STRESS AND PSYCHIATRY[1, 2]

HANS SELYE, M. D., PH. D., D. SC., D. SC. (HON.), F. R. S. (C), F. I. C. S. (HON.),[3] MONTREAL, CANADA

INTRODUCTION

Most of our work on the relationship between stress and the nervous system has been concerned with the endocrine aspects of this problem. It is the primary object of this review to present a synopsis of these investigations, but my presentation would be very one-sided if it did not mention at least some of the most important key-references to the purely neurophysiologic and psychiatric aspects of this topic(1-6, 15).

The concept of stress is as old as medical history. More than 24 centuries ago, Hippocrates had already taught his disciples that disease is not only suffering (pathos), but also toil (pónos), that is, the fight of the body to restore itself toward normalcy. About a century ago, Claude Bernard pointed out that one of the most characteristic features of all living beings is their ability to maintain the constancy of their internal *milieu,* that steady state which Walter Cannon named "homeostasis." It was then felt that perhaps any deviation from the steady state—or, at least, the effort of restoring a homeostatic equilibrium—is stress. If so defined, the concept of stress would include all physiologic deviations from the normal resting state and, yet, in conversational English, it implies a particularly strenuous and usually damaging condition. Furthermore, the term was used by some authors as virtually synonymous with nervous stress and strain, while others employed it to denote the consequences of any noxious agent. Additional confusion was created by the indiscriminate use of the same term for the agent (trauma, emotions, infections, cold) and the effect (morphologic and functional changes in the body) of exposure. This vagueness in the formulation of the subject is probably responsible for the fact that, although the importance of stress in medicine had always been recognized, it had not been possible to submit it to systematic investigation until quite recently.

AN "OPERATIONAL DEFINITION" OF STRESS

It was the discovery that stress always manifests itself in the form of a definite, stereotyped syndrome that helped us to arrive at what philosophers call an "operational definition" of this condition. It became evident that stress, no matter how produced, elicits certain quite typical and specific changes in the body, such as adrenocortical stimulation, involution of the lymphatic organs, and gastrointestinal disturbances. These alterations served as objectively measurable indicators of stress and led to the following definition: *Stress is the state manifested by a specific syndrome which consists of all the nonspecifically induced changes within a biologic system.* In this sense stress has its own characteristic form but no particular cause.

This is an essentially "operational definition," in that it tells us what must be done to produce and recognize stress. A state can be recognized only by its manifestations; for instance, the state of stress by the manifestations of the stress-syndrome or "general adaptation syndrome" (G.A.S.). Therefore, we must observe a great many living beings exposed to a variety of agents before we can see the shape of stress as such. Those changes which are specifically induced by only one or the other agent must first be rejected; if we then take what is left—that which is nonspecifically induced by many agents—we have unveiled the picture of stress itself.

It was tempting, at first, to define stress merely as *"the rate of wear and tear"* within the body, because this is the immediate nonspecific result of both function and damage. Reactions which tend to diminish or repair wear and tear (*e.g.,* corticoid-secretion) are not strictly stress but rather defenses

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[3] Professor and Director, Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada.

against stress. In practice it is impossible, however, always to differentiate sharply between a change which represents repair and one which is merely damage. Therefore, this formulation—though more concise and theoretically more satisfying—could not have acted as a basis for a truly operational definition such as was needed to give the concept of stress a solid, objective foundation.

The enormous literature on stress, the general adaptation syndrome, and the so-called "adaptive hormones"—which now comprises more than 25,000 references to original articles and books—has been reviewed in detail elsewhere(9-14). In all these reviews special emphasis has been placed upon the relationship between stress and neuropsychiatric problems. Hence it will not be necessary to complicate this review by a confusingly voluminous bibliography, and I shall limit myself here to a brief discussion of certain experimental observations which, to my mind, may have interesting applications in psychiatry.

STEROID ANESTHESIA

In the course of experimental studies on the pharmacology of steroids, it had been noted accidentally that corticoids and related compounds exert singular effects upon the central nervous system in animals. For example, sudden, intense overdosage with *desoxycorticosterone acetate* (DOCA) produced an initial state of excitation, followed by complete surgical anesthesia in the rat, mouse, dog, and in many other mammals. This response appeared to be a fundamental biologic reaction common to all species so far examined, because later it could also be demonstrated in fish, birds, and even in primates, such as the monkey.

These findings raised the question whether excessive endogenous production of certain steroid hormones might play a role in determining mental reactions during stress. When subsequently ACTH and various glucocorticoids (cortisone, cortisol, prednisolone) were introduced into clinical practice, it became evident that these substances may also produce excitement or depression in man.

Additional animal experiments showed that *progesterone* can likewise act as an anesthetic and this was again confirmed in man(7). It was then thought that perhaps the somnolence of pregnancy and certain nervous derangements in eclampsia, premenstrual tension, and other clinical conditions, accompanied by increased steroid-hormone production, may find their explanation in this phenomenon. Still, in 1941, when these experiments were first performed, we did not even dare to hope that they might form the basis for a new type of anesthesia, which could be employed in clinical surgery, because the extraordinary expense involved in the synthesis of steroid hormones precluded their practical use at the required dose-levels.

However, the great progress made by synthetic chemists has now rendered various steroid derivatives abundantly available at a relatively low cost and one of these, *hydroxydione,* proved capable of producing anesthesia in man(8). Future research will have to show the possible advantages and disadvantages of this compound in comparison with other anesthetics, but, in any event, in the steroids we now have a new tool for the study of nervous responses to natural compounds.

THE ANTICONVULSIVE AND TRANQUILIZING EFFECT OF STEROIDS

In the course of our animal experiments on steroid anesthesia, we also noted that the excitement and the convulsions, normally produced by such stimulants as *metrazol* or *picrotoxin,* are effectively combated by various steroids. Independently, D. M. Woodbury and his associates, at the University of Utah, demonstrated similar effects with regard to electroconvulsive seizures.

It may be profitable to explore the possible use of steroids as anticonvulsive agents in epilepsy and perhaps even as tranquilizing drugs in diverse conditions of excitement. Clinical studies along these lines have not yet been conducted, but H. Laborit, in France, has just published rather encouraging observations on the use of hydroxydione in the treatment of delirium tremens.

CORTICOIDS AND MUSCULAR PARALYSIS

In dogs given prolonged treatment with DOCA, R. Loeb and his associates, in New

York, have observed a syndrome, reminiscent of the *periodic muscular paralysis*. We have obtained quite similar changes in a primate, the Rhesus monkey, and noted that attacks of paralysis can be produced in DOCA-treated animals at will, by giving them large amounts of sodium chloride. In the production of these paralytic spells there appears to be some synergism between mineralocorticoids and sodium. Conversely, intravenous infusion of a potassium-chloride solution can restore the DOCA-overdosed dog or monkey to normalcy within a few minutes.

It is especially noteworthy, in this connection, that Dr. J. W. Conn observed quite comparable manifestations of muscular paralysis in a woman in whom an adrenocortical tumor produced an excess of aldosterone (a mineralocorticoid, chemically and functionally closely related to desoxycorticosterone). Interestingly, in Dr. Conn's patient (as well as in several others observed since), the *hyperaldosteronism,* which led to these motor disturbances, did not produce edema; conversely, in nephrosis, when urinary aldosterone elimination becomes excessive, there is much edema but no muscular paralysis. Future research will have to show why an excess of such a mineralocorticoid can produce more or less selectively one or the other type of manifestation in different patients. Animal experiments have already shown that hormones, such as DOCA, can act rather specifically on one or the other target, depending upon what we call "conditioning factors." For instance, DOCA produces nephrosclerosis, hypertension, and periarteritis nodosa in rats, or muscular paralysis in dogs and monkeys, much more easily when the sodium-intake is high, but the anesthetic effect of the same hormone is not thus enhanced by the salt-intake.

MORPHOLOGIC CHANGES IN THE BRAIN PRODUCED BY CORTICOIDS

In rats heavily overdosed by desoxycorticosterone (especially if they are sensitized by a high NaCl intake and unilateral nephrectomy), there develops an encephalopathy with periarteritis nodosa of the cerebral vessels, marked edema and often multiple massive hemorrhages in the brain. These lesions are accompanied by convulsions or paralytic changes in the skeletal musculature and by an extreme irritability of the animals. It is possible to prevent such changes by the administration of acidifying salts, for instance, ammonium chloride or calcium chloride.

The question arises whether cerebral changes, such as are seen in clinical periarteritis nodosa and in hypertensive disease, are related to the excessive production of mineralocorticoids, or an excessive conditioning for their actions. In any event, this experimental encephalopathy now serves us as a useful test object for the screening of drugs which may have clinical applications in these diseases of man which are simulated by DOCA-overdosage.

STRESS AND THE INFLAMMATORY DISEASES

It is now a generally accepted fact that certain adaptive hormones produced during stress (ACTH, cortisol) have definite anti-inflammatory actions; it is less certain but highly probable that, under special circumstances, stress and the so-called "prophlogistic" hormones (*e.g.,* STH, DOCA, aldosterone) actually stimulate inflammation and the development of the so-called "collagen diseases" in man.

Our attention was called to this relationship between inflammation and the adrenal in the course of experiments on the "anaphylactoid inflammation." It had been noted, in 1937, that the intraperitoneal or intravenous administration of egg-white produces a peculiar hypersensitivity reaction in the rat. This is characterized by a pronounced inflammatory edema in the snout, the paws, and the ears. It was immediately obvious that the adrenal plays an important role in this response, because after adrenalectomy stress failed to prevent this reaction to egg-white. From this we had concluded that stress presumably inhibits inflammation, through the excessive production of ACTH and antiphlogistic corticoids. At the time of our first experiments, purified preparations of ACTH or synthetic anti-inflammatory corticoids were not yet available, but more recently we were able to show that these hormones also inhibit this type of inflammatory hypersensitivity reaction, just as exposure to stress does.

All these facts have been confirmed with a variety of other tests which we have developed for the quantitative assessment of inflammation caused by ordinary chemical irritants (*e.g.*, topical irritation arthritis with formalin, "granuloma pouch" produced with croton oil). In all these instances, inflammatory changes due to tissue irritation have been inhibited, not only by stress due to somatic causes (trauma, burns), but also by such neuromuscular stress as is induced by forced immobilization. Still, stress, no matter how induced, did not exert this inhibitory effect after removal of the adrenals.

The converse effect, namely, the stimulation of inflammation by stress and by adaptive hormones, has also been demonstrated in animal experiments, but it is not yet clear to what extent these findings are applicable to the problems of clinical medicine. Prolonged overdosage with DOCA (especially after sensitization by excess salt-intake) produces periarteritis nodosa and myocarditis; it also sensitizes for the production of various types of experimental arthritis in the rat. Furthermore, under suitable experimental conditions, the antiphlogistic effect of cortisone or cortisol can be inhibited by DOCA or aldosterone in animals. It is clear, therefore, that—at least in certain mammals—the "inflammatory potential" (the ability of tissues to undergo inflammation) depends largely upon the balance of pro- and anti-inflammatory hormones. It is highly probable that, in man, the hormonal regulation of inflammation obeys essentially the same rules, but the clinical effectiveness of the prophlogistic principles has not yet been explored as completely as that of the inversely acting hormones.

The importance of the balance between pro- and anti-inflammatory hormones for the regulation of inflammation has several interesting implications in the field of psychosomatic medicine. For example, it had long been known that certain infectious diseases, for instance, tuberculosis, may be greatly aggravated by exposure to virtually any kind of severe stressor. The rest cures for tuberculosis are based upon the empirically established fact that protection from stress is an important aspect in the healing of tuberculous lesions. Animal experiments have shown that, for instance, in the rat (a species normally resistant to tuberculosis), overdosage with cortisone can induce great sensitivity to tuberculosis bacilli, while the antiphlogistic STH restores resistance to normal, despite continued cortisone-treatment. Even normally saprophytic microorganisms tend to spread and to become highly pathogenic in rats overdosed with ACTH or cortisone and, here again, STH exerts a protective effect. It is probable that, to a large extent at least, the antiphlogistic hormones favor the spreading of infection because they remove the inflammatory barricades around the foci of microorganisms, while the pro-inflammatory hormones act inversely by stimulating granuloma formation and the encapsulation of potentially pathogenic germs. Numerous clinical observations have shown that, in man, heavy and prolonged overdosage with antiphlogistic hormones can also induce the spreading of an originally innocuous and well-delimited tuberculous process.

One of the first observations concerning the alarm reaction—the first stage of the general adaptation syndrome—was that stress produces gastric and duodenal ulcers in animals. It had since been shown—both in experimental animals and in man—that overdosage with antiphlogistic hormones may likewise cause the development and even the perforation of peptic ulcers. This may explain the empirically established relationship between stress (particularly neurogenic stress) and peptic ulcer formation.

In experiments designed to elucidate the mechanism of this phenomenon, we could show that peptic gastric juice, introduced into an experimentally prepared granuloma pouch, does not digest the wall of this sac, because the inflammatory tissue is extraordinarily resistant to peptic digestion. On the other hand, exposure to the stress of forced immobilization causes such a weakening of the granulomatous barricade that it is now readily attacked by peptic juice. In the absence of the adrenals, exposure to similar stress does not thus affect the resistance of granulomatous tissue. It is highly probable, therefore, that the antiphlogistic effect of the adaptive hormones produced during stress plays an important part in the perforation of peptic ulcers; it diminishes the resistance of

the granuloma tissue which normally covers the crater of gastroduodenal ulcers.

The important clinical observations of Dr. Seymour Gray have shown that the secretion of peptic enzymes is enhanced during the alarm reaction by stress and also during treatment with antiphlogistic hormones (*e.g.*, ACTH and cortisone). Consequently, during stress, the perforation of peptic ulcers is presumably facilitated through a dual mechanism: (1) the resistance of the protective granuloma wall is diminished; (2) the secretion of the aggressive enzymes is augmented.

STRESS AND SEXUAL DERANGEMENTS

During stress, when the anterior pituitary has to secrete a great excess of ACTH in order to maintain life, the gland apparently cannot simultaneously produce optimal amounts of gonadotrophic hormones. Thus, it was found that prolonged exposure to various physical or emotional stressors results in a cessation of estrus, with ovarian atrophy, and involution of the accessory sex organs in female rats. During lactation, milk secretion ceases. In male rats exposed to chronic stress, there is involution of the testes.

This change in the secretory activity of the anterior pituitary from the normal pattern to one in which ACTH secretion is favored at the expense of other hormones, has been referred to as the "stress-shift in anterior-pituitary activity."

There is ample clinical evidence to show that this "stress-shift" also occurs in man. There is a decrease in libido and fertility in both sexes during stress and this may be accompanied by amenorrhea in women and impotence in men. In such patients, a vicious circle may develop, because continuous worry, fear or pain may lead to sexual disturbances which, in their turn, again cause stress.

We are presently engaged in experiments designed to elucidate the mechanism of the "stress-shift" and, although this work is still incomplete, it may be said already that, in addition to a decreased secretion of sex-hormones, their peripheral activity upon the accessory sex-organs also appears to be impeded by the conditioning effect of stress.

SUMMARY

After a brief enumeration of key-references to the literature on stress in psychiatry, the following specific problems are discussed on the basis of personal experiments:

1. An "operational definition" of stress, based on measurable indicators of this state.
2. Steroid anesthesia.
3. The anticonvulsive and tranquilizing effect of steroids.
4. Corticoids and muscular paralysis.
5. Morphologic changes in the brain produced by corticoids.
6. Stress and the inflammatory diseases.
7. Stress and sexual derangements.

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