbit so that it will react with a THP-G to a subsequent i.v. injection of bacterial endotoxins. However, other

RES-blocking agents such as glycogen, starch, PVP, tissue extracts and antigens are ineffective in this respect. It is possible that only particulate substances, having certain physicochemical properties, can block that particular RES-function which furnishes relative resistance to THPs.

Bacterial endotoxins labelled with radiophosphorus or fluoresceine-tagged γ -globulin can be shown to be taken up rather selectively by the RES. Furthermore, pretreatment with Thorotrast or with endotoxin depresses the initial phagocytosis elicited by a subsequent second injection of endotoxin.

An SSP-G can be produced in rabbits by pretreatment with Thorotrast i.v. and subsequent induction of a hemorrhagic shock, terminated after 90 minutes by the return of all the shed blood. A similar THP-G is produced by Thorotrast i.v. followed by endotoxin or by two successive i.v. injections of Thorotrast. All these reactions were regarded as examples of true endotoxic shock induced by eliminating the ability of the RES to detoxify endogenous endotoxin.

These, and similar observations led to the concept that blockade of the RES acts by preventing the removal of blood-borne SSP-active substances or of the initial minute fibrin precipitates themselves. It has been postulated that fibrin coating of blood-borne particles is essential for their subsequent phagocytosis by RES-cells; this activity might also influence sensitivity to THPs.

The fact that blockade of the RES by Thorotrast, denatured albumin or EACA so prepares the rabbit that it reacts to thrombin i.v. with a particularly severe THP-G, has been ascribed to interference with the removal of fibrin, not of endotoxin. EACA i.v. interferes with carbon clearance from the blood; hence, it could act through the blockade of the RES rather than through the activation of fibrinolysis as is generally supposed. Of course, even in these experiments in which no endotoxin is administered, it could always be argued that RES-blockade acts through interference with the removal from the blood of endogenous endotoxins.

In any event, the participation of the RES in the THP is still far from being understood. Recent experiments performed in our Institute show that certain forms of pluricausal THPs can actually be inhibited by pretreatment with RES-blocking agents (e.g., egg yolk, ferric dextran, India ink). It is also dubious that THPs induced by RES-blocking agents act by interfering with the detoxification of endogenous endotoxins. The endotoxin sensitivity of the normally resistant rat can be increased 100,000 times by pretreatment with lead acetate; still, this species will not respond with a THP to single or repeated endotoxin injections although pluricausal THPs are readily produced in the rat by various particulate substances.

Shwartzman G23,070/32: Precipitates derived from mixtures of serum precipitinogen with precipitating antiserum, cause an SSP-L in rabbits at sites prepared by typhoid endotoxin i.c. The provocative potency did not depend upon the size of the aggregates formed, and even clear supernatant fluids obtained by centrifugation were effective, while a variety of colloidal suspensions (India ink, silicic acid, etc.) were ineffective. Hence, it was concluded that the "potency of serum precipitates is not

due to the mechanical effect of colloidal particles in the blood stream but to some toxic factors liberated or formed in the serum through the colloidal disturbance induced by the process of precipitation."

Beeson D2,409/47: Following repeated injections, the pyrogenic response of various bacterial endotoxins diminishes considerably in rabbits. This resistance is ascribed to an activation of the RES, because: "Pyrogenic substances disappeared from the circulating blood

more rapidly in rabbits rendered pyrogen-tolerant than in normal animals. Lack of specificity was shown by the fact that rabbits previously injected with *Eberthella typhosa* bacterial vaccine were able to remove the pyrogens of *Serratia marcescens* and *Pseudomonas aeruginosa* from their blood more rapidly than normal animals." Blockade of the RES by trypan blue or Thorotrast retarded the disappearance of pyrogens from the circulating blood of tolerant animals and abolished their pyrogen resistance.

Beeson B64,425/47: In rabbits which became immune to the SSP-L after repeated cutaneous and i.v. injections of *E. typhosa* filtrate washings, as well as in naturally immune rabbits, i.v. injection of Thorotrast or trypan blue restored reactivity, presumably by blocking the RES. "Consideration of these results leads to the assumption that immunity to the Shwartzman reaction depends on ability of the R-E system to remove the bacterial toxin from the blood stream to such an extent that the tissues at the site of skin preparation are spared serious injury. R-E blockade permits the toxin to be delivered to the prepared skin area in a concentration sufficient to produce capillary damage and hemorrhagic necrosis."

Becker B28,260/48: Benzol, nitrogen mustard and x-irradiation inhibit the SSP-L in the rabbit. "It is postulated that the mechanism of suppression by these agents is exerted through their specific but common suppressive action on the reticulo-endothelial system, primarily the vascular endothelium. These endothelial cells being rendered anergic are not able to react to the active principles in a way that otherwise would be self-destructive."

Bennett G21,296/52: Review of the literature on the gradual induction of resistance to the SSP-L during attempts to elicit the reaction repeatedly in the same rabbit. Thorotrast or colloidal organic iodide abolishes this resistance if administered before the provocative injection. This sensitizing effect is ascribed to a blockade of the RES.

Good & Thomas B80,500/52: Unlike Thorotrast or trypan blue, other RES-blocking agents such as glycogen, starch, PVP, tissue extracts and antigens i.v. failed to prepare rabbits in such a manner that subsequent i.v. injection of suitable bacterial toxins would have produced an SSP-G. "The foregoing experiments do not furnish evidence concerning the specificity of the action of Thorotrast or trypan blue on the reticulo-endothelial system. They indicate, however, that other types of colloidal or particulate materials do not affect the susceptibility to bacterial toxin in the same manner."

Thomas & Good B79,249/52: Any explanation of the SSP-G "would have to account for the fact that two injections of toxin must be given to produce the reaction." This cannot be explained "on the basis of a cumulative action, since renal necrosis can be caused by amounts of toxin which are considerably smaller than doses which have no effect when given in a single injection. A more reasonable explanation would be that the first dose of toxin impairs the capacity of the rabbit to remove or detoxify the toxin, so that the second dose is permitted to act directly on susceptible cells or tissues." . . . "In view of the dissolution of lymphoid tissues caused by cortisone, it was suggested that the susceptibility to toxin might be due to interference with protective functions of the reticulo-endothelial system."

Braude et al. D90,610/55: *E. coli* endotoxin, labelled with radioactive chromium and injected i.v. in the rabbit, rapidly passes into the liver and the buffy coat of the blood.

Rowley et al. C20,862/56: A purified lipopolysaccharide fraction prepared from *E. coli* and labelled with P^{32} , injected i.v. in mice or guinea pigs, is rapidly taken up by the RES. The clearance from the blood of a second dose, given 30 min. after the first, is delayed but after an interval of 48 hrs. the clearance may actually be accelerated unless the first dose was very large.

Benacerraf & Sebestyen D998/57: Using colloidal carbon, chromium phosphate labelled with P^{32} , or heat-denatured human serum albumin labelled with I^{131} , it could be shown that the endotoxins of *S. abortus equi* or *E. coli* decrease the ability of RES cells to store particulate matters and to break down phagocytosed albumin in the rabbit.

Cremer & Watson C37,986/57: The distribution of *S. typhosa* endotoxin in the RES was determined in rabbits by its ability to complex with fluorescein-tagged gamma globulin. Pretreatment with cortisone and x-irradiation did not affect the initial phagocytosis of toxin by the RES-cells of the liver, spleen and lung, but inhibited its degradation and elimination after a single i.v. injection, as judged by the rate of its disappearance from the RES-cells. Pretreatment with Thorotrast and preliminary injection of toxin caused depression of initial phagocytosis following a subsequent second injection of toxin. "Thorotrast and the first injection of toxin by incapacitating the initial phagocytic ability of the RES, probably keep the provoking dose of toxin in the systemic circulation where it can effect its deleterious action at its primary site for a longer period of time."

Thomas D1,020/57: An SSP-G can be produced in the rabbit by a single i.v. injection of bacterial endotoxin if this is preceded by the i.v. administration of RES-blocking agents, but not if it is followed by RES-blockade. In rabbits pretreated by Thorotrast or Fe-OS i.v., the i.c. injection of endotoxin does not produce the usual immediate inflammatory reaction, but after approximately 18 hrs. numerous petechiae appear which coalesce and develop into hemorrhagic necrosis indistinguishable from that of the typical SSP-L. Normally, the endotoxin is retained at the injected skin site, while after RES-blockade it is absorbed into the general circulation since systemic manifestations of an SSP-G are then superimposed upon the SSP-L. It is assumed that the preparatory i.v. injection of endotoxin, like the RES-blocking agents, inactivates the RES and thus prevents it from removing endotoxin from the circulation. This is supposed to be the basis of "preparation." [Yet, a single dose of endotoxin, no matter how large, does not duplicate the effect of two doses given within an interval of 24 hrs. Thus, mere interference with detoxification does not appear to explain the phenomenon of "preparation" completely (H.S.).]

Fine et al. D85,444/59: An "SSP-G" can be produced in the rabbit by pretreatment with Thorotrast i.v. and subsequent induction of a hemorrhagic shock, terminated after 90 min. by transfusion of all the shed blood. The animals recover, but die 24 hrs. later with diffuse hemorrhagic lesions. A similar "SSP-G" is produced in the rabbit by Thorotrast i.v. followed by endotoxin or by two successive injections of Thorotrast. "Thus, we had produced what we regard as endotoxic shock, without giving endotoxin, and achieved this simply by eliminating the endotoxin-detoxifying power of the reticuloendothelial system."

Fine et al. D98,173/59: Review of numerous animal experiments, suggesting that endotoxins derived from intestinal microorganisms play a decisive role in the production of the SSP-G and that blockade of the RES by Thorotrast increases sensitivity to the SSP-G by diminishing the capacity of the body to cope with endotoxin.

Ravin et al. D15,460/60: "Coliform-free rabbits fed P³² labeled E. coli 0111:B₄ prior to the induction of experimental hemorrhagic shock were shown to have a substantial amount of the type-specific 0111:B₄ antigen in the circulating blood, liver, and spleen, whereas normal rabbits, fed the same amount of these bacteria, and held under identical conditions, but not exposed to shock, have the antigen within the liver, and occasionally in the kidney, but

not in the blood." . . . "The accumulation of biologically active endotoxin in the blood and tissues of the shocked animal appears to be due to a reduction in the detoxifying potential of the reticulo-endothelial system, and not to a greater than normal absorption of endotoxin from the intestine." [Decreased detoxification by the RES of normally circulating endotoxin may, thus, play a role in the production of a THP by various nonbacterial agents (H.S.).]

Spaet et al. E41,903/61: Blood thromboplastin, given i.v. to rats, is cleared by the RES because: 1. Thromboplastin given into the jugular vein or aorta causes more profound defibrination than when it is injected into the portal circulation; 2. RES-blockade reduces the protective effect of portal administration; 3. radioactive thromboplastin i.v. is rapidly cleared from the blood and distributed in various organs in proportion to their RES-cell content; 4. thromboplastin i.v. depresses carbon clearance from the blood. Through the constant removal of blood thromboplastin, the RES may play an important role in preventing intravascular clotting.

Lee E41,395/62: The ability of thrombin i.v. to produce an "SSP-G" in the rabbit is greatly augmented by pretreatment with Thorotrast, denatured albumin or E. coli endotoxin i.v., all of which depress the function of the RES. Presumably blockade of the RES increases susceptibility to the production of an SSP-G by interfering with the removal of fibrin (not, as had previously been thought, through the removal of endotoxin). This view was further supported by the finding that EACA (which likewise enhances the development of an "SSP-G" after single injections of E. coli endotoxin or thrombin) interferes with carbon clearance by the RES. Presumably, this compound also acts through blockade of the RES rather than through the activation of fibrinolysis.

Spaet G26,874/62: Experiments on rats suggest that both thromboplastin and "product I" (a blood coagulation intermediate which develops prior to blood thromboplastin formation) are cleared by the RES.

Lee G26,187/63: After RES-blockade by Thorotrast, the i.v. injection of protein antigen into specifically immunized rabbits, or of soluble immune complexes into normal rabbits, causes bilateral renal cortical necrosis with hyaline thrombi in the glomerular capillaries. Like the SSP-G, this response is prevented by heparin and associated with the appearance of "heparin precipitable fibrinogen" in the circulation. Apparently, antigen "antibody reactions in vivo can activate the

blood-clotting system and endotoxins may act here on an immunologic basis."

McKay E4,788/65: The literature on the role of the RES in the production of disseminated intravascular blood coagulation suggests that it is not the interference with the removal of endotoxin or of fibrin that plays the leading role, but the inhibition of plasma thrombo-

plastin clearance as suggested by *Spaet et al.* (E41,903/61; G26,874/62).

Selye et al. G32,080/66: Following pretreatment by a single i.v. injection of lead acetate, the sensitivity of the rat to various endotoxins rises up to 100,000 times, but an SSP is not produced even under these conditions.

LEUKOCYTES

There is some evidence that the leukocytes also participate in the pathogenesis of THPs. At first, it was thought that the leukopenia induced by endotoxins is due to a direct toxic effect of the bacterial products upon the leukocytes. However, it can be shown histologically that leukocytes, as well as platelets and fibrin, accumulate in the microthrombi and are thus sequestered in the microcirculation.

Certain agents which cause leukopenia (nitrogen mustard, benzene) inhibit the SSP-L, while sulfapyridine, which blocks the benzene-induced leukopenia, also tends to prevent its protective effects against the SSP-L. These facts, as well as the observation that polymorphonuclear leukocytic infiltration is the most typical expression of local "preparation," led to the assumption that the leukocytes participate decisively in the production of the SSP. Further evidence, apparently supporting this view, was obtained by the demonstration that cysteine and inflammation produced by mild irritants, which inhibit the leukopenia normally elicited by nitrogen mustard, also block the protective effect of the latter against the induction of the SSP-L.

The native levan of *Aerobacter levanicum* produces an SSP-L when given in the usual manner (an i.c. followed by an i.v. injection) to rabbits. The response is inhibited and leukopenia is elicited if native levan or native dextran is given i.v. just before the preparatory i.c. injection. This SSP-blocking activity of the polymers was considered to result from the leukopenia they produce. Indeed, it has been suspected that the leukocytes, like exogenous synthetic acidic polymers may bring about a state of preparation in that they precipitate fibrinogen. In this event, the usual latency period of 24 hours would be necessary for the return of precipitable fibrinogen into the blood when the animal's own acidic polymer (presumably derived from leukocytes) becomes available to induce fibrinogen precipitation. This concept received support from recent observations showing (by histochemical and S^{35} -labelling techniques) that sulfated mucopolysaccharides are carried by leukocytes and can be incorporated into fibrinoid during the SSP-G.

It is especially significant in this connection that the granule fraction of leukocytes can act both as a preparative and a provocative factor when given with *E. coli* endotoxin as the other factor. On the other hand, it has been said that the production of leukopenia by nitrogen mustard and similar SSP-blocking drugs is not necessarily the result of leukopenia, since such agents also cause thrombocytopenia. Furthermore, doses of nitrogen mustard or of γ -irradiation conducive to severe leukopenia do not always completely prevent the SSP-L; hence, allegedly, "the presence of normal numbers of circulating polymorphonuclear leukocytes is not an obligatory prerequisite condition to the localized hemorrhagic necrosis

of the Shwartzman phenomenon." In rabbits made tolerant to epinephrine, an SSP-L can also be produced by two injections of endotoxin even when a considerable drop in polymorphonuclear leukocytes results both in the blood and in the area of challenge.

Stetson B73,457/51: It had previously been assumed that the leukopenia produced by materials capable of eliciting the SSP-L, is due to a direct toxic effect upon the leukocytes. However, histologic studies indicate that the leukocytes accumulate in the capillaries of the lung after treatment with meningococcal endotoxin i.v. in the rabbit; hence, it is assumed that they are sequestered in the microcirculation, presumably together with platelets, thereby facilitating the production of microthrombi.

Stetson & Good C69,100/51: Pretreatment with either nitrogen mustard or benzene (both of which cause leukopenia) inhibits the SSP-L normally produced by two injections of meningococcal toxin. Sulfapyridine, which prevents the benzene-induced leukopenia, also tends to prevent its protective effect against the SSP-L. Leukocytic infiltration of the intradermal injection site is the most evident morphologic expression of local "preparation." It is assumed "that polymorphonuclear leucocytes play an essential role in the preparation of the skin for the Shwartzman phenomenon."

Bennett & Cluff B90,942/52: Nitrogen mustard inhibits the SSP-L produced by two injections of *S. marcescens* endotoxin in the rabbit concurrently with the production of a leukopenia. This protective effect is abolished by cysteine, which also prevents the leukopenia, but not by Thorotrast. The pyrogenic action of bacterial endotoxin is uninfluenced by nitrogen mustard; hence, it is apparently independent of the presence of normal numbers of circulating leukocytes.

Schlang B75,461/52: Both cysteine and inflammation, produced by mild irritants, inhibit the leukopenia normally elicited by nitrogen mustard in the rabbit. Simultaneously, the inhibitory effect of nitrogen mustard upon the development of an SSP-L, induced by two injections of *E. coli* endotoxin, is blocked by these agents. These findings furnish "additional support for the correlation between the presence of the heterophil granulocyte and the production of the Shwartzman phenomenon."

Berthrong & Cluff D83,712/53: Observations on tissue culture fragments from the buffy coats of centrifuged blood, using the glass slide method, revealed that *S. marcescens* and *Sh. flexneri* endotoxins i.v. inhibit the migration of leukocytes from the buffy coat of their

blood. The response is obtained both when an SSP-L is produced by two injections and when a single dose is given i.v. Inhibition of the SSP-L by heparin fails to alter this response.

Cluff D79,025/53: Various bacterial endotoxins i.v. inhibit the migration of leukocytes from the buffy coat of centrifuged blood. Repeated daily injections of endotoxin resulted in resistance to this effect. "In view of the participation of the leukocyte in the pathogenesis of the Shwartzman reaction, the presence of leukocytes resistant to endotoxin may be responsible in part for the development of resistance to the Shwartzman phenomenon."

Hestrin & Davies C23,684/56: The native levan of *Aerobacter levanicum*, given i.c. and then i.v., produces a typical SSP-L in the rabbit. The response is inhibited if native levan or native dextran is given i.v. just before the preparatory i.c. dose of toxin. Since i.v. injection of the levan or dextran produced leukopenia, it was concluded that "the leukopenogenic activities of polymers and their ability to depress diapedesis and block skin preparation in the Shwartzman reaction are seen to be correlated properties. The findings support the view that induction of skin reactivity in the Shwartzman phenomenon requires infiltration of the prospective site by leukocytes during the phase of skin preparation."

Rall & Kelly C36,395/57: The fact that nitrogen mustard inhibits the SSP does not necessarily indicate an important participation of leukocytes, since this drug produces not only leukopenia but also thrombocytopenia. Hence, "it is possible that this compound acts to minimize or prevent the formation of the leukocyte platelet clumps which normally develop after the provocative dose."

Thomas D1,020/57: Since nitrogen mustard protects against the SSP-G allegedly by producing leukopenia, it is assumed that the leukocytes (like exogenous synthetic acidic polymers) may bring about a state of preparation, in that they precipitate fibrinogen. Perhaps the latency period of 24 hrs. is necessary for the return of precipitable fibrinogen into the blood when the animal's own acidic polymer (presumably derived from leukocytes) is available to cause precipitation. The fact that nitrogen mustard does not prevent the SSP-G produced by endotoxin plus synthetic

acidic polymers appears to support this assumption.

Johnstone & Howland G22,057/58: The SSP-L normally produced by two injections of *S. marcescens* endotoxin in the rabbit is inhibited, but not totally prevented by nitrogen mustard or x-irradiation conducive to severe leukopenia. "It is concluded (a) that the presence of normal numbers of circulating polymorphonuclear leukocytes is not an obligatory prerequisite condition to the localized hemorrhagic necrosis of the Shwartzman phenomenon, and (b) the mechanisms of action of nitrogen mustard and whole body irradiation on body tissues differ in relation to the Shwartzman reaction."

Collins & Wood G33,268/59: Rabbit polymorphonuclear leukocytes, as well as their cell-free extracts inactivate the endotoxin of *Sh. flexneri*. On the other hand, the release of leukocytic pyrogen in serum is markedly stimulated by endotoxin. These findings may have a bearing upon the participation of leukocytes in endotoxin reactions.

Hall et al. G9,421/64: In rabbits made tolerant to epinephrine, the SSP-L can be produced by two injections of *E. coli* endotoxin, even though a considerable drop in polymorphonuclear leukocytes is produced both in the blood and in the area of challenge. These findings "suggest that presence of leukocytes may not be necessary for development of the local reaction."

Halpern F2,441/64: An SSP-L can be elicited in the rabbit by preparation with *E. coli* endotoxin and provocation with isolated leukocyte granules, and this response can be inhibited by pretreatment with a potent anti-proteinase. "It is hypothesized that the tissue damage observed in the Shwartzman reaction is conditioned by release or activation of intracellular lysosomal enzymes contained in granulocytes."

Herion et al. F10,884/64: "Endotoxin, injected intravenously in small doses, is removed from the blood of nongranulocytopenic and granulocytopenic, HN_2 -treated rabbits at a rate similar to normal controls." . . . "Thus, granulocytes would not appear to contribute significantly to the removal of small doses of endotoxin."

Horn & Spicer G25,934/64: In rabbits in which an SSP-G is elicited by two injections of *Salmonella enteritidis*, an unusually large number of heterophil leukocytes with distinctive cytoplasmic granules appear in the blood. "These granules, which were histochemically identical to azurophil granules of rabbit bone marrow, stained with azure A

above pH 4.0, with aldehyde fuchsin, high iron-diamine, alcian blue, and alcoholic PAS, and were associated with the incorporation of S^{35} -sulfate, indicating the presence of a sulfated mucopolysaccharide. Affinity of the same granules for Biebrich scarlet at highly alkaline pH indicated the presence of a strongly basic protein; blocking reactions suggested that the basic nature of the protein was attributable to high arginine content." The granulated leukocytes appear both following the first and the second endotoxin injection used to produce the SSP-G. The authors also report "histochemical and autoradiographic studies indicating that a sulfated mucopolysaccharide is present in the fibrinoid occlusive glomerular lesions of the generalized Shwartzman reaction." . . . "It is tempting to speculate that some pathophysiologic mechanism, e.g., leukocyte sticking in sites of injury, might be related to the coincidence of an acid mucopolysaccharide constituent of the heterophil and locally engendered partially polymerized fibrinogen, leading to the production of an acid polymer-fibrinogen complex with adhesive characteristics."

Horn & Spicer G33,272/64: The presence of a sulfated mucopolysaccharide in the azurophil granules of rabbit neutrophils and basophils is demonstrated by histochemical and autoradiographic techniques.

Jókay et al. G28,485/64: Earlier experiments had shown that in vitro cysteine prevents platelet aggregation as well as the release of histamine and 5-HT which normally occurs under the influence of endotoxin in rabbit blood. It is now found that simultaneous administration of the provoking dose of *E. coli* endotoxin and cysteine i.v., in rabbits prepared for the SSP-L, inhibits thrombopenia and enhances leukopenia. At the same time, the resulting SSP-L is aggravated. It is concluded that platelet aggregation is less important than leukopenia in the production of an SSP.

Thomas F738/64: A THP-L can be elicited in the skin of the rabbit by i.c. injection of the granule fraction obtained from peritoneal granulocytes followed by i.v. provocation with *E. coli* endotoxin. "It is suggested that one or more of the acid hydrolases contained in granules may be implicated in the pathogenesis of vascular damage." Cortisol i.v. prevents this response, allegedly because of its stabilizing effect upon the lysosomes.

Horn & Spicer G25,692/65: An SSP-G was produced by two i.v. injections of *S. enteritidis* in the rabbit and the fibrinoid thrombi were stained with the aldehyde-fuchsin and high iron-diamine techniques which are character-

istic for sulfated mucopolysaccharides. The staining of fibrinoid by these methods suggests that sulfated mucopolysaccharides may be constituents of fibrinoid. The incorporation of S³⁵-sulfate by fibrinoid was regarded as additional evidence in support of this view. Since numerous leukocytes were present in the renal glomeruli during the early period of fibrinoid deposition, it is postulated that the sulfated mucopolysaccharide, which becomes incorporated into fibrinoid, may originate from circulating leukocytes.

McKay E4,788/65: A review of the somewhat contradictory literature concerning the mechanism through which endotoxins produce an SSP-G, leads to the conclusion that "endotoxin acts independently of leukocytes and red blood cells, and does not act as pre-formed thromboplastin or thrombin."

Taichman & Uriuhara G28,156/65: Brief abstract suggesting that enzymes of polymorphonuclear leukocyte lysosomes are responsible for the SSP. [No experimental details are given (H.S.).]

THE KIDNEY

(cf. also: renal changes in THP, p. 157; effect of nephrectomy on THP, p. 164.)

Usually, the kidney is most severely affected by THP-Gs and the localization of thrombi in the glomerular capillaries may be enhanced by vasodilatation. However, there is no evidence of any significant renal participation in the pathogenesis of extrarenal lesions. Bilateral nephrectomy does not protect against such changes; indeed it may even increase the severity of an SSP-G subsequently elicited by two i.v. injections of endotoxin. In fact, allegedly, bilateral nephrectomy suffices in itself to produce a THP reminiscent of Moschcowitz's disease in dogs (cf. p. 124).

Merriam & McKay C66,400/59; McKay & Rowe D14,807/59; C80,265/60: An SSP-G was produced in the rabbit by two i.v. injections of Shear's polysaccharide. "No alteration was noted in the kidney until 2-4 hrs. after the second injection. At this time the glomerular capillaries dilated and filled with ink. This

stasis of blood in these vessels precedes or is concomitant with the intravascular deposition of fibrin in the same locations. It is suggested that dilation and stasis of blood in the renal glomeruli may constitute one of the major mechanisms of preparation in the generalized Schwartzman reaction."

STRESS

Stress is undoubtedly an important conditioning factor for the THP. The influence of various stressors (trauma, temperature variations, ionizing rays, hemorrhage, etc.) and stress hormones (catecholamines, ACTH, glucocorticoids) has been discussed in Chapter III.

Let us merely add here that several investigators postulate close relations between various forms of THPs and the general adaptation syndrome (G.A.S.). Indeed, it has been said that the thrombohemorrhagic "malignant syndrome," Reilly's syndrome, and the alarm-reaction phase of the G.A.S. are actually the same. This view is obviously not tenable, since the alarm reaction is unaccompanied by thrombohemorrhagic phenomena and, unlike the THP, it can be produced by any stressor.

The hemorrhagic stress syndrome of Jaques, elicited by exposure to nonspecific stress after pretreatment with anticoagulants, is undoubtedly dependent upon the production of an alarm reaction but, being unaccompanied by thromboses, it cannot be regarded as a THP.

Yet, a good deal of evidence suggests that stress can predispose for the production of THPs by various means, a subject which has been dealt with at some length in the section on the pluricausal THPs.

Shwartzman et al. D71,760/50: The authors state that "our observed suppression of the phenomenon (SSP) by ACTH and cortisone indicates that provocation of the phenomenon depends on adrenal cortical function."

Algire et al. G22,055/52: Using the transparent-chamber technique, it was possible to follow the vascular reactions which accompany the production of hemorrhagic necrosis in strain-L sarcoma and sarcoma-37 transplants following single or repeated injections of *S. marcescens* endotoxins i.p. in the mouse. Irreversible ischemic damage to tumor capillaries was indicated by stasis, hemorrhage or thrombus formation. "It is concluded that the tumor-necrotizing effect of this agent is brought about by the ischemia and circulatory stasis induced by hypotension." . . . "There are many indications that the effects on the host of this polysaccharide, as well as of other bacterial endotoxins, are related to the general adaptation syndrome as described by Selye."

Decourt B72,103/52: The general adaptation syndrome is considered to be identical with Reilly's phenomenon [! (H.S.)].

Verge & Paraf B96,396/54: If ACTH is given i.v. 24 hrs. after i.c. preparation with *E. coli* endotoxin to the rabbit, a typical "SSP-L" results. It is assumed that activation of the pituitary-adrenocortical axis by stress plays an important role in the SSP.

Marquézy E65,247/58: The thrombohemorrhagic syndrome, known in the French literature as "syndrome malin," is considered to be identical with Reilly's syndrome and with the alarm reaction phase of the G.A.S.

Ravin et al. G27,057/58: The toxin that appears in the blood of dogs and rabbits during irreversible hemorrhagic shock resembles bacterial endotoxin in many of its pharmacologic and chemical properties. Concentrates of this toxin can act as the provocative factor of the SSP-G in rabbits prepared by *E. coli* endotoxin or Thorotrast i.v. It is concluded "that the circulating toxin in shock is similar to, or identical with, bacterial endotoxin."

Katz D87,740/59: Hemorrhagic duodenitis associated with intense dilatation of the duodenal microcirculation is frequently seen in patients under severe stress and particularly after myocardial infarction. "It is certainly plausible that hemorrhagic duodenitis represents one part of the shock phase of the alarm reaction."

Zweifach et al. E95,298/61: A THP is elicited in the rabbit by *E. coli* endotoxin i.c. combined with epinephrine given either i.v. or topically in combination with the endotoxin, both agents being administered at the

same time. Both these forms of THP were prevented by such classical inhibitors of proteolytic activity as EACA, tosylarginine methyl ester (TAME), and soybean trypsin inhibitor (SBTI). No effect was observed on the classical SSP-L induced by two injections of *E. coli* endotoxin. "The working hypothesis is advanced that local or systemic stress through the release of epinephrine may result in an increase of a circulating activator of proteolysis and that this in turn may give rise to the release of vasoactive substances, possibly histamine, serotonin, or a polypeptide."

Rapin G27,052/63: Detailed description of the hemorrhagic "malignant syndrome" which can occur in the course of various infectious diseases, particularly scarlet fever, typhoid, various other septicemias due to Gram-negative organisms, but also in viral infections such as influenza, rubella, poliomyelitis and varicella. It can even occur in parasitic infestations with *Plasmodium falciparum*. This condition is possibly related to the general adaption syndrome, Reilly's syndrome and the Shwartzman phenomenon, but a definite interpretation of its pathogenesis is not yet possible.

Hoak et al. E33,389/63: In rabbits injected with ACTH or crude anterior pituitary extract s.c., thromboses developed in isolated jugular-vein segments, simultaneously with a 5 to 7-fold increase in plasma-free fatty acids. Thrombi were also found in branches of the pulmonary artery, liver, kidney and the cardiac cavities. "These results suggest that rapid lipid mobilization resulting in high plasma-free fatty acids can be associated with a thrombotic state and acute heart failure in the rabbit."

Levin & Cluff G8,713/64; G25,181/65: In rabbits pretreated with Thorotrast or ACTH, *E. coli* endotoxin i.v. produces severe adrenal hemorrhages and other organ lesions reminiscent of the Waterhouse-Friderichsen syndrome and the SSP. However, unlike the SSP, this response is not inhibited by heparinization, although both reactions are prevented by nitrogen-mustard pretreatment. The adrenal hemorrhages are also prevented by certain adrenergic blocking agents such as phenoxybenzamine, alderlin, or 1(3',4'-dichlorophenyl)-2-(isopropylamino) ethanol. Since ACTH, Thorotrast and *E. coli* endotoxin all increase the blood-cortisol level of the rabbit, it is assumed that the localization of the hemorrhages is connected with increased adrenocortical activity.

Nordøy & Rørvik F56,815/65: After a review of the literature on the probable role of stress and epinephrine in the production of

thrombo-embolic disorders, the authors describe observations showing that in heparinized platelet-rich plasma aggregation, adhesion of platelets occurs upon incubation with epinephrine. "In plasma from rats given adrenaline in oil to induce a state of 'adrenaline

stress,' a higher total platelet count was found than in control animals." Intravenous injection of an LD₅₀ of ADP elicits pulmonary platelet thrombi in control rats while in "adrenaline-stressed" animals, the mortality is reduced and platelet thrombi are absent.

LIPIDS

Derangements in lipid metabolism may also play a part in the production of THPs. We have already mentioned that a THP can be produced in pregnant rats kept on a vitamin-E-deficient diet rich in oxydized lipids. The classic SSP-G in the rabbit is associated with a rise in blood lipids (particularly cholesterol), β -lipoproteins and the cholesterol:phospholipid ratio. These and other observations suggested that an increase in blood lipids not only accelerates intravascular coagulation but also blocks the RES, thereby interfering with the effective removal of fibrin and fibrin polymers.

Berken & Wolman D85,445/62: A variety of conditions resulting in the precipitation of serum lipoproteins with coprecipitation of other protein fractions produces an SSP-G in the rabbit; hence these blood components are considered to play an essential role in the SSP.

Kaunitz et al. E29,696/63: In pregnant rats in which an SSP-G was produced by a vitamin-E-deficient diet containing ethyl esters of oxidized cod-liver oil, the kidney and perirenal adipose tissue contained more water than in similarly treated rats in which the "SSP-G" was inhibited by supplements of vitamin E. In the sera of the experimental animals, there was an increase in long-chain fatty acids with relative diminution of phospholipids, triglycerides and unesterified fatty acids, suggesting an interference with the mobilization of depot fat. The palmitate:stearate and linoleate:arachidonate ratios of the tissue lipids were also lower in the rats with the "SSP-G" than in those in which the reaction was prevented by vitamin E. Apparently, the "SSP-G" is associated with a disturbance of fat mobilization and lipogenesis.

Renaud G31,776/63: In rats kept on a high fat low protein diet, i.v. injection of living or killed cultures of *Proteus mirabilis* or *E. coli* endotoxin produces multiple infarcts concurrently with an enormous increase in blood cholesterol.

Shore & Alpers G5,157/63: "Addition of small quantities of stearic, arachidic, or behenic acids, as the sodium salts, to heparinized platelet-rich rabbit plasma in vitro causes platelet clumping and other damage as re-

flected by marked release of platelet serotonin and histamine" . . . "The results suggest that certain pathologic changes in blood and vascular system, some already associated with altered fat metabolism, may be mediated in part through the actions of certain platelet damaging free fatty acids."

Hoak et al. E33,389/63: In rabbits injected with ACTH or crude anterior pituitary extract s.c., thromboses developed in isolated jugular-vein segments, simultaneously with a 5 to 7-fold increase in plasma-free fatty acids. Thrombi were also found in branches of the pulmonary artery, liver, kidney and the cardiac cavities. "These results suggest that rapid lipid mobilization resulting in high plasma-free fatty acids can be associated with a thrombotic state and acute heart failure in the rabbit."

Müller-Berghaus D13,794/64: An SSP-G elicited by two i.v. injections of *E. coli* lipopolysaccharide in the rabbit results in a rise in blood lipids, particularly cholesterol, β -lipoproteins and the cholesterol:phospholipid ratio. Administration of "essential" phospholipids at the proper time restores the cholesterol:phospholipid ratio to normal and renders the second dose of endotoxin ineffective in eliciting the SSP-G. The authors believe that the increased blood lipids not only accelerate intravascular coagulation but also block the RES and thus prevent the effective removal of fibrin and fibrin polymers.

Bouvier G28,393/65: Review of the literature on the role of platelet and other lipids in the initiation of a consumption coagulopathy and, consequently, an SSP.

ENZYMES

The participation of enzymes in the production of THPs has been suspected mainly because in skin prepared with endotoxin there is active aerobic glycolysis and lactic-acid production. Furthermore, rabbits given endotoxin i.v. become highly susceptible to the local necrotizing effect of proteolytic enzymes. Possibly in endotoxin-induced reactions, lipopolysaccharides activate proteolytic enzymes which in turn act upon plasma globulins to release vasoactive polypeptides.

Thomas & Good B79,249/52: "It was shown by Thomas and Stetson that prepared skin tissues consistently exhibit a striking metabolic abnormality, which consists of the aerobic production of large amounts of lactic acid. On the basis of this observation, plus the finding that rabbits given intravenous toxin become highly susceptible to the local necrotizing effect of proteolytic enzyme injected into the skin, it was suggested that the local Shwartzman reaction might be due to an activation of tissue protease in the skin."

Zweifach et al. E95,298/61: A THP is elicited in the rabbit by *E. coli* endotoxin i.c. combined with epinephrine given either i.v. or topically in combination with the endotoxin, both agents being administered at the same time. Both these forms of THP were prevented by such classical inhibitors of proteolytic activity as EACA, tosylarginine methyl ester (TAME), and soybean trypsin inhibitor (SBTI). No effect was observed on the classical SSP-L induced by two injections of *E. coli* endotoxin. "The working hypothesis is advanced that local or systemic stress through the release of epinephrine may result in an increase of a circulating activator of proteolysis and that this in turn may give rise to

the release of vasoactive substances, possibly histamine, serotonin, or a polypeptide."

Antopol & Chryssanthou D56,730/63: "It is suggested that in endotoxin-induced reactions lipopolysaccharides activate proteolytic enzymes which in turn act upon plasma globulins to release vasoactive polypeptides," because: "(1) Bacterial lipopolysaccharide increases serum proteolytic activity in vitro, (2) immune human globulin potentiates the Shwartzman phenomenon in rabbits and mice, (3) combined globulin-lipopolysaccharide treatment produces toxic effects on mice and rabbits, (4) bradykinin potentiates and amidopyrine inhibits the local Shwartzman and Thomas reactions, (5) bradykinin inhibits fibrinolysis in vitro."

Halpern F2,441/64: An SSP-L can be elicited in the rabbit by preparation with *E. coli* endotoxin and provocation with isolated leukocyte granules and this response can be inhibited by pretreatment with a potent anti-proteinase. "It is hypothesized that the tissue damage observed in the Shwartzman reaction is conditioned by release or activation of intracellular lysosomal enzymes contained in granulocytes."

CATECHOLAMINES

Numerous observations suggest that catecholamines participate in the induction of THPs. Following suitable pretreatment, epinephrine and norepinephrine are highly effective in producing a THP-L (cf. Chapter III). Apparently, endotoxin has the property of altering the reactivity of blood vessels to catecholamines so that these exhibit thrombohemorrhagic and necrotizing properties. On the other hand, dibenamine, and other adrenergic blocking agents, prevent THP-Gs, produced by various techniques.

Thomas C27,073/56: The fact that epinephrine i.c. produces a local THP in rabbits given various endotoxins i.v., leads to the conclusion "that endotoxin has the property of altering the reactivity of blood vessels to epinephrine in such a way that this hormone becomes a potent necrotizing agent."

Lillehei & MacLean D59,725/58: In the dog, *E. coli* endotoxin i.v. produces irreversible shock with hemorrhagic necrosis of the bowel, plasma loss, a rise in hematocrit and in plasma hemoglobin. These changes "apparently result from sympathomimetic action of endotoxin on the bowel." The syndrome is in-

hibited by adrenergic blocking agents (chlorpromazine, dibenzyline), artificial hypothermia and, to a lesser extent, by cortisol. Previous sterilization of the intestinal contents by sulfasuxidine and neomycin has no effect, while vasopressor drugs (norepinephrine, metaraminol) "actually potentiate the shock caused by endotoxin by increasing intestinal ischemia."

Fine et al. D98,173/59 Dibenamine prevents the "SSP-G" normally produced by one large or two smaller i.v. doses of Thorotrast or by a small dose of Thorotrast combined with hemorrhagic shock. "It appears that the hemorrhages and the peripheral vascular collapse require the participation of the adrenergic system."

Atkins G22,701/60: Review of the literature showing "that the profound vasomotor disturbances which follow an injection of endotoxin may be due to sensitization of the sym-

pathetic nervous system to small amounts of adrenaline."

Gilbert C88,049/60: Detailed review of the literature suggesting that epinephrine and norepinephrine are involved in the mediation of endotoxin-induced vascular disturbances. 1. There are morphologic similarities between the lesions induced by catecholamines and by endotoxins. 2. The catecholamine content of the blood increases sharply following endotoxin administration, while the epinephrine content of the adrenals drops. 3. Following endotoxin i.v., epinephrine produces intense topical vascular disturbances with hemorrhages and necrosis in vivo and in vitro. 4. Increased sympathoadrenal activity may act adversely in different types of shock. 5. Large doses of epinephrine can produce bilateral cortical necrosis in themselves. 6. Protection against various types of shock and against THPs has been obtained by dibenamine and ganglionic blocking agents, which would be expected to reduce vascular tone.

HISTAMINE, SEROTONIN, ANTISEROTONIN, BRADYKININ, ANTIBRADYKININ, KALLIKREIN (cf. also Chapter III)

The role of *histamine* is not clearly demonstrable. Histaminase fails to prevent the classic SSP-L, and the data on the action of various antihistaminics are somewhat contradictory.

The literature on the possible role of *serotonin*, *antiserotonins*, *bradykinin*, *antibradykinins* and *kallikrein* has already been discussed. It is not yet clear to what extent these agents participate in the mechanism of THP-production, but there is suggestive evidence that at least some of them do play a role. Apparently several mast-cell products (heparin, 5-HT, and perhaps even histamine) are important conditioning factors in the production of THPs and particularly pluricausal THPs.

THE MAST CELLS AND ANAPHYLACTOID INFLAMMATION

The role of the mast cells and of the anaphylactoid inflammation also deserves attention. It has occasionally been noted that mice develop a hemorrhagic exantheme of the "naked parts of the body" upon parenteral treatment with single doses of bacterial extracts. However, here (unlike in the anaphylactoid form of the pluricausal THP), these changes are not preceded by any anaphylactoid swelling of the affected parts and there is no record of microthrombosis or of mast-cell discharge; hence, the possible relationship between such exanthemas and the THP remains problematic.

An SSP-L induced by the usual techniques in the cheek-pouch of the hamster is unaccompanied by any significant mast-cell degranulation and cannot be prevented by prior depletion of the cheek-pouch mast-cell population. Hence, it was con-

cluded that the mast cells play no role in the production of the SSP-L. It must be remembered, however, that the mast cells may discharge products without showing any obvious depletion of their metachromatic granules and that, under certain circumstances, degranulation may so rapidly be followed by regranulation that the response can easily be missed.

Heyrovsky G23,661/07: In mice treated with single or multiple i.p. or s.c. injections of filtrates of streptococcus mucosus (designated as "Stojan's strain"), there develops "especially at the naked parts of the body (ears, paws, tail, snout, genitals), a localized hemorrhagic exanthema in the form of livid flat or slightly elevated round or irregularly circumscribed often confluent efflorescences." The hairy parts of the skin are not affected except where the filtrate was injected and where the skin was mechanically traumatized. There is also bloody diarrhea with hemorrhages in the palate, lungs, intestine and urinary bladder, enlargement of the spleen and hyperemia of the kidney. Histologically, the hemorrhagic regions show signs of inflammation. The condition is considered to be an experimental

equivalent of the purpuric types of septicemia seen in man.

Reimann & Julianelle D93,175/26; Julianelle & Reimann D88,216/26: Mice given pneumococcus extract i.p. develop a cutaneous purpura often affecting the ears, feet or tail. At the same time, there is thrombocytopenia and hemolytic anemia.

Gustafson & Cronberg D61,874/63: An SSP-L elicited in the classic way by *E. coli* endotoxin in the hamster's cheek pouch was not accompanied by any significant mast-cell degranulation, nor did previous depletion of the cheek pouch mast-cell population prevent the response. "Mast cell alterations do not seem to be an essential or a primary effect in endotoxin reactions."

THE POSSIBLE DEFENSIVE VALUE OF THE THP

The possible adaptive value of THPs has been considered by several investigators. It has been thought that the SSP-L may be a fundamentally defensive response designed to prevent the absorption of toxic microbial products by localizing them in the thrombosed and necrotic tissue, or by inducing an inflammation which could destroy them. However, there is little experimental evidence to support these theoretic considerations. The SSP protects animals against serum shock but this may merely be a phenomenon of "cross resistance" elicited by the nonspecific stressor effect of the endotoxin pretreatment.

Bordet G23,543/31: Killed *E. coli* organisms, injected i.v. or s.c. into BCG-vaccinated guinea pigs, produce systemic or topical hemorrhages respectively. This is considered to be a manifestation of a defence reaction. "The immunologic significance of Koch's phenomenon, an essentially specific response, is well established; can one put a different interpretation upon the same phenomenon when it is produced by the injection of nonspecific microbes?" . . . "One is inclined to assume that the allergic reactions just described (the Bordet phenomenon) can be detrimental when the provocative factors are too suddenly introduced into the body, but they represent fundamentally defensive responses designed to prevent the absorption of inoculated toxic products which thus become localized and remain in situ concentrated to such an extent that a necrosis of the injection site ensues."

Debonera et al. B78,075/32: Theoretic considerations suggest that the function of the preparatory injection in the SSP-L may be to induce local inflammation which will then fix the toxic materials given for provocation so that they may be locally destroyed or eliminated to the outside. [However, the experiments quoted in support of this theory merely showed that local inflammation, induced by bacteria or vaseline in guinea pigs, can prepare for the production of an SSP-L by the subsequent i.v. injection of *E. coli* endotoxin. No evidence is presented that this response did in fact increase resistance to the provocative factors (H.S.).]

Gratia & Linz G23,092/33: The SSP protects the rabbit and guinea pig against serum shock; the efficacy of this protection is proportionate to the intensity of the SSP.

Apitz G25,132/34: If rabbits are first given *E. coli* endotoxin i.v. and 24 hrs. later cultures of live *staphylococcus aureus* i.v., the course of the resulting septicemia is greatly altered. Depending upon dosage, there may be complete protection against infection, no effect, or a combination of the usual septicemia with endocarditis. Topical protection against infection may also be obtained by pretreatment of the cutaneous inoculation site with endotoxin, as shown by the author's earlier experiments.

McKay et al. G22,384/58: In rabbits in which an SSP-G was produced by two i.v. injections of bacterial endotoxin (kind not stated), fibrin

could be demonstrated by staining with fluorescein-labeled antibody to rabbit fibrin in the thrombi, in the lungs, liver, spleen and kidney. "It is concluded that the thrombi of the generalized Shwartzman reaction contain an immunologically active derivative of fibrinogen which is the essential constituent of the thrombi."

Schimpf et al. F16,327/64: The blood heparin level drops sharply (though only transiently) during an SSP-G elicited by two i.v. injections of *E. coli* endotoxin as well as after rabbit-serum infusion in the rabbit. Presumably this represents a physiologic defense reaction.

NONSPECIFIC MESENCHYMAL REACTION

According to a recent theory, the SSP should be considered as a nonspecific mesenchymal reaction. In the production of an SSP-L or SSP-G, an i.c. injection induces a local, an i.v. injection a general increase in sulfur incorporation into chondroitin-sulfuric acid as judged by S³⁵-sulfate tracer experiments. This response is allegedly indicative of an "acceleration of mesenchymal metabolism."

Hauss et al. D23,337/62: In rabbits in which an SSP-L or an SSP-G is elicited by two injections of *S. abortus equi* endotoxin, a marked incorporation of radioactive sulfate into chondroitin sulfuric acid can be demonstrated in the affected organs by treatment with S³⁵-sulfate. An i.c. injection induces a local, an i.v. or i.p. injection a universal, increase in the sulfur incorporation into chondroitin sulfuric acid. If two injections are given at 24-48 hr. intervals, an "addition ef-

fect" is noted because, at this time, the mesenchymal response is optimally developed. In this event, the "acceleration of the mesenchymal metabolism" is so pronounced that severe disturbances of capillary permeability with hemorrhages and necroses, that is an SSP, ensues.

Emmrich et al. F8,082/64: The SSP-G is considered to be a "universal nonspecific mesenchymal reaction."

LOCALIZATION OF BACTERIAL ENDOTOXIN

In the production of the SSP-L, localization of bacterial endotoxins in prepared skin sites has been regarded as the main function of i.c. preparation for subsequent i.v. provocation. However, several observations are incompatible with this interpretation: 1. Even very large single doses (or repeated injections of endotoxin into the same skin site) fail to produce an SSP-L-like lesion, 2. allegedly, the prepared skin does not exhibit increased permeability to circulating dyes.

Clinical observations on thrombohemorrhagic forms of infantile diarrhea due to *E. coli* suggested that the microbial toxin attacks the intestinal mucosa and permits SSP-active material of the intestinal flora to penetrate into the circulation. Yet, we have no direct evidence that such a penetration actually occurs.

In certain strains of mice SSP-L-like lesions can be produced by single i.c. injections of *E. coli* endotoxin. Since this response is largely prevented by terramycin, it was thought that the natural flora of the animals may be responsible for their sensitivity.

Thomas & Good B79,249/52: "It has been suggested that it (the SSP-L) may be due to an excessive concentration of toxin in the prepared skin site after the intravenous, or 'provocative' injection, due to a supposed localizing effect of the inflammatory reaction in the skin. This explanation is contradicted by several items of evidence. First, the local injection of extremely large amounts of toxin, much larger than the amount required for intravenous provocation of the reaction, does not cause local hemorrhage in the skin. Second, repeated injections of toxin into the same skin site do not cause hemorrhage, regardless of the dosage of toxin. Third, the prepared skin site does not exhibit increased permeability to circulating dye, as is the case with other types of skin inflammation; on the contrary, the penetration of trypan blue or Evans blue into the prepared area is much less than in normal skin."

McKay & Wahle D6,653/54: In an epidemic of often fatal infantile diarrhea due to *E. coli*, the clinical and pathologic features closely resembled the SSP-G as it occurs in the rabbit. Allegedly, here, the pathogenic agent "attacks the mucosa of the small intestine and allows Shwartzman active materials—whether from a specific micro-organism, from the bacteria of the intestinal flora, or from products of cellular necrosis—to gain access repeatedly to the blood-stream and thus to prepare and to provoke the local and generalized Shwartzman phenomena in these infants."

Arndt & Schneider D9,369/58: The "SSP-L" which can occasionally be elicited in certain strains of mice by a single i.c. injection of *E. coli* endotoxin is largely prevented by Terramycin. This finding appears to confirm "the hypothesis that the 'natural' flora in the animals was related, in some way, to the observed variability."

VARIOUS OTHER THEORIES

A variety of other theories requires only brief mention. It has been thought, for example, that *smooth muscle products*, extruded into the circulation from damaged blood vessels, may be responsible for local thrombus formation when THP-like phenomena are elicited in dogs by bilateral nephrectomy. It has also been postulated that *erythrocytes*, histamine, derangements in *glucose metabolism*, or *physicochemical changes* in the constitution of the blood play a cardinal role in the production of THPs but there is still little experimental evidence to support such views.

Smooth Muscle Products. *Muirhead C15, 392/56:* Following bilateral nephrectomy, occlusive vascular lesions develop in the dog with a syndrome reminiscent of the "thrombotic thrombocytopenia" of Moschcowitz's disease. The small arteries and arterioles throughout the viscera exhibit hyaline thrombi which often appear to be continuous with similar substances within the necrotic vascular wall and give the histologic reactions of fibrinoid. "It is suggested that several features of the experimental lesions support an origin of the occlusive masses via extrusion or herniation of the necrotic smooth muscle of the media into the lumen."

Erythrocytes. *Botkin G20,883/1858:* First description of what later became known as "erythrocyte agglutination thrombi." By applying 15% NaCl to the frog mesentery, the capillaries become dilated and packed with agglutinated erythrocytes so that the circulation stops. Similar results are obtained with other inorganic salts and concentrated sugar or urea

solutions. The phenomenon is ascribed to deformation and consequent adhesiveness of the erythrocytes.

Hueter G24,671/1874: Upon topical treatment with ammonia, glycerin, chloroform or phenol, the capillaries of the frog mesentery and skin become engorged with closely packed and partially deformed erythrocytes. This erythrocyte stasis ("globulöse Stase") may be followed by the loosening of entire erythrocyte cylinders which then can cause microembolisms ("globulöse Embolie") in other organs (e.g., the lung). The process is ascribed to primary erythrocyte damage which makes the surface of the red blood corpuscles irregular and sticky. A few observations on rabbits and man suggest that erythrocyte embolism may also occur in mammals and have clinical significance.

Nestel G24,196/59: When homogenized clots of their own blood were injected i.v. in rabbits, it was noted "that the clots were incorporated into the intima of the larger pul-

monary arteries and frequently produced lesions containing lipid and haemosiderin." Thrombi of blood, deprived of its erythrocytes, produced similar lesions "probably due to secondary thrombosis." . . . "The question whether the presence of erythrocytes was necessary for the production of lesions containing fat was not answered because of the failure to produce lesions in which erythrocytes were not involved."

Histamine. *Schayer et al. D58,948/63:* *S. enteritidis* endotoxin suppresses histidine decarboxylase activity in the rabbit kidney. "The findings are consistent with the view that suppression of induced histamine synthesis, at a time of markedly increased catecholamine release, might potentiate the actions of these vasoconstrictors on the kidney. This event may be a factor in the early endotoxin-induced changes in the glomerular capillaries which prepares them for the subsequent events of the generalized Shwartzman reaction."

Mast cells. *McGovern D28,931/55:* In the rat, injury to blood vessels (by various chemical irritants) stimulates the endothelium to produce a granular material which closely resembles the ground substance of intercellular cement. At the same time, a metachromatic substance, probably derived from mast cells, diffuses through the endothelium. These processes may play a role in thrombus formation.

Collagen. *Solum & Stormorken F56,817/65:*

In experiments on washed human blood platelets, it was found that thrombin and collagen, unlike ADP and epinephrine, require externally added fibrinogen for the induction of platelet aggregation. The participation of these phenomena in the production of thromboses is discussed.

Glucose Metabolism. *Szilágyi et al. E23,139/63:* The SSP-L elicited by two injections of *E. coli* endotoxin in rabbits, is markedly inhibited by alloxan and glucose but augmented by insulin. "A disturbance of carbohydrate metabolism is assumed to play a role in the mechanism of the Shwartzman reaction."

Physicochemical Changes. *Zdrodowski et al. G23,347/31:* The serum of rabbits infected with cholera vibrios, readily flocculates upon dilution with physiological saline or distilled water in vitro. This instability is ascribed to the precipitation of globulins and considered to be the fundamental change in the preparation for the SSP.

Enoki D60,740/62: Physicochemical changes in the serum are thought to be responsible for thrombosis and hemorrhage during the SSP. This conclusion is reached on the basis of measurements of surface tension, serum viscosity and capillary resistance. [The English of this Japanese author is difficult to follow (H.S.).]

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INDEX

Since the entire book deals with thrombohemorrhagic phenomena (THP), it would defeat the purpose of this index were we to place "THP" constantly as the first key word. Therefore, entries are indexed in the alphabetic order of the factors concerned with the thrombohemorrhagic phenomena. When a "target" A is influenced by an agent B, this is indicated by an arrow pointing from B to A, thus: $A \leftarrow B$ or $B \rightarrow A$. Inter-relations between A and B are indexed thus: $A \rightleftharpoons B$. If two stimuli (B and C) act upon the same target (A), this is indexed thus: $B \rightarrow A \leftarrow C$. Page numbers printed in bold face numerals (e.g., 46) refer to principal discussions of a subject.

A

- Abscesses, pulmonary, 163
Aboral anaphylactoid shock organs, 149
 \leftarrow tannic acid + Thorotrast + norepinephrine, 148
THP syndrome, 142, 143, **Plates V, VI**
Abortion, 207
Abruptio placae, 90, 207, 208
Abstracting of literature, vii
Abstracts, evaluation of, vii
"Acceleration of mesenchymal metabolism," 264
Accelerator globulin; *cf.* Prothrombin factor V
Acetylcholine, 99, 101, 110; *cf. also* Nerve drugs,
 choline
Acrodynia, 219
Acrolein \rightarrow THP, 101
ACTH, 133, 258; *cf. also* Stress hormones
 \rightarrow adrenals \leftarrow endotoxin i.v., 171
 \rightarrow THP, 71, 75
"Acute-phase" phenomenon, 194
Acute rheumatic fever, 225
Adenosine-5-phosphoric acid \rightarrow THP, 102
Adjvant effect of tissue fluid, 34
 of blood, 35
Adjvants, 37
 \rightarrow THP \leftarrow nonmicrobial agents, 37
Administration, route of, 32
ADP \rightarrow THP, 101
Adrenalectomy \rightarrow THP, 75
Adrenals, 138, 149, **Plate II**
morphologic changes, 171
 \leftarrow ACTH, 171
 \leftarrow diphtheria toxin, 171
 \leftarrow endotoxin, 249
 \leftarrow Thorotrast + ACTH, 148
 \leftarrow thrombin infusion + ACTH, 171
Adrenaline; *cf.* Epinephrine
"Adrenaline hypersensitivity," 72
Adrenergic blocking agents \rightarrow THP, 246, 261
Aerobacter levanicum, 255
Aerobic glycolysis, 184, 261
Afibrinogenemia, 193
 symptomatic, 216
Agammaglobulinemia, 233
Agar, 132, 151
 \rightarrow anaphylactoid shock organs \leftarrow egg white,
 148
 \rightarrow duodenum \leftarrow age, 148
 \rightarrow jejunum \leftarrow age, 148
 \rightarrow kidney, 151
 \rightarrow kidney \leftarrow stress, 141, **Plate IV**
 \rightarrow THP, 98, 102
 \rightarrow THP \leftarrow mast-cell dischargers, 150
 \rightarrow THP (monocausal), 131
 \rightarrow THP \leftarrow stress, 150
 \rightarrow THP \leftarrow unilateral nephrectomy, 151
 \rightarrow THP-L, 134
 \rightarrow uterus \leftarrow cyproheptadine, 148
Age \rightarrow THP, 42, 148
Agents, preparatory, 21
 provocative, 21

- "Agglutinative thrombi," 4, 239
 Agranulocytosis, 197
 Alarm reaction, 155
 phase of G.A.S., 258
 Albumin-globulin ratio, 186
 Albumin → THP ← thrombin, 252
 Albuminuria; *cf.* Clinical implications
 Allergic diseases, 232
 immunologic reactions, 234
 Alypin → THP, 102
 Amidopyrine → THP, 98, 102
 Amino acids → THP, 102
 Amniotic fluid → THP, 90, 91
 → THP (monocausal), 131
 → THP ← norepinephrine, 90
 embolism, 90, 207, 210
 Amphibia; *cf.* Species
 N-Amylamine → THP, 102
 "Analytico-synthetic style," v
 Anaphylactic shock, 236
 Anaphylactoid inflammation, 150, 262
 purpura, 133, 212, 213, 215
 ↔ intussusception, 232
 ↔ periarteritis nodosa, 225
 shock, 234
 organs, 133, 149, 150
 ← agar + egg white, 148
 ← cyroheptadine, 151
 THP, 151
 Anaphylatoxin → THP, 239
 Anaphylatoxin-like "angiotoxin," 246
 Anaphylaxis, 190
 ↔ allergic immunologic phenomena, 234
 Anemia, hemolytic, 212
 Anesthetics, general, 99
 local, 99
 general and local → THP, 248
 Aneurysms, 173, 213
 Animal serum → THP, 87
 tissue extracts → THP, 92
 "Antenergetics," 98
 Antiadrenergic agents → THP, 151
 → pluricausal THP, 150
 Antibiotics → THP, 98, 102
 → THP ← pregnancy + diet, 98
 → THP ← spontaneous infections, 197
 Antibodies → SSP, 48
 Antibradykinin → THP, 85, 86, 262; *cf. also*
 Hormones and hormone-like substances
 Anticoagulants → THP, 240
 → pluricausal THP, 150
 Antigens, 252
 → blood coagulation, 194
 Antihemophilia globulin, 193
 Antihistamine; *cf.* Hormones and hormone-like substances
 Antihistaminics → THP, 83, 84, 151, 262
 → pluricausal THP, 150
 Anti-5HT; *cf.* Antiserotonin; Hormones and hormone-like substances
 Antiplatelet serum, 239
 → blood coagulation, 71, 240
 → hemorrhagic syndrome, 15
 → THP, 71
 Antiserotonin → THP, 85, 240, 262
 Aorta, canine, 122
 ← epinephrine, 249
 Aortic wall ↔ blood clotting, 239, 246
 Apitz phenomenon, 15
 Appendicitis, 220, 223
 hemorrhagic, 168
 in man, 168
 Appendix, morphologic changes, 168, 169
 mucosa, 221
 Aqueous humor, aspiration of, 173
 coagulation of, 173
 removal of, 173
 Arsenic → THP, 103
 Arteries, renal, 157
 Arthus phenomenon, 3, 15, 48, 236
 Artificial hypothermia → THP, 121
 Ascaridiosis, 198
 Ascaris → THP, 95
 coelomic fluid of, 198
 Aspiration of aqueous humor, 173
 Assessment of SSP-G intensity, 29
 of SSP-L intensity, 29
 of THP- intensity, 29
 Atropine → THP, 99, 110; *cf. also* Nerve drugs
 intoxication, 99
 Auer phenomenon, 3, 15, 238; *cf. also* Immune reactions
 Autonomic blocking agents, 99
 nerves, 198
 Axial periodicity of fibrin, 158

B

- Bacteria, Gram-negative, 21
 (live) i.v. → THP (monocausal), 131
 Bacterial endocarditis, subacute, 203
 endotoxin, localization of, 264
 → THP, 225
 products → THP, 5
 toxin, 18, 131
 reviews, xix
 BAL → THP, 103
 Benadryl; *cf.* Antihistaminics; Nerve drugs
 Benzene ↔ sulfapyridine, 100

- THP, 104, 255
 - Bilateral cortical necrosis; *cf.* Thomas reactions
 - nephrectomy → THP, 119, 124, 258
 - Biliary passages, morphologic changes, 170
 - Biologic fluids → THP, 92
 - materials → THP, 86
 - materials, various, 86
 - Biotin; *cf.* Vitamin-B complex
 - Birds; *cf.* Species
 - Bleeding, massive, 123
 - menstrual, 233
 - Blocked circulation → THP, 164, 174
 - Blocking defect of THP, 240
 - Blood-borne immune bodies, 239
 - humoral substances → THP, 96
 - provoking agents, 119
 - Blood → THP, 86
 - adjuvant effect of, 35
 - clotting, 63, 71
 - ↔ aortic wall, 239, 246
 - ↔ calcium, 229
 - coagulation, 189, 190, 234, 239
 - ↔ antigens, 194
 - ↔ antiplatelet serum, 240
 - ↔ dicoumarol, 240
 - ↔ drugs, 194
 - ↔ functional changes, 189
 - ↔ heparin, 63, 64, 240
 - in vitro, 240
 - ↔ Liquoid, 68
 - ↔ microbial products, 189
 - ↔ sodium oxalate, 240
 - THP, 62
 - ↔ thrombin, 63
 - ↔ thrombin infusion, 193
 - ↔ thromboplastin, 63
 - ↔ vitamin K, 240
 - cortisol level, 187
 - count, 155
 - dyscrasia, 217
 - fibrinogen, 194
 - heparin content, 190
 - lipids, 185, 260
 - intravascular coagulation, 260
 - RES, 260
 - physicochemical changes of, 265, 266
 - platelet count, 239
 - potassium level, 187
 - pressure ↔ THP, 195
 - sugar concentration, 184
 - transfusion → THP, 224, 249
 - THP ← norepinephrine, 146
 - (heterologous) → THP, 134, 229
 - vessels ← endotoxin, 246
 - ↔ epinephrine, 246
 - BMR ↔ body temperature, 184
 - ↔ THP, 184
 - Body temperature, 121, 184
 - Bone marrow, 156
 - Booster dose, 134
 - Bordet phenomenon, 3, 13
 - Bovine γ-globulin s.c. → THP ← Liquoid i.v., 68
 - Bradykinin → THP, 85, 86, 262; *cf. also* Hormone and hormone-like substances
 - plasmin fibrinolysis in vitro, 240
 - Brain, hemorrhages in, 172
 - Buerger's disease, 14, 227
 - Burns → THP, 121
 - gastrointestinal tract, 121
 - infected, 197
 - "Burr" cells, 212
- C**
- Calcery, xiv
 - ↔ metals, 131
 - Calciphylaxis, xiv, xv, 127, 132
 - comparison with pluricausal THPs, 130
 - ↔ cyproheptadine, 131
 - ↔ metals, 131
 - Calcium → blood clotting, 229
 - in blood, 187
 - THP, 104
 - Caffeine → THP, 104
 - Canine aorta, 122
 - Capillary permeability → THP, 195, 246
 - "Capillary permeability-promoting" factor, 195
 - Carbohydrate metabolism → THP, 184
 - Carcinolytic substances → THP, 178
 - Carcinoma, prostatic, 230
 - Cardiac necroses, chemical production of, 127
 - Cardiopathies, pluricausal, 128
 - Cardiovascular collapse; *cf.* Clinical implications
 - system ← microbial products, 165, 166, 167
 - morphologic changes, 164
 - ↔ nonmicrobial agents, 167
 - Carotid-jugular cross transfusion, 35
 - Carrageenin → kidney ← stress, 148, 150
 - nose ← cold, 140, **Plate III**
 - paws ← cold, 140, **Plate III**
 - salivary glands ← 5-HT, 141, 148, **Plate IV**
 - snout ← 5-HT i.p., 141, **Plate IV**
 - spleen ← norepinephrine, 148
 - THP, 104, 134
 - THP + cold, 147
 - THP ← stress, 150

- Carrageenin
 → THP + walk on ice, 135
 → toes ← cold, 141, **Plate IV**
 → tumor transplants ← cold, 140, 148, **Plate III**
- Casein → THP, 104
- Catecholamines, 133; *cf. also* Hormones; Stress Hormones; Theories
 → blood vessels ← endotoxin, 261
 → pluricausal THP, 151
 → THP, 14, 71, 72, 134, 246, 249, **261**
- CeCl₃, 132, 134, 135
- Cecum, 148, 149
- Cell types, 212
- Cerebral thrombohemorrhagic lesions, 172
- Cervical sympathectomy → THP, 248
- Cevanol; *cf.* Nerve drugs
- Challengers, 126, 127, 130, 132, 147
 systemic, 133
 topical, 133
- Chemical agents → THP, 98
 changes, 184
 irritation (nonspecific) → THP ← trauma, 119
 production of cardiac necroses, 127
 techniques → THP, 184
 trauma → THP, 119
- Chemotherapeutic agents → THP, 197
- Chemotherapy, secondary syndrome of, 198, 199
- Chicks, THP in, 43
- Chloral hydrate → THP, 110
- Chlorpromazine → THP, 99, 110
- Cholera, 198, 203; *cf. also* Clinical implications
- Cholesterol, esterified, 185
 in blood, 260
- Cholesterol—phospholipid ratio, 185, 260
- Choline → THP, 101, 104; *cf. also* Vitamin-B complex
- Choriamnionitis, 209
- Circulation (blocked) → THP, 164, 174
- Circulation, extracorporeal → THP, **124**
 → THP, 164, 174
- Circulatory arrests, 122
- Citrin → THP, 101, 104
- Classification, monocausal THPs, 153
 pluricausal THPs, 152
- Clinical implications, 14, 38, **197**
 reviews, 197
 manifestations of SSP, 197
 observations, 264
- Coagulation defects → THP, 194, 230, 239
 factors → THP, 239
 depletion of, 193
 ⇔ hemorrhagic shock, 193
 utilization of, 190
- intravascular, 217
 ← incompatible blood, 194
 ← thrombin infusion, 193, 240
 of aqueous humor, 173
- Cocaine, 99, 111; *cf. also* Procaine
- Coelomic fluid of ascaris, 198
- Colchicine → THP, 98, 104, 178
- Cold hypersensitivity, 140, **Plate III**
 → THP, 195
 → pluricausal THP-G, 147
- "Coley's fluid," 6
- Colitis, ulcerative, 168, 220, 222
- Collagen diseases, 127, 194, 213, **224**
- Collagenoses, 227
- Colloidal silver → THP ← zymosan, 95
- Colon, morphologic changes, 168, 169
 perforation → THP ← stillbirth, 220
- Compounds, localizing potency of, 133
- Compound 48/80 → THP-L, 135
 → THP-L ← tannic acid, 134
- Conditioning factors, 126, 152
 → pluricausal THPs, 150
- Condroitin-sulfuric acid, 264
- Connective-tissue, topographic position of, 150
- Consumption coagulopathy, 63, 190, 213, 230, 232, 240
- Convulsions, 198
- Copper → THP, 105
- Cornea, morphologic changes, 173
- Coronary infarction, 231
 lesions, 225
- Corticoids → THP, 71, 75
- Cortisol in blood, 187
- Cortisone → THP, 75, 76
- Co-sensitizers, 132, 134
- Coumadin; *cf.* Warfarin
- CrCl₃ → parathyroids, 127
 → THP-L ← tannic acid, 134
- Critical period, 21, **29**, 165, 190
 ← endotoxin, 30
 prolongation with neosalvarsan, 30
 ⇔ species, 130
- "Cross protection," 93
- Cross-reacting antibodies, 48
- Cross-transfusion, 35
- Crush syndrome, 206
- Cryoprotinin, 189, 190, 193, 194, 240
- Curare, 99, 111; *cf. also* Nerve drugs
- Cutaneous gangrene, 218
- Cyproheptadine, 131, 151
 → anaphylactoid shock organs, 151
 → calciphylaxis, 131
 → internal lesions, 151
 → mortality rate, 151

Cysteine → THP, 98, 105
 → THP ← nitrogen mustard, 100

D

Decapsulation of kidney, 124
 Definition of SSP, 12
 of THPs, 3
 Denervation → THP, 96, 248
 Depletion of coagulation factors, 193
 Dermal necrosis, 119
 Dermatitis nodularis necrotica, 218, 219
 Dermatoses (other than purpuras), 218, 219
 Detection of malignant tumors, 178
 Dextran → THP, 99, 105, 133, 150
 sulfates → THP, 99
 Diabetes mellitus, 233
 Diabetic glomerulosclerosis, 205, 232
 retinopathy, 173, 232
 Diapedesis of erythrocytes, 154
 Diarrhea, 198; *cf. also* Clinical implications
 infantile, 220, 221
 Diathesis, hemorrhagic, 223
 Dibenamine; *cf.* Nerve drugs
 → THP, 99, 111, 261
 → pluricausal THP, 150
 Dibenzylidine → THP, 111
 Dicoumarol → blood coagulation, 240
 → pluricausal THP, 150
 → THP, 69, 151
 Diet + pregnancy → THP ← antibiotics, 98
 → THP, 195
 → THP ← pregnancy, 4, 43, 45, 260
 → THP + progesterone, 81
 Digestive tract, diseases of, 220
 morphologic changes, 168
 Diphtheria; *cf.* Clinical implications
 toxin → adrenals ← hypophysectomy, 171
 → ovary ← gonadotrophic hormones, 176
 → testis ← gonadotrophic hormones, 175
 Disease proneness, 126, 128
 Diseases, immunological, 223
 renal, 205
 spontaneous → THP, 231
 of the digestive tract, 220
 of the ear, eye, 233
 pregnancy, 207
 urinary passages, 207
 Distilled water; *cf.* H₂O
 Distribution (nonspecific) of pluricausal
 THP-G, 147
 (organ specific) of pluricausal THP-G, 148
 Dog, 123; *cf. also* Species
 Dosage of preparatory injection, 34
 of provocative injection, 34

 → THP, 34
 → THP ← route of administration, 133
 → THP ← species, 131
 Double-challenge procedure, 134
 Drugs → blood coagulation, 194
 → sympathetic nerves, 250
 → THP, 98
 Duodenal ulcers ⇔ hyperparathyroidism, 229
 Duodenitis, hemorrhagic, 221
 necrotizing, 220
 Duodenum, 138, 139
 morphologic changes, 169
 Dyes i.v. → skin, 264
 → skin ← endotoxin i.c., 196, 246
 → skin ← inflammatory irritants, 246
 Dyspnea; *cf.* Clinical implications
 Dysproteinemic purpura, 213, 217

E

EACA → THP, 63, 70
 → THP ← thrombin, 252
 Ear, diseases of, 223
 morphologic changes, 174
 petechial hemorrhages in, 175
 Eclampsia, 185, 207, 211
 Eclampsia-like syndrome, 43, 44, 76, 81, 101
 E. coli endotoxin i.c. → THP ← terramycin,
 264
 Eczema, 218, 219
 EDC → tumor ← THP, 87
 Edema, 119
 in lymph nodes, 156
 in skin, 154
 Eel serum → THP, 87
 Egg albumen → THP, 105, 133
 yolk → THP, 252
 Electrical stimulation → sympathetic nerves,
 250
 Electric currents → thrombus formation, 122
 Electricity → THP, 119, 122
 Electron-microscopy, 158
 Ellagic acid → THP, 105
 Embolism, pulmonary, 163
 Encephalopathy, 197
 Endocarditis, subacute bacterial, 203
 Endocrine-kidney procedure, 124
 Endogenous sensitizers, 134
 Endothelial cells, 154
 Endotoxic shock, 252
 Endotoxin; *cf.* Bacterial toxin, microbial
 products
 → adrenal, 249
 → blood vessels, 246
 → blood vessels ← catecholamines, 261

- Endotoxin
 content in heart, kidney, liver, lung, skin, 187
 $\Leftarrow\Rightarrow$ critical period, 30
 \rightarrow dermal necrosis \leftarrow rotational stress, 119
 \rightarrow ganglia, 250
 \rightarrow kidney \leftarrow Liquoid i.v., 158
 \rightarrow skin \leftarrow dyes i.v., 196, 246
 \rightarrow splanchnic nerves, 250
 \rightarrow THP, 225, 229
 \rightarrow THP \leftarrow Liquoid, 193
 \rightarrow THP \leftarrow RES-blocking agents, 185
 \rightarrow THP \leftarrow rotational stress, 119
 \rightarrow THP \leftarrow x-irradiation, 194
- Endotoxin-detoxifying component; *cf.* EDC
- Enterocolitis, pseudomembranous, 222
- Enzymes \rightarrow THP, 98, 99, 106, 261
- Epidemic hemorrhagic fever, 203
- Epinephrine, 132, 134
 \rightarrow aorta, 249
 \rightarrow blood vessels, 246
 endogenous discharge, 249
 \rightarrow hemorrhagic necrosis, 3
 \rightarrow pluricausal THP-G, 147
 \rightarrow skin, 3
 \rightarrow THP, 72, 261
 \rightarrow tissues, 14
 tolerance, 155, 256
- "Epithalaxis," 7, 8; *cf. also* Sanarelli phenomenon
- Epsilon-aminocaproic acid; *cf.* EACA
- Ergot; *cf.* Nerve drugs
- Ergotamine \rightarrow THP, 99
- Erythrocyte agglutination, 100, 164
 \rightarrow thrombus formation, 239
- aggregation in kidney, 157
- count, 155
- diapedesis in kidney, 157
- Erythrocytes, sickle-shaped, 217
 diapedesis of, 154
 \rightarrow THP, 239
- Esophagus, morphologic changes, 168
- Estradiol \rightarrow THP, 81
- Ether; *cf.* Nerve drugs
 anesthesia, 99
- Etiology of THPs, 152
- Evaluation of abstracts, vii
- Evans Blue i.v. \rightarrow skin, 246
- Exanthema, hemorrhagic, 262
- Experimental THPs, 3, 15
 thrombosis, xix
- Exposure to cold \rightarrow THP-L, 135
 \rightarrow pluricausal THP-G, 147
- Extracorporeal circulation \rightarrow THP, 124
- Extracts of mammalian tissues \rightarrow THP, 178
 (microbial), 18
- Extrarenal lesions, 258; *cf. also* Kidney
- Extremities \leftarrow Thorotrust + tannic acid + norepinephrine, 142, 143, Plates V, VI
- Exudates \rightarrow THP, 89
- Eye, diseases of, 233
 morphologic changes, 173
- F**
- Favism, 232, 233
- FeCl₃, 132, 134, 135
- Female sex organs, morphologic changes, 176
- Fe-OS \rightarrow heart \leftarrow glucocorticoids + Na₂HPO₄, 148
 \rightarrow THP, 107, 134, 135
 \rightarrow THP-L \leftarrow LaCl₃, 134
 \rightarrow THP-L \leftarrow polymyxin, 147
- Ferric dextran \rightarrow pancreas, 127
 \rightarrow THP, 150, 252
 dextrin \rightarrow THP-L \leftarrow Thorotrust, 134
 oxysaccharate; *cf.* Fe-OS
- Ferrihemate; *cf.* Hematin
- Ferritin \rightarrow THP, 107
- Fe-sorbitol \rightarrow THP-L \leftarrow CeCl₃, 134
- Fe₂(SO₄)₃ \rightarrow THP-L \leftarrow Thorotrust, 134
- Fetus, intra-uterine death of, 207
- Fibrin, axial periodicity, 158
 thrombi formation, 190
 \rightarrow THP, 71
- Fibrinogen in blood, 194
- Fibrinogenopenia, 193
- Fibrinoid, transfer of, 35
 formation, 186
- Fibrinolysin \rightarrow THP, 106
- Fibrinolysis, 154, 193
- Fibrinolytic activity of serum, 190
- Filtrates, microbial, 18
- Fluorescent antibody techniques, 165, 212
- Focal infections in man, 197
 \rightarrow THP, 199
- Folic acid; *cf.* Vitamin-B complex
- Formic acid \rightarrow THP, 107
- Forssman antigen and antibody, 239
- Freezing of skin \rightarrow THP, 195
- Frostbite \rightarrow THP, 121
- Functional changes, 189
- G**
- Galactose \rightarrow THP, 107
- Gallbladder, morphologic changes, 170
- γ -globulin, 68
 $\Leftarrow\Rightarrow$ RES, 252

- Ganglia ← endotoxin, 250
 Ganglionic blocking agents, 99
 → THP, 248
 Gangrene, cutaneous, 218
 hemorrhagic, 142, 143, **Plate VI**
 intestinal, 221
 G.A.S. (General Adaptation Syndrome), 258;
 cf. also Stress
 Gastric mucosa, 220
 Gastroduodenal hemorrhages, 220
 ulcers, 220, 248
 Gastroenteritis, 220, 221
 Gastrointestinal diseases of man, 220
 lesions, hemorrhagic, 168
 mucosa, 198
 system, 168
 tract ← burns, 121
 Gelatin → THP, 107
 General adaptation syndrome (G.A.S.), 258;
 cf. also Stress
 General THP, *cf.* THP-G
 Genetic predisposition, 37
 Giant cells, multinucleated, 225
 Glomerular nephritis, subacute, 225
 Glomerulonephritis, 213
 Glomerulosclerosis, diabetic, 232
 Glossary, xvii
 Glucocorticoids → THP, 76, 148; *cf. also* Stress hormones
 Glucose → THP, 107
 metabolism, 265, 266
 Glutathione → THP, 107
 Glycogen → THP, 107, 252
 Glycyrrhizin → THP, 107
 Goat; *cf. Species*
 Gonadal hormones (female) → THP, 81
 (male) → THP, 82
 Gonadotrophic hormone → ovaries ←
 diphtheria toxin, 176
 → testis ← diphtheria toxin, 175
 → THP, 80
 Gram-negative bacteria, 21, 178
 Granulated leukocytes in blood, 155
 Granulocyte lysosomes, 92
 Growth hormone → THP, 80; *cf. also* STH
 Guaiacol → THP, 108
 Guanethidine, 108
 Guinea pig; *cf. Species*
- H**
- Hamster, 262; *cf. also* Species
 Heart, 149
 endotoxin content, 187
- ← Fe-OS + Glucocorticoids + Na₂HPO₄, 148
 ← manucl + norepinephrine, 148
 ← microbial products, 165, 166
 ← Moschowitz's disease, 212
 ← nonmicrobial agents, 167
 ← ScCl₃ i.v. + epinephrine i.m., 145, **Plate VIII**
 ← thromboplastin, 193
 Heat stroke → THP, 121
 "Helmet" cells, 212
 Hemangiomas (giant); *cf.* Tumors
 Hematemesis, 198
 Hematin → THP, 108
 Hematology, 155
 Hematuria; *cf.* Clinical implications
 Hemoglobin count, 155
 Hemolysis, 217, 223
 Hemolytic anemia, 212
 (acquired), 217, 218
 Hemophilic arthropathy, 176
 Hemopoietic organs, 156
 Hemorrhage, 258; *cf. also* Stress
 in brain, 172
 gastroduodenal, 220
 in lymph nodes, 156
 myocardial, 165
 (petechial) in ears, 175
 retroplacental, 185
 in spinal cord, 172
 splenic, 135
 testicular, 175
 → THP, 119, 123, 194
 valvular, 165
 Hemorrhagic diathesis, 223
 duodenitis, 221
 exanthema, 262
 fever, epidemic, 203
 gangrene, 142, 143, **Plates V, VI**
 leukoencephalitis, 233
 necrosis, cutaneous, 3, 72
 pancreatitis, 171
 peritonitis, 95, 101
 response, ocular, 173
 shock ⇛ coagulation factors, 193
 → THP, 194
 stress syndrome of Jaques, 119, 125, 258
 syndrome ← antiplatelet serum, 15
 thrombocythemia, 213, 216
 thromboses, organ distribution of, 131
 tumor necrosis, 3, 6, 178
 Henoch's purpura, 213
 Heparin in blood, 190
 → blood coagulation, 63, 64, 240

- Heparin
 → pluricausal THP, 150
 → THP, 151, 240, 262
 → thrombus formation, 240
- Heparinoids → THP, 69
- Hepatic lesions → THP, 125
- Hepatitis, 197
- Herpes virus i.v. → THP, 248
- Herpes zoster, 218, 219
- Hesperidin, 101
- Heterologous serum → THP, 86
- Hexamethonium; *cf.* Nerve drugs
 → THP, 99; *cf. also* Ganglionic blocking agents
- Hexosamine content of skin, 184
- Hirudin → THP, 71
- Histaminase → THP, 83, 84
- Histamine content of skin, 187
 dischargers → THP, 83, 85
 → THP, 72, 83, 178, 262, 265, 266
- Histology of skin, 154
- History of THP, 3
 of pluricausal THPs, 125
- Hog cholera, 199, 205
- Hormone-like substances → THP, 71
- Hormones → THP, 71, 82
- Horse serum → THP, 87
- Humoral conditioning, 126
 substances → THP, 96
- Hyalinosis syndrome, 124
- Hyaluronidase → THP, 99, 106
- Hydatidiform mole, 207, 211
- Hydroxyproline, 186
- 5-hydroxytryptamine; *cf.* 5-HT
- Hypercholesterolemia, 185
- Hypercoagulability, 193
- Hyperemia, iridoconjunctival, 173
 in lymph nodes, 156
 in spleen, 156
- Hyperfibrinogenemia, 240
- Hyperlipemia, 185
- Hyperparathyroidism, 229
- Hypersensitivity to cold, 140, **Plate III**
- Hypertensin → THP, 82
- Hypertension, 127
 malignant, 227
- Hypertensive nephrosclerosis, experimental, 127
- Hypertonia labyrinthi, 232
- Hypertonic NaCl → THP, 101
- Hypofibrinogenemia, 193
- Hypophysectomy → THP, 80
- Hysterectomy → THP, 125
- 5-HT, 132, 133, 240
 blocking agents, inhibitors; *cf.* Antiserotoninins
 → pluricausal THP-G, 147
 → salivary glands, 127
 → THP, 85, 262
 → THP-L, 135
 → THP ← pregnancy, 44, 47
- H_2O → THP, 101

I

- Ileum, morphologic changes, 169
- Immune bodies, blood-borne, 239
 → THP, 178, 188
- Immune reactions, 3
 ⇔ THP, 47
- Immunity, serologic, 234
- Immunological diseases, 223
 sensitization, 34
- InCl₃, 132, 134
- Incompatible blood → coagulation, 194
- Incomplete sensitizers, 132
- Increased body temperature → THP, 121
- India ink → THP, 132, 134, 251, 252
- Induction of Sanarelli phenomenon, 3
 of Shwartzman phenomenon, 3
- Infantile diarrhea, 220, 221, 264
- Infarction, coronary, 231
 pulmonary, 231
- Infections → erythrocytes, 239
 focal, 197, 199
 intranasal, 225
 spontaneous, 177, 197, 199
 → THP ← antibiotics, 197
 → THP ← sulfonamides, 197
 systemic, 171
- Infectious diseases, 197
- Inflammation, 126
 skin, 154
 → THP ← nitrogen mustard, 100
- Inflammatory diseases ⇔ plasma, 194
 exudates → THP-L, 134
 irritants → skin ← dyes i.v., 246
- Influenza; *cf.* Clinical implications
- Injection, preparatory, 21
 provocative, 21
 (single) → THP, 18, 165, 189
 site → THP-L, 134
- Injections, timing, 20
 (variably spaced) → cardiovascular system, 165
 → THP, 18
- Inositol, 101
- Internal lesions ← cyproheptadine, 141
- Interval between treatments; *cf.* Critical period
- Intestinal flora, 264
 gangrene, 220, 221

mucosa ← microbial toxin, 264
 Intestine, morphologic changes, 168
 Intoxication → erythrocytes, 239
 Intrarenal "preparation," 96
 Intra-uterine death of fetus, 207
 Intravascular clotting, 122
 coagulation, 217
 Intussusception, 232
 ↳ anaphylactoid purpura, 232
 In vivo observations, 177
 Involution of lymphosarcomas, 177
 of neoplasma, 178
 Ionizing rays → THP, 119, 123; cf. also Stress
 Iridoconjunctival hyperemia, 173
 Irritants, nonspecific → THP, 119

J

Jejunitis, 220
 Jejunum, 148, 149
 morphologic changes, 169
 Joints, morphologic changes, 176

K

Kallikrein → THP, 72, 85, 86, 262
 Kidney, 3, 148, 198, 246, 258; cf. also Renal;
 Nephrectomy; Nephritis
 ← agar, 151
 ← agar i.v. + restraint, 141, Plate IV
 ← agar i.v. + stress, 141, Plate IV
 ← carrageenin s.c. + restraint, 150
 decapsulation, 124
 endotoxin content, 187
 ← endotoxin + Liquoid i.v., 158
 ← hyperparathyroidism, 229
 ← microbial products, 158
 morphologic changes, 157
 ← Moschcowitz's disease, 212
 ← nonmicrobial agents + microbial products,
 161
 obliterating thromboangiitis, 144, Plate VII
 ← shock, 232
 thrombi formation in, 193
 ← thrombin infusion, 240

L

LaCl_3 , 134, 135
 Lacrimal glands, 149
 ← carrageenin + 5-HT, 141, 148, Plate IV
 Lacrimation, 173
 Lactic acid, 261
 content of skin, 184
 Lead acetate; cf. Pb-acetate
 Leishmaniosis, 203

"L.E. phenomenon," 225
 Lesions, thrombohemorrhagic, 127
 Leukemia, 218
 lymphatic → THP, 195
 myelogenous, 217
 Leukocyte count, 155
 extracts → THP, 92
 granules, 92, 155
 Leukocytes, polymorphonuclear, 154, 155
 → THP, 255
 Leukocytosis, 155
 Leukoencephalitis, hemorrhagic, 233
 Leukopenia, 100, 155, 255
 "Leukotaxin" → THP, 92
 Lipid embolism, 232, 233
 metabolism → THP, 185, 260
 Lipids → THP, 99, 260; cf. also Diets
 → THP ← pregnancy + vitamin-E
 deficiency, 99
 Lipogenesis, 185
 Lipopolysaccharides, 261
 β -Lipoproteins, 185, 260
 Liposarcomas, transplantable, 178; cf. also
 Tumors
 Liquoid → blood coagulation, 68
 → THP, 68, 100, 131, 194, 240
 → THP ← endotoxin, 193
 Literature, abstracting of, vii
 collection of, vi
 Live bacteria i.v. → THP (monocausal), 131
 Liver cirrhosis, 232, 233
 endotoxin content, 187
 fluke extract → THP, 95
 morphologic changes, 170
 ← Moschcowitz's disease, 212
 sclerosis, 232
 ← thrombin infusion, 240
 Local hemorrhagic thromboses, 133; cf. also
 THP-L
 ischemia, 119
 THP, 17; cf. also THP-L
 Localization of bacterial endotoxin, 264
 THP, 246
 Localizing potency of compounds, 133
 Lower nephron nephrosis, 206
 Lung, 163, 198; cf. also Pulmonary
 endotoxin content, 187
 morphologic changes, 163
 ← thrombin infusion, 240
 Lupus erythematosus, 165, 225
 Luviskol; cf. PVP
 Lymph nodes, 156, 198
 mesenteric, 250
 Lymphatic leukemia → THP, 195

- Lymphatic organs, morphologic changes, 156
- Lymphosarcomas, involution of, 177
- M**
- Malaria, 203
- Male sex organs, morphologic changes in, 175
- Malignant hypertension, 225, 227
neoplasms, 177; *cf. also* Tumors syndrome, 198, 200
- Malnutrition, 126
- Mammalian tissues (extracts) → THP, 178
- Manucol → cecum ← histamine, 148
→ heart ← norepinephrine, 148
- Mapharsen → THP, 109
- Masson phenomenon, 3, 15, 76
- Mast-cell degranulation, 263
discharge, 142, 143, **Plates V, VI**
dischargers → THP, 150, 151
→ THP-L, 135
→ pluricausal THP-G, 147
- products → THP, 262
regranulation, 263
- Mast cells → THP, 262
- McKay phenomenon, 4, 15
- Measles; *cf.* Clinical implications
- Mechanical trauma → THP, 119
- Mecholyl, 99; *cf. also* Nerve drugs
- Megakaryocytes, 212
- Melena, 198
- Meninges, 198
- Meningococcic septicemia, 198
- Menstruation, 232, 233
- Mercury → THP, 110
- Mesenchymal metabolism, acceleration of, 264
reaction, nonspecific, 264
- Mesenteric lymph nodes, 250
- Metabolism, carbohydrate, 184
glucose, 265, 266
lipid, 185
protein, 186
- Metabolites, 187
- Metals → calcergy, 131
→ calciphylaxis, 131
→ THP, 131, 134
- Metrorrhagia, 233
- Microbial agents → RES, 58
→ tumors, 178
diseases, 126
products, 18, 165, 178, 189, 193
→ blood coagulation, 189
→ cardiovascular system, 165, 166
→ cardiovascular system ← nonmicrobial agents, 167
- hemorrhagic tumor necrosis, 3
→ kidney, 158
→ kidney ← nonmicrobial agents, 161
→ SSP, 190
→ THP, 18, 21, 193
→ THP ← pregnancy, 44
terminology, 11
toxin → intestinal mucosa, 264
- Microcirculation, 3, 232
- Microorganisms, 3
→ renal glomeruli, 3
- Microthrombi, first observations, 4 formation, 229
- Mineralocorticoid overdosage, 124
- Missed abortion, 207
- Monocausal THPs, 131
classification, 143
- Monocausal and pluricausal THPs, comparison of, 131
- Monkey; *cf.* Species
- Morbid lesions ← stress, 126
- Morphologic changes, 154
in appendix, 168, 169
cornea, 173
gallbladder, 170
nasal mucosa, 175
ovary, oviducts, 176
peritoneum, 177
pleura, 177
rectum, 168, 169
small intestine, 168
testis, 175
uterus, 176
vagina, 176
- Morphine, 99; *cf. also* Nerve drugs
- Morphology of THP, 154
- Mortality rate, 178
← cyproheptadine, 141
- Mouse; *cf.* Species
- Mousepox, 205
- Moschcowitz's disease, 212, 213, 225, 258
- Mucopolysaccharides, sulfated, 155, 255
- Mucos of appendix, 221
gastric, 220
intestinal ← microbial toxin, 264
nasal, 175; *cf. also* Nose
oral, 221
- Multipurpose polychrome technique, 142, 143, **Plates V, VI**
- Murine neoplasma, 178; *cf. also* Tumors
sarcomas ← sulphuramide, 101
- Myelogenous leukemia, 217
- Myelosclerosis, 213
- Myocardial hemorrhage, 165

N

- Na-caseinate, 134, 135
 NaCl-supplements, 151
 Na_2HPO_4 , 148
 Nasal mucosa, morphologic changes, 175
 Necrosis (dermal), 119
 Necrotizing diseases → plasma, 194
 duodenitis, 220
 Neo-Antergan → pluricausal THP, 150
 Neodymium → THP, 110
 Neomycin → THP, 98; *cf. also* Antibiotics
 Neoplasms; *cf.* Tumors
 involution of, 178
 malignant, 177
 spontaneous, 178
 transplantable, 178
 Neosalvarsan; *cf.* Arsenic
 ↔ critical period, 30
 Nephrectomy → THP, 124, 164
 bilateral → THP, 124, 258, 265
 unilateral, 127, 141
 Nephritis, 197, 207
 Nephrotoxic effect of agar, 141
 Nerve drugs → THP, 96, 98, 99, 110
 Nerves, autonomic, 198
 Nervous factor → THP, 248; *cf. also* Reilly phenomenon
 Nervous stimulation → THP, 124
 nonspecific → THP, 119
 Nervous stimuli → THP, 96; *cf. also* Nerve drugs
 Nervous system, morphologic changes, 172
 → THP, 248
 "Neurovegetative irritation," 250
 Nialamide → THP, 110
 Nicotinic acid, 101
 "Ninth-day erythema," 197
 Nitrogen mustard → inflammation, 100
 → THP, 98, 100, 113, 255
 Noble-Collip drum; *cf.* "Rotational shock"
 Nonmicrobial agents → cardiovascular system, 167
 → kidney, 161
 → RES, 61
 → tumors, 182
 → THP, 15, 21, 37, 193
 Nonspecific distribution of pluricausal THP-G, 147
 irritants → THP, 119
 mesenchymal reaction, 264
 THP-G, 132
 THPs, 4; *cf. also* Pluricausal THPs
 trauma → THP, 119

Norepinephrine, endogenous discharge, 249

- pluricausal THP-G, 147
 - THP, 72, 132, 134, 261
 - THP ↔ amniotic fluid, 90
 - THP ↔ injection site, 135
- Normal pregnancy → THP, 44
 Nose, 175, 225
 ↔ carrageenin + cold, 140, **Plate III**
 morphologic changes, 175
 NPN in blood, 186

O

- Obliterating thromboangiitis, experimental, 142, 143, **Plates V, VI**
 → kidney, 144, **Plate VII**
 Obstetrical hemorrhagic syndrome, 207
 Ocular hemorrhagic response, 173
 Oral cavity, 221
 morphologic changes, 168
 mucosa, 221
 Organ affinity, 127, 131
 changes, characteristic of THP, 136, **Plate I**
 distribution of hemorrhagic thromboses, 131
 Organ-specific distribution of pluricausal THP-G, 148
 Organs, predisposed, 131, 132
 Ovalbumen → THP, 150
 Ovary, morphologic changes, 176
 Oviducts, morphologic changes, 176
 Oxalate → THP, 115
 Oxytocic posterior lobe extracts → THP, 80

P

- Pancreas ↔ hyperparathyroidism, 229
 morphologic changes, 171
 ↔ parathyroid hormone + ferric dextran, 127
 Pancreatic hormones → THP, 82
 Pancreatitis, 229
 hemorrhagic, 171
 Pantothenic acid, 101
 Papain → THP, 115
 Para-aminobenzoic acid; *cf.* Vitamin-B complex
 Parathyroid hormone → pancreas ↔ ferric dextran, 127
 → salivary glands ↔ 5-HT, 127
 → THP, 82
 Parathyroids ↔ parathyroid hormone + CrCl_3 , 127
 Paroxysmal hemoglobinuria, 223, 224
 Passive transfer, 34, 47
 Pathogenic constellation, xiv, 127
 situation, 128
 → pluricausal THP, 152

- Paws \leftarrow carrageenin + cold, 140, **Plate III**
 \leftarrow Thorotrust + tannic acid + norepinephrine, 142, **Plate V**
- Pb-acetate, 134, 135
- Peliosis rheumatica, *cf.* Schönlein's purpura
- Pemphigus, 218
- Pendiomid, *cf.* Nerve drugs
- Peptic ulcers, 127, 220, 221
- Peptone \rightarrow THP, 178
- Periarthritis nodosa, experimental, 127, 165, 225, 226
- Pericardium, 198
- Periodicity, axial, 158
- Peritoneum, morphologic changes, 177
- Peritonitis, 197
- Petechial hemorrhages; *cf.* Thomas reactions in ears, 175
- Peyer's plaques, 32, 124, 198, 250
- Phagocytosis of toxin, 76
- "Phenomenon of tissue sensitivity to bacterial filtrates," xiii, xiv, 239
- Phenothiazine derivatives \rightarrow THP, 112
- Phenylbutanzone \rightarrow THP, 115
- Phosphohexoseisomerase activity, 184
- Phospholipids, 185
- Photophobia, 173
- Physical agents \rightarrow THP, 119
- Physostigmine; *cf.* Nerve drugs
- Picryl chloride \rightarrow THP, 116
- Pig; *cf.* Species
- Pilocarpine; *cf.* Nerve drugs
- Pituitary hormones \rightarrow THP, 80
- Placental extracts \rightarrow THP, 90
 \rightarrow THP \leftarrow pregnancy, 44, 46
 \rightarrow THP (monocausal), 131
- Placentitis, 209
- Plant pollens \rightarrow THP, 95
- Plasma globulins, 261
 \Leftarrow inflammatory diseases, 194
 \Leftarrow necrotizing diseases, 194
 transfusion reaction; *cf.* PTR
- Plasmin fibrinolysis in vitro, 240
- Platelet aggregation in thrombi, 212
 count, 213, 217, 239
 \Leftarrow squamous cells, 91
 factors \rightarrow THP, 71
 precipitation, 240
- Pleura, morphologic changes, 177
- Pluricausal cardiopathies, xv, 127, 128
 "Pluricausal diseases," 126
- "Pluricausal thrombohemorrhagic phenomena," xv
- Pluricausal THPs, 17, 83, 125, 128, 131, 252, 262
- THPs and calciphylaxis, comparison of, 130
- and monocausal THPs, comparison of, 130
- THPs, classification of, 152, 153
 history, 125
 production of, 132
- THP factors, 132
 activity of, 133
- THP-G, 147
- THP-L, 134
- Pneumonia, 197
- Poisoning, 126
- Pollen-antigen—pollen-antibody complex, 96
- Polyarteritis nodosa, 68, 218
- Polyarthritis, 225
- Polycythemia vera, 213, 217, 218
- Polymorphonuclear leukocytes, 154, 155
- Polymyxin \rightarrow THP, 134, 135, 147
- Polyvinylpyrrolidone; *cf.* PVP
- Posterior lobe extracts (oxytocic) \rightarrow THP, 80
- Potassium in blood, 187
- Praseodymium \rightarrow THP, 116
- Predisposed organs, 131, 132, 134, 147
- Predisposition, genetic, 37
- Pregnancy, diseases of, 207
 toxicooses, 90
 \rightarrow THP, 43, 44
 \rightarrow THP \leftarrow colchicine, 44, 46, 98
 \rightarrow THP \leftarrow diet, 4, 43, 45, 98, 260
 \rightarrow THP \leftarrow 5-HT, 44, 47
 \rightarrow THP \leftarrow microbial products, 44
 \rightarrow THP \leftarrow placental extracts, 44, 46, 90
 \rightarrow THP \leftarrow progesterone, 3, 43, 46, 81
 \rightarrow THP \leftarrow renal artery constriction, 44, 47
 \rightarrow THP \leftarrow thrombin, 44, 46
 \rightarrow THP \leftarrow thromboplastin, 90, 91
 \rightarrow THP \leftarrow vitamin-E deficiency + lipids, 99
- Preparation \rightarrow THP \leftarrow provocation, 21
 route of, 32
- Preparatory agents, 21
 injection, 21
 route of, 32
 dosage, 34
 treatment, 20
- Prevention of THP, 53
- Procaine, 99, 116; *cf. also* Nerve drugs
- Production of THP-L, 133
- Progesterone \rightarrow THP, 81
 \rightarrow THP \leftarrow diet, 81
 \rightarrow THP \leftarrow pregnancy, 3, 43, 46, 81
- Promazine \rightarrow THP \leftarrow "rotational shock," 99
- Prostatic carcinoma, 230
- Prostration, 198
- Protamin \rightarrow THP, 71
- Protein; *cf.* Immunity
 metabolism, 186

- Proteolytic enzymes, 261
 Prothrombin time, 190
 factors V, VII, VIII, IX and X, 190, 193
 Provocation, route of, 32
 Provocative agents, 21
 blood borne, 119
 injection, 21
 dosage, 34
 Pseudomembranous enterocolitis, 220, 222
 Pseudomonas septicemia, 198, 204
 PTR, 4, 16, 224
 Pulmonary abscesses in man, 163
 arteriolitis, 163
 embolism, 163
 infarction, 231
 THP, 163
 Purpuras, 212
 Purpura necrotica, 213, 217
 Purpuric smallpox, 198, 204
 PVP, 116, 252
 Pyoderma, 218, 219
 Pyridin derivatives → THP, 116
 Pyrogens → THP, 121
- R**
- Rabies neurovaccine, 172
 virus, 172
 Rabbit; *cf.* Species
 serum → THP, 87
 Raynaud's disease, 14, 227
 Rat; *cf.* Species
 Ratio, albumin-globulin, 186
 cholesterol-phospholipid, 185
 Rays, ionizing → THP, 119, 123
 ultraviolet → THP, 119
 "Reactive" treatment, 21
 Rectum, morphologic changes, 168, 169
 "Red infarct," xiii
 Regional differences in sensitivity, 146
 Rheumatic fever, 165, 176, 213, 224, 225
 → procryofibrin level ← salicylate +
 cortisone, 225
 Reilly phenomenon, 4, 16, 32, 96, 124, 198, 250,
 258
 Renal arteries, 157
 artery constriction → THP ← pregnancy, 44,
 47
 changes, 144, 157, **Plate VII**
 cortical necrosis, 205
 diseases, 205
 glomeruli ← microorganisms, 3
 lesions, 186
 operations → THP, 124
 "Renal shunt," 141, **Plate IV**
- Renaud phenomenon, 4, 16
 Renin → THP, 82
 Reptiles; *cf.* Species
 RES, 58, 251
 ← blood lipids, 260
 ↔ γ-globulin, 252
 ← microbial agents, 58
 ↔ nonmicrobial agents, 61
 blockade, 99, 230, 245
 ↔ SSP-active substances, 252
 → THP ← protein antigen i.v., 195
 → THP ← thrombin i.v., 252
 RES-blocking agents, 54, 58, 63, 185, 240
 (nonmicrobial) → THP, 58, 61
 → THP, 251
 → THP ← endotoxins i.v., 185
 RES-cells, 76
 Reserpine → THP, 113
 Restraint → kidney ← agar i.v., 141, **Plate IV**
 → THP ← agar, 150
 Reticulo-endothelial system; *cf.* RES
 Retinopathy, diabetic, 173, 232
 Retroplacental hemorrhage, 185
 Reviews on bacterial toxins, xix
 clinical implications, 197
 SSP, xix
 Riboflavin; *cf.* Vitamin-B complex
 Ricin → THP, 100, 116
 Rocky Mountain spotted fever, 203
 "Rotational shock," 64, 72, 99, 100, 119
 Route of administration → THP ← dosage, 133
 preparation and provocation, 32
 Rutin, 101
- S**
- Salicylate → THP, 100
 Salicylic acid → THP, 116
 Salivary glands, 149
 ← carrageenin + 5 H-T, 141, 148, **Plate IV**
 ← parathyroid hormone + 5-HT, 127
 Sanarelli phenomenon (general), 7, 10
 induction of, 3
 "Sanarelli reaction," 58
 Sanarelli Shwartzman phenomenon (SSP), xiv
 Saprophytic organisms, 197
 Scarlet fever, 157; *cf. also* Clinical implications
 ScCl₃, 132, 134, 135, 148
 i.v. → heart ← epinephrine i.m., 145, **Plate VIII**
 Schönlein's purpura, 213
 Scleroderma, 225
 Sclerosing agents → THP, 113
 Sclerosis of the liver, 232

- "Secondary syndrome of chemotherapy," 197,
198, 199
- Sensitivity, regional differences, 146
gradient, determination of, 150
- Sensitization, immunological, 34
- Sensitizers, 126, 132
→ calciphylaxis, 127
↔ challengers, 130
complete, 132, 134
endogenous, 134
incomplete, 132
pluricausal THP-G, 147
→ THP-L, 135, 146
- "Sensitizing factors," 126
- Septic abortion, 207, 209
- Sequential development of vascular changes, 177
- Serologic immunity, 234
- Serosae, morphologic changes, 176
- Serotonin → THP, 72, 85, 262; *cf. also* 5-HT
- Serum, fibrinolytic activity of, 190
(heterologous) → THP, 86
- Sevenal → THP, 113
anesthesia, *cf.* Ganglionic blocking agents
- Sex organs (female), morphologic changes, 176
(male), morphologic changes, 175
- "Shwartzman-active factors"; *cf.* "SSP factors"
- "Shwartzman-like reaction," 16
- Shwartzman phenomenon (local), 2, 10, 256
induction of, 3
- Shwartzman reaction, mechanism of, 245
- Shwartzman-Sanarelli phenomenon (SSP), 152
- Shock, 232
→ kidney, 232
organs, anaphylactoid, 149
syndrome, 232
- Shwartzman phenomenon, 9
- "Shwartzman-like reaction," 16
- Sickle cell disease, 217, 218
- Sickle-shaped erythrocytes, 217
- Silicic acid, 251
- Silver, 116
nitrate → THP, 100
- Skin, 195, 196; *cf. also* Dermal; Cutaneous
↔ dyes, 264
endotoxin content of, 187
↔ epinephrine, 3
hexose-content of, 194
hexosamine-content of, 184
histamine content of, 187
lactic acid content of, 184
morphologic changes, 154
uronic-acid content of, 184
- Smallpox, purpuric, 198, 204
- Smooth muscle products → THP, 265
- Snake venoms → THP, 93, 178
- Snout ← carrageenin s.c. + 5-HT i.p., 141,
- Plate IV**
- Sodium oxalate → blood coagulation, 240
- Sodium polyanetholesulfonate; *cf.* Liquoid
"Soil factor," 126
- Somatotrophic hormone; *cf.* STH
- Species, 21, 37
↔ critical period, 130
→ THP ↔ age, 37
→ THP ↔ dosage, 131
→ THP ↔ nonmicrobial agents, 37
- Spinal cord, hemorrhages in, 172
- Splanchnic nerves, 248
← endotoxin, 250
- Spleen, 149, 156
← carrageenin + norepinephrine, 148
- Splenectomy → THP, 125
- Splenic hemorrhages, thrombosis, 135
- Sponge exudate, 34
- Spontaneous diseases of man, 4; *cf. also*
Clinical implications
infections, 177, 197
→ THP, 199
→ THP ↔ antibiotics, sulfonamides, 197
- Squamous cells, 91
- SSP, 10, 190; *cf. also* Sanarelli-Shwartzman
phenomenon
- SSP-active material, 264
- principles, 21
blood borne, 221
substances, 187
↔ RES-blockade, 252
- SSP, clinical manifestations, 197
definition, 12
passive transfer, 34
reviews, xix
and variants, terminology, 11
- SSP-factors, 21
- SSP-G, 20; *cf. also* Sanarelli phenomenon
(general)
- SSP-L, 20; *cf. also* Shwartzman phenomenon
(local)
↔ artificial hypothermia, 121
↔ hemorrhage, 123
↔ increased body temperature, 121
ocular, 173
↔ pyrogens, 121
- Starch → THP, 100, 116, 252
- STH → THP, 80
- Stillbirth → THP ↔ colon perforation, 220
- Stomach, morphologic changes, 168
- Streptococci → heart ← *S. typhosa* toxin, 225

- type 28 group A, 225
 Streptokinase → THP, 99, 106
 Stress hormones, 126, 258
 Stress → kidney ← agar i.v., 141, **Plate IV**
 → morbid lesions, 126
 → THP, 4, 119, 152, 258; *cf. also* Pluricausal THPs
 → THP ← agar, 150
 Style of this book ("analytico-synthetic"), v
 Subacute bacterial endocarditis, 203
 glomerular nephritis, 225
 Sulfa drugs → THP, 100, 116
 Sulfapyridine ⇌ benzene, 100
 Surgical intervention → THP, 119
 trauma → THP ← agar, 150
 Swine erysipelas, 199, 205
 Symeonidis phenomenon, 3, 16
 Sympathectomy (cervical) → THP, 248
 Sympathetic nerves, 250
 Symptomatic afibrinogenemia, 213, 216
 "Syndrome malin," 198
 Syndrome of hyalinosis, 127
 Systemic challengers, 133
 infections, 171
 "Systemic fibrinoid disease," 225, 227
 SY-28 → THP, 99; *cf. also* Ganglionic blocking agents; Nerve drugs
 S^{35} -incorporation studies, 184
 Sulfapyridine → THP, 255
 Sulfated mucopolysaccharide, 155
 Sulfonamides → THP, 98
 → THP ← spontaneous infections, 197
 Sulphanilamide → THP ← murine sarcomas, 101
- T**
- TABDT vaccine → THP, 224
 Tannic acid → THP, 134, 135, 148
 Talcum → THP, 101, 117
 Target organs, 127, 133
 TEAB → THP, 99; *cf. also* Ganglionic blocking agents; Nerve drugs
 Temperature variations → THP, 119, 121;
 cf. also Stress
 Terminology, microbial products, 11
 SSP and variants, 11
 of THPs, 3; *cf. also* Classification
 Terramycin → THP, 98; *cf. also* Antibiotics
 Testicular hemorrhages, 175
 Testis ← gonadotrophic hormones + diphtheria toxins, 175
 morphologic changes, 175
 Theophylline → THP, 101, 117
 Theories, 234, 265
- Thiamine; *cf. Vitamin-B complex*
 Thomas, Lewis, 14
 reactions, 3, 14
 THP-G, 17
 THP-L, 17
 production of, 133
 THP in man, 16, 38; *cf. also* Clinical implications
 Thorotrust → adrenals ← ACTH, 148
 → adrenals ← endotoxin i.v., 171
 + tannic acid + norepinephrine → extremities, 142, 143, **Plates V, VI**
 → paws, 142, **Plate V**
 → THP, 61, 100, 252
 → THP ← bacterial endotoxin i.v., 251
 → THP ← protein antigen, 195
 → THP ← thrombin, 252
 → THP-L, 134, 135
 Thrombi formation in kidney, 193
 Thrombin → blood coagulation, 63
 → THP, 194
 → THP (monocausal), 131
 → THP ← pregnancy, 44, 46
 infusion → adrenals ← ACTH, 171
 → blood coagulability, 193
 → kidney, liver, lung, 240
 Thromboangiitis obliterans, 135
 Thrombocyte factors 2, 3 and 4, 190
 Thrombocythemia, hemorrhagic, 216
 Thrombocytopenia, 155, 180, 190, 193, 217,
 223, 230, 232, 234, 240, 255
 Thrombocytosis, 193
 Thromboembolic diatheses, 229
 phenomena, 213
 Thrombohemorrhagic lesions, 5, 127
 cerebral, 172
 in man, 197
 "malignant syndrome," 258
 phenomena, experimental, 15
 in man, 16
 pluricausal, 17
 Thrombophlebitis, 231
 migrans, 230
 visceral, 213, 217
 Thromboplastin → blood coagulation, 63
 formation, accelerated, 193
 → heart, 193
 → THP, 194
 → THP (monocausal), 131
 → THP ← pregnancy, 90, 91
 Thrombosis, experimental, reviews, xix
 of large vessels, 232
 splenic, 135

- Thrombotic diathesis \Leftrightarrow tumors, 230
 tendency, 229
 thrombocytopenic purpura, 124; *cf. also*
 Moschcowitz's disease
- Thrombus formation, 239, 265
 \leftarrow electric current, 122
 \leftarrow heparin, 240
- Thyroid hormones \rightarrow THP, 82
- Time lapse, 30; *cf. also* Critical period
- Timing of injections, 20; *cf. also* Critical period
- Tissue extracts \rightarrow THP, 178, 252
 \rightarrow tumors, 182
 fluid, adjuvanting action of, 84
 hypersensitivity, 133
- Tissues \leftarrow epinephrine, 14
 neoplastic, 178; *cf. also* Tumors
- Toes \leftarrow carrageenin + cold, 141, **Plate IV**
- Tonsils, morphologic changes, 175
- Topical challengers, 133
 thrombohemorrhagic lesions, 133; *cf. also*
 THP-L
- Topographic position of connective tissue, 150
- Toxic drugs \rightarrow THP \leftarrow agar, 150
 "Toxic ocular reaction," 173
- Toxin, phagocytosis of, 76
- Toxins, bacterial, reviews, xix
- Transfer of fibrinoid, 35
- Transparent chamber technique, 178
- Transplantable liposarcomas, 178; *cf. also*
 Tumors
 tumors, 87
 \leftarrow carrageenin + cold, 148
- Trauma \rightarrow THP, 119; *cf. also* Stress
 \rightarrow appendix \leftarrow intestinal microbes, 221
 mechanical \rightarrow sympathetic nerves, 250
 surgical \rightarrow THP \leftarrow agar, 150
- Traumatic deliveries; *cf.* Pregnancy, diseases of
- Tranquilizers, 99
- Treatment, preparatory, 20
 provocative, reactive, 21
- "Triangular cells," 212
- "Trueta shunt," 246
- Trypan blue i.v. \rightarrow THP \leftarrow bacterial endotoxin i.v., 251
- Trypsin \rightarrow THP, 106
- Tuberculosis, 198, 204; *cf. also* Clinical implications
- Tumor extracts \rightarrow THP, 91
 necrosis, hemorrhagic, 6, 178
 regression, 178
 transplants, 138, **Plate II**
 \leftarrow carrageenin + cold, 140, **Plate III**
- Tumors, 150, 230
 \leftarrow carrageenin + cold, 148
 detection of, 178
 \leftarrow microbial agents, 178
 morphologic changes, 177
 nonmicrobial agents, 182
 tissue extracts, 182
 transplantable, 87
 \leftarrow yeast, yeast extracts, 181
- Turpentine \rightarrow THP, 101, 117
- Typhoid fever, 187, 202; *cf. also* Clinical implications
- U**
- Ulcerative colitis, 220, 222
 in man, 168
- Ulcers, duodenal \Leftrightarrow hyperparathyroidism, 229
 gastroduodenal, 220, 248
 peptic, 221
- Ultraviolet rays \rightarrow THP, 119, 123
- Unilateral nephrectomy, 127
 \rightarrow THP \leftarrow agar, 141
- Uranium salts \rightarrow THP, 101, 117
- Urethane; *cf.* Nerve drugs
 anesthesia, 99
- Urinary passages, diseases of, 207
 morphologic changes, 163
- Uronic-acid content of skin, 184
- Uterus, 148, 149
 morphologic changes, 176
- V**
- Vaccination \rightarrow THP, 223, 224
- Vaccinia, 204
- Vagina, morphologic changes, 176
- Vagus nerves, 248
- Valvular hemorrhage, 165
- Varicella, 204
- Vascular changes, sequential development of, 177
- Vascular factor \rightarrow THP, 245
 manifestation of THPs, 164, 175
 system, functional changes, 189
 wall, 239, 246
- "Vasculokinase," 246
- Vaseline, 177
- Vasoactive polypeptides, 261
- Vasoactive substances \rightarrow pluricausal THP, 151
- Vasoconstriction, 151, 246
- Vasodilatation \rightarrow THP, 151, 258
- Vasomotion \Leftrightarrow THP, 195

Vasopressin → THP, 80, 132, 133
→ pluricausal THP, 151
Vessels, 149
 ← endotoxin, epinephrine, 246
 (large), thrombosis of, 232
 ← $\text{ScCl}_3 + 5\text{-HT}$, 148
Vincaleukoblastine, 117
Visceral thrombophlebitis migrans, 213, 217
Vitamins → THP, 98, 117
Vitamin-B complex → THP, 101, 117
Vitamin C → THP, 101, 117
Vitamin E → THP, 101, 118
Vitamin-E deficiency → THP ← pregnancy
 lipids, 99
Vitamin K → blood coagulation, 240
 → THP, 101, 118
Vitamin-P complex, 101, 119
Vomiting; cf. Clinical implications

W

Warfarin → THP, 69, 240
Waterhouse-Friderichsen syndrome, 171, 187,
 198, 200
"Wire-loop" appearance of glomerular capil-
 laries, 144, **Plate VII**
 formation, 158
 lesions, 225

X

X-irradiation → THP, 123, 194, 195, 225

Y

Yeast → tumors, 181
 extracts → THP, 95, 178, 181

Z

ZnCl_2 → THP-L ← Thorotrast, 134
Zymosan → THP, 95, 178



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