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STUDIES IN RHEUMATIC FEVER

I. THE PHYSIOLOGIC EFFECT OF SODIUM SALICYLATE ON THE HUMAN BEING, WITH PARTICULAR REFERENCE TO THE PROTHROMBIN LEVEL OF THE BLOOD AND THE EFFECT ON HEPATIC PARENCHYMA

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UNITED STATES NAVAL RESERVE

In the course of many years the therapeutic usefulness of salicylates has become well established. With dosages within reasonable limits, the untoward reactions which sometimes have developed always have been of minor importance. Recently, however, several papers and editorials have appeared which suggest that even with relatively small doses of salicylates the tendency to hemorrhage is increased; this tendency is indicated by the fall in the prothrombin content of the blood and, in some instances, by an increase in the blood coagulation time.[1]

During the treatment of large numbers of young adults with active and inactive rheumatic fever hemorrhagic tendencies have been noted infrequently in this hospital, and even when this tendency has occurred it did not appear to be correlated with the administration of salicylates. This broad clinical impression was so divergent from those results recently reported that a control study was undertaken to determine primarily the effect of salicylates administered orally on the level of prothrombin in the blood. Secondarily it was thought useful also to correlate the salicylate level in the blood with any change in prothrombin levels that might occur and to observe the effect of such salicylate levels on the liver, sedimentation rate, blood count and renal function.

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Ensign W-V(S) Rosalie Ruth Ryan, U.S.N.R., supervised and aided in the laboratory procedures used in this study, and Ruth F. Stribey, HA2/c, U.S.N.R., aided in making the charts.

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1. Meyer, O. O., and Howard, Beryl: Production of Hypoprothrombinemia and Hypocoagulability of the Blood with Salicylates, Proc. Soc. Exper. Biol. & Med. **53**: 234-237 (June) 1943. Shapiro, Shepard: Studies on Prothrombin: VI. The Effect of Synthetic Vitamin K on the Prothrombinopenia Induced by Salicylate in Man, J. A. M. A. **125**: 546-548 (June 24) 1944. Shapiro, Shepard; Redish, M. H., and Campbell, H. A.: Studies on Prothrombin: IV. The Prothrombinopenic Effect of Salicylate in Man, Proc. Soc. Exper. Biol. & Med. **53**: 251-254 (June) 1943.

PLAN OF STUDY AND METHODS

The group for study comprised 113 young men who were afflicted with rheumatic fever. The large majority of these patients at the start of the study had inactive rheumatic fever and were ambulatory; a small group (22) were having a recurrence of active polycyclic rheumatic fever at the start of the study or had one during the study. All of the 113 patients were given the same general diet furnished by the Navy and all except those who were confined to bed were allowed to continue their usual routine activities under military supervision. Arbitrarily the 113 patients were divided into two groups. One group of 57 served as controls. The remaining 56 were given varying daily doses of salicylates for four weeks, while the 57 control patients were given orally only sodium bicarbonate in varying doses during the same period of time.

During the first week the 56 patients who received salicylates were given 25 grains (1.6 Gm.) of sodium salicylate orally together with 10 grains (0.65 Gm.) of sodium bicarbonate twice daily; the controls received only 10 grains of sodium bicarbonate twice daily. The medication given to both groups during the four weeks is listed in the accompanying table. No medication was administered during the fifth week to either group of patients except for a few who still remained ill.

During the study 5 of the 56 patients receiving salicylates had to discontinue their medication and were dropped from the study. Two of the 5 developed acute appendicitis, 1 required confining disciplinary action and 2 developed severe nausea and vomiting. The results, therefore, are based on study of only 51 patients who received salicylates. Only 3 of the controls had to be eliminated from the study. One of the 3 required an operation for severe cellulitis of the leg, 1 required disciplinary action and, after careful study of the third, it was decided that the correct diagnosis was rheumatoid arthritis and not rheumatic fever. The final results concerning the controls represent data from 54 patients.

The prothrombin content of the blood was measured by modification of the method first proposed by Quick in which the prothrombin time of whole plasma is measured in seconds.[2] During the course of this experiment more than 1,500 prothrombin times were determined and certain observations were made that would be evident only in such a large group. The factors of

2. Magath, T. B.: A Method for Determining the Prothrombin Clotting Time, in Walters, Waltman, and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940, pp. 563-564.

time, room temperature and kind of thromboplastin used were found to be extremely important. Determinations on normal controls were done at the beginning, middle and end of the series of determinations on the two groups of patients. On one or two occasions it was necessary to record a longer normal prothrombin time for the half of our group of patients whose tests were run last. The prothrombin times on the patients receiving sodium salicylate were always determined before those on the "control" patients. This procedure lessened any effect of greater lapse of time on the prothrombin time of this group of patients. Experiments showed that on a typical hot southern California day the prothrombin time was lengthened from one to four seconds if the plasma stood for two hours, and if the plasma was allowed to stand even longer the prothrombin time was proportionately increased. Stored plasma from the plasma bank showed no prothrombin activity. The source of thromboplastin used for the tests varied. From June 14 to June 25, 1944 dried rabbit brain prepared by Magath's method was employed. From June 26 to July 7 Bacto Thromboplastin as prepared by the Difco Laboratories was used, and from July 8 to July 26 fresh rabbit lung prepared by the method outlined in the "Clinical Chemistry Notes of the Naval Medical School" was employed. These frequent changes in source of thromboplastin were undesired but forced by necessity of obtaining material. Diluted plasma (12.5 per cent) was tried, but the rather indefinite end point led us to discard this method. To rule out individual variations in so-called normals, our daily normal values were determined from the blood from two or three members of the laboratory staff.

Plan for Administration of Drugs

Time	Control Group	Patients Given Sodium Salicylate
First week	10 grains (0.65 Gm.) of sodium bicarbonate 2 times a day	10 grains of sodium bicarbonate plus 25 grains (1.6 Gm.) of sodium salicylate 2 times a day
Second week	10 grains of sodium bicarbonate 4 times a day	10 grains of sodium bicarbonate plus 25 grains of sodium salicylate 4 times a day
Third week	10 grains of sodium bicarbonate every 4 hours day and night	10 grains of sodium bicarbonate plus 25 grains of sodium salicylate every 4 hours day and night
Fourth week	10 grains of sodium bicarbonate every 4 hours day and night	10 grains of sodium bicarbonate plus 30 grains (2 Gm.) of sodium salicylate every 4 hours day and night
Fifth week	No medication	No medication

The sedimentation rate was measured by the method of Westergren. Liver function was measured by the intravenous sulfobromophthalein method;[3] the blood samples were taken at intervals of five and thirty minutes after injection of 2.5 mg. of sulfobromophthalein per kilogram of body weight. The serum bilirubin was measured by the method of Malloy and Evelyn[4] and the van den Bergh reaction by the method described by Kolmer and Boerner.[5]

The method outlined by Brodie, Udenfriend and Coburn[6] was used for the determination of blood salicylates. A few minor changes were made to allow the work to be done more conveniently in the necessarily large volumes of the experiment. It was more convenient to use serum rather than the plasma recommended by the authors. A large series of comparative studies on the salicylate content of plasma and serum was run and the difference of + or — 2 mg. per hundred cubic centimeters was considered insignificant. Owing to the difficulty of obtaining a large supply of Pyrex glass stoppered bottles, an attempt was made to find an adequate substitute. The common 4 ounce "French Square" bottle with a bakelite screw cap was highly satisfactory and is in wide use in pharmacies. The inner layer of cork and paraffin in the bottle cap must be removed before use. Screw caps of plastics other than bakelite are dissolved by ethylene dichloride and therefore cannot be used. The ordinary Kahn shaker in use in most clinical laboratories is adequate for shaking the mixture and has the additional advantage of holding thirty-six to fifty bottles.

There is no loss of salicylates by allowing the blood to stand overnight, and the procedure may be interrupted at any point for a considerable length of time. Ethylene dichloride is toxic and should be used only with forced ventilation. Since ethylene dichloride should not be pipetted, a tapered small graduated cylinder holding 30 cc. was found suitable for measuring the chemical for the purpose of the test.

In ten days prior to the start of the study all 113 patients had the routine tests just described. The prothrombin time was determined three times and the sedimentation rate twice during this period. All prothrombin times were well within normal limits. The sedimentation rates of a few patients were elevated. During the four weeks of the study the concentration of hemoglobin, number of erythrocytes and leukocytes, urinalysis, dye retention test, serum bilirubin and van den Bergh reaction were determined once weekly on the 51 patients who were receiving sodium salicylate. The Quick prothrombin time was determined three times a week, as were the sedimentation rate and the level of salicylate in the blood. All studies were carried out only once a week on the 54 controls.

In the course of the study of the 105 patients it was observed that some of the subjects were not taking the medicaments properly in spite of strict supervision. This fact was easily determined by observing the blood salicylate levels of these patients. In another study in which the primary purpose was to determine the effect of the administration of sodium bicarbonate on the level of salicylates in the blood the prothrombin time was watched closely. In this group of 9 patients supervision of medication was extremely strict and all 9 patients received the prescribed medications. They were given 150 grains (10 Gm.) of sodium salicylate daily for three weeks either with or without sodium bicarbonate. The Quick prothrombin time and blood salicylate level were determined daily except on Sundays on these 9 patients. The results on this group will be mentioned in connection with the results of the study of prothrombin content of the blood.

3. Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**: 1112-1114 (April 11) 1925.

4. Malloy, Helga T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**: 481-490 (July) 1937.

5. Kolmer, J. A., and Boerner, Fred: Approved Laboratory Technic: Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical and Histological, ed. 3, New York, D. Appleton-Century Company, Inc., 1941, p. 234.

6. Brodie, B. B.; Udenfriend, Sidney, and Coburn, A. F.: The Determination of Salicylic Acid in Plasma, J. Pharmacol. & Exper. Therap. **80**: 114-117 (Jan.) 1944.

In order to correlate our results with the recent work of others we reviewed the literature on the various points we were studying and have compared the pertinent observations of others with our observations.

COMPARISON OF RESULTS OF OUR STUDY WITH DATA FROM LITERATURE

Prothrombins.—In February 1943 Link and his associates [7] at the University of Wisconsin reported in their continued studies on hemorrhagic sweet clover disease that the quantitative chemical degradation product of dicumarol was salicylic acid.[8] This finding prompted these workers to study the effect of salicylates on the prothrombin level of the blood in rats. They found that a single dose of salicylic acid induced a temporary hypoprothrombinemia in rats when the rats were maintained on a ration low in vitamin K. This phenomenon did not occur when the rats were on a diet containing sufficient vitamin K. Furthermore, menadione protected the rat against the hypoprothrombinemic producing action of salicylic acid. It was observed that a dose of 25 mg. of sodium salicylate administered intravenously to rats on a diet deficient in vitamin K increased the prothrombin time of diluted plasma (12.5 per cent) from a normal of 39 to 72 seconds. In addition, it was found that on the low vitamin K ration rats receiving 100 mg. of salicylic acid daily developed severe hypoprothrombinemia in twenty days. Rats on the artificial ration, which was extremely low in vitamin K, developed a temporary mild hypoprothrombinemia even after single oral doses of 10, 25 or 100 mg. of salicylic acid.

Shortly after this report, two studies appeared which indicated that salicylates administered to man had an effect on the prothrombin level similar to that observed originally by Link and his associates in rats. Meyer and Howard reported that the prothrombin level of most of 13 subjects who received 80 grains (5.3 Gm.) of acetylsalicylic acid daily for periods of three to eleven days was reduced to about 50 per cent of normal, and in addition the coagulation time increased from an average control level of 18 to 25 minutes. These authors usually noted an effect on the prothrombin level the day after the first administration of the drug, but in most instances the maximal effects were not observed until the drug had been administered for three or four days or more. When administration of the drug was discontinued, the prothrombin level and coagulability of the blood usually returned to normal in from two to four days. From 75 to 80 grains (5 to 5.3 Gm.) of sodium salicylate was administered to 6 patients in divided doses for periods of seven to eight days and 40 grains (2.6 Gm.) in divided doses to three others for periods ranging from three to eight days. The effects on the prothrombin and coagulation time were similar in all respects to those of acetylsalicylic acid. It was noted further that the administration of menadione would protect the persons receiving salicylates from hypoprothrombinemia. Similar observations were made by Shapiro also, who reported that from his clinical studies approximately 1 mg. of synthetic vitamin K would counteract the prothrombinemic inducing action of 1 Gm. of acetylsalicylic acid.

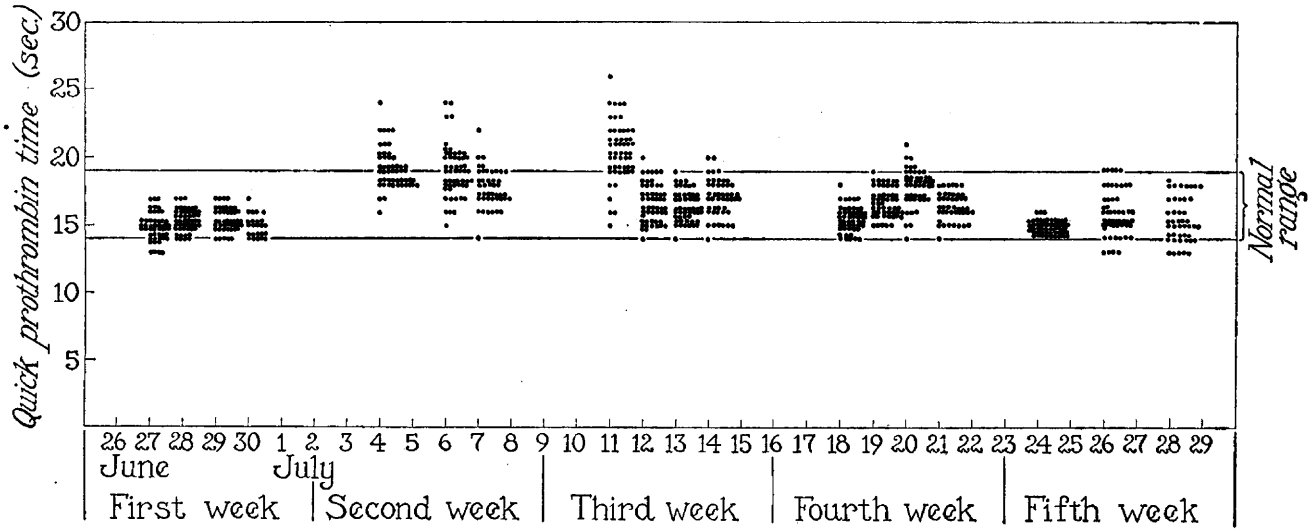

Chart 1.—Effect of progressively higher dosages of sodium salicylate on the prothrombin time of the blood of 51 patients who had rheumatic fever.

Since the appearance of these two clinical studies, several editorials have pointed out that the administration of salicylates might not only be a factor in production of hemorrhagic manifestations among patients with rheumatic fever who are receiving salicylates but also might account for some of the unexplained hemorrhages that occur in acetylsalicylic acid addicts.

In chart 1 is demonstrated graphically the effect of the administration of sodium salicylate over a long period on the prothrombin content of the blood of the 51 patients. It will be observed that during the first week when the daily dosage was 50 grains (3.2 Gm.) of sodium salicylate there was no change in the prothrombin time from normal levels. In the second week, however, two days after the dosage had been increased to 100 grains (6.6 Gm.) the prothrombin time began to increase. It was not, however, until the patients had been receiving 150 grains (10 Gm.) of sodium salicylate daily for two days that a good percentage of them had an elevation in the prothrombin time. Even with increased salicylate dosage the prothrombin time did not increase beyond the initial increase or remain high in all cases. This phenomenon is difficult to explain but tends to support the original observation

7. Link, K. P.; Overman, R. S.; Sullivan, W. R.; Huebner, C. F., and Scheel, L. D.: Studies on the Hemorrhagic Sweet Clover Disease: XI. Hypoprothrombinemia in the Rat Induced by Salicylic Acid, J. Biol. Chem. **147**: 463-474 (Feb.) 1943.

8. A side observation in our present study is pertinent; namely, that salicylate could not be detected in the blood of a patient who had great prolongation of the Quick prothrombin time following the ingestion of dicumarol.

by Link and his associates [7] that the prothrombin time in rats is affected little by increase in dosage of salicylic acid from 10 to 100 mg. It is difficult to compare our results with previous reports primarily because our studies have been carried out over a much longer period and the dosages employed have been increasingly larger. At no time during this study were any abnormal hemorrhagic manifestations noted in the 51 patients taking salicylates.

In chart 2 are represented graphically the weekly prothrombin determinations on the controls. This group showed no appreciable change in their prothrombin time over the period of four weeks during which they received sodium bicarbonate.

In chart 3 are represented graphically the prothrombin determinations for 9 patients who received 150 grains (10 Gm.) of sodium salicylate daily with or without sodium bicarbonate over a period of three weeks. As previously noted by other investigators, the prothrombin time did not rise until about the second or third day. The salicylate level in the blood of all these patients was between 30 and 50 mg. per hundred cubic centimeters throughout the study. In spite of this high level of salicylates in the blood there was no great progressive increase in the number of patients who had an abnormal prothrombin time. Even on this therapeutic dosage of salicylates the increase of prothrombin time was not pronounced, and at no time in any case was any hemorrhagic manifestation noted.

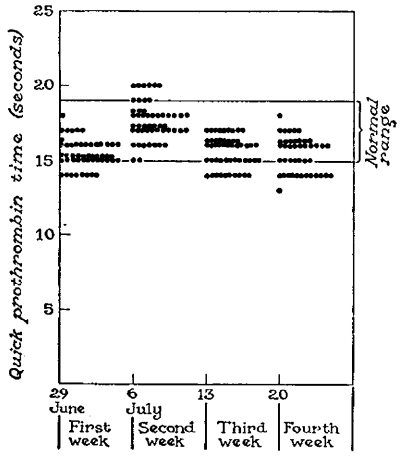

Chart 2.—Effect of progressively higher dosages of sodium bicarbonate on the prothrombin time of the blood of 54 patients who had rheumatic fever and were serving as controls for this study.

Hepatic Parenchyma.—Hanzlik and Wetzel [9] have reported that salicyl is not chemically changed by the liver. They reported that in dogs with hepatic degeneration from phosphorus poisoning the urinary secretion of salicyl was as prompt and as good as in normal control dogs. Smyth and Whipple [10] found no effect from sodium salicylate, in therapeutic doses, on the excretion of bile salts in dogs with permanent biliary fistulas. In the present studies the van den Bergh reaction was indirect for all patients in both groups before, during and after the study. Likewise the serum bilirubin was not increased above normal in any instance nor was the hepatic function altered as measured by the dye retention method. It is realized that there are many more sensitive tests of liver function which might have detected some minor degree of hepatic parenchymal damage in these cases. However, the interpretation of such minor alterations in liver function is indeed difficult. It is our impression from this study that sodium salicylate, even in large doses, has little, if any, deleterious effect on the hepatic parenchyma.

9. Hanzlik, P. J., and Wetzel, N. C.: The Salicylates: XI. The Stability and Destruction of the Salicyl Group Under Biological Conditions, J. Pharmacol. & Exper. Therap. **14**: 25-42 (Sept.) 1919.

10. Smyth, F. S., and Whipple, G. H.: Bile Salt Metabolism: IV. Negative Influence of Drugs, Atropine, Pilocarpine, Phlorhizin, Quinine, etc., J. Biol. Chem. **59**: 655-659 (April) 1924.

Levels of Salicylate in the Blood.—Only for a short period have satisfactory methods been available which could measure the salicylate level in the blood of man. Although the salicylate level was determined three times a week for five weeks on the 51 patients who were taking salicylates, these results are not shown for several reasons. It was noted in this study that even in the third and fourth weeks of medication there were instances in which the salicylate level of the blood was still less than 20 mg. per hundred cubic centimeters. It was difficult to believe that any of these patients with such low levels possessed any abnormality in regard to absorption of the drug. In light of some of our more recent studies on absorption, the only explanation is that these subjects in some manner did not take the salicylates which were ordered for them. In fact, some later admitted that this was the truth. Such an unfortunate circumstance is nearly unpreventable in a large military institution and parallels closely the experience of medical officers attempting to maintain adequate prophylaxis with atabrine in troops in the South Pacific area and of those trying to give prophylactic dosages of sulfadiazine.

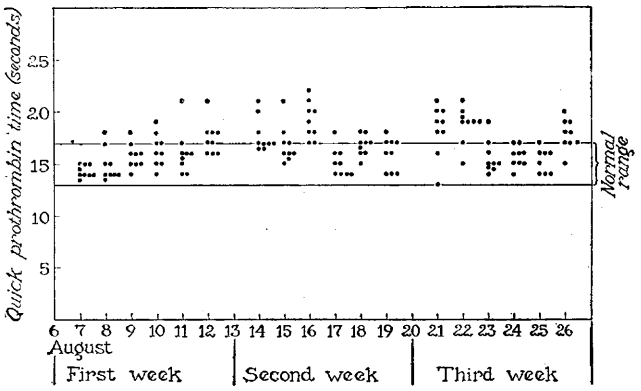

Chart 3.—Effect of the daily administration of 150 grains (10 Gm.) of sodium salicylate with and without sodium bicarbonate on the prothrombin time of 9 patients who had rheumatic fever. The daily level of salicylates in the blood of all these varied between 30 and 50 mg. per hundred cubic centimeters.

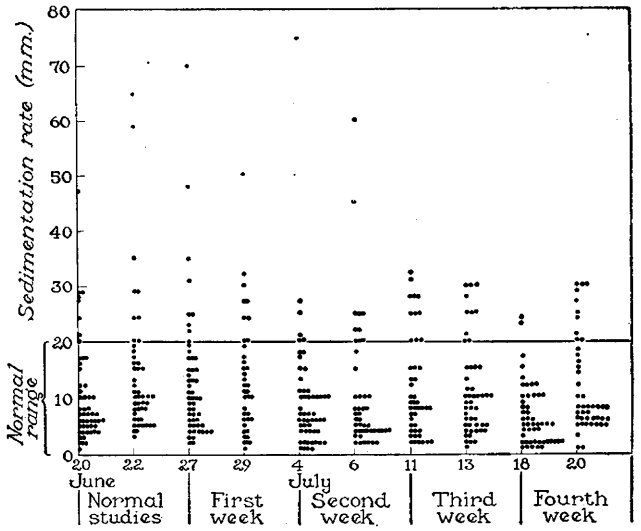

Chart 4.—The normal and triweekly blood sedimentation rates of 51 patients with rheumatic fever who were taking sodium salicylate in increasing amounts.

A large majority of the patients, however, took the drugs as ordered and the blood salicylate level of all

of these when they received 150 grains (10 Gm.) of sodium salicylate a day varied between 30 and 50 mg. per hundred cubic centimeters. After medication was discontinued, the blood salicylate level fell rapidly and was nearly zero at the end of three or four days. From this study it would seem that adequate level of salicylate in the blood is maintained in most persons on an oral dosage of 100 to 150 grains (6.6 to 10 Gm.) of sodium salicylate daily.

Sedimentation Rate.—The effect of administration of salicylates on the sedimentation rate has been a subject of considerable controversy for many years. Some students believe that the administration of salicylates in most instances is followed by a fall in the sedimentation rate. Others feel that the fall in the sedimentation rate is at least speeded by the administration of this drug. Many others, however, are equally convinced that the administration of salicylates has little effect on the alterations, up or down, of the blood sedimentation rate in rheumatic fever. Charts 4 and 5 represent graphically the sedimentation rates for

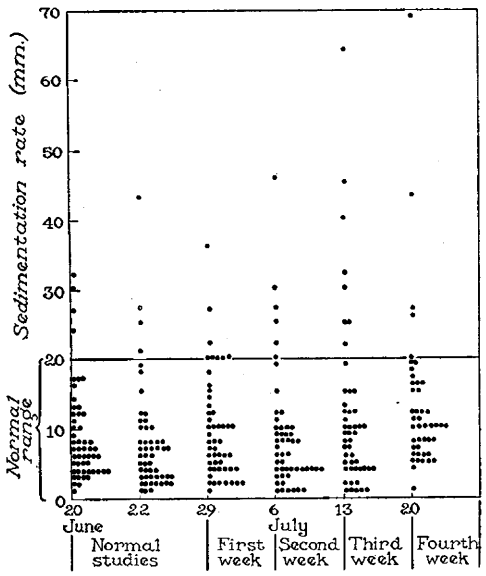

Chart 5.—The normal and weekly blood sedimentation rate of 54 patients with rheumatic fever serving as controls. These patients were receiving sodium bicarbonate in increasing amounts.

both groups of patients studied. It will be observed in chart 4 that in spite of continuous administration of salicylate a few patients, as mentioned before, had recurrence of acute polycyclic rheumatic fever with a subsequent rise in the blood sedimentation rate. Most of these men had an adequate salicylate level in the blood. In spite of the continued high dosage of salicylates, the sedimentation rate remained elevated in a few of these patients throughout the study. The controls, however, had nearly the same number of rises in the blood sedimentation rate as the patients treated with sodium salicylate; in most instances these too represented a recurrence of rheumatic fever.

It has been shown by Coburn [11] and others that the administration of large doses of salicylates in a first acute attack of rheumatic fever is followed by a rather rapid fall in the blood sedimentation rate. The present studies suggest that patients with polycyclic rheumatic fever do not respond clinically, nor does the sedimentation rate respond to the administration of salicylates in a manner comparable to that observed in a first acute attack. At present there is no known explanation for this interesting phenomenon.

Urine.—Hanzlik [12] reported that the administration of sodium salicylate in full therapeutic doses invariably causes the appearance of albumin, leukocytes and granular casts or castlike bodies in the urine of normal, rheumatic, convalescent, febrile and afebrile persons. They observed that quantitatively the albuminuria reached its maximum at the time of symptoms of salicylism and then gradually diminished and eventually disappeared. They further noted that the administration of sodium bicarbonate in amounts equal to the dosage of salicylates had no effect on the albuminuria. Our findings are nearly exactly opposite to those reported by Hanzlik. A few leukocytes were found in specimens of urine from only 6 of the 51 patients who received large doses of sodium salicylate. In each of these 6 cases the leukocytes were found in only one specimen of urine. Similar observations were made on 8 of the controls. In neither group of patients was albuminuria noted on any occasion.

Blood.—In charting the effect of salicylates and sodium bicarbonate on the hemoglobin and erythrocyte count, it is our impression that both the hemoglobin level and the erythrocyte count decreased slightly. This, however, may result from the disease rather than from the drug. The leukocyte count was unaffected in either subjects or controls.

COMMENT

This study confirms previous reports that the administration of sodium salicylate results in some effect on prothrombin content of the blood. This study made with undiluted plasma shows, however, that this effect is not great and that with even large dosage the prothrombin content of the blood is not dangerously reduced and hemorrhage from therapeutic administration of salicylates is certainly unlikely. Many instances have been recorded in the literature [13] in which administration of salicylates in fatal doses has been followed by hemorrhagic changes as noted at necropsy. Purpura, however, occurs in many cases of rheumatic fever in which the prothrombin time is normal and salicylates are not being given. To assume that such objective findings in cases of rheumatic fever are a result of salicylate therapy is misleading. On the other hand, if any surgical procedure is contemplated or arises as an emergency in case of rheumatic fever in which large doses of salicylates are being administered, vitamin K obviously should be given before and after operation.

As with dicumarol, the increase in prothrombin time following administration of salicylates is not noted until twenty-four to thirty-six hours after administration of the drug. There seems to be little correlation between the increase in prothrombin time and the level of salicylates in the blood. In other words, when once the rise in the prothrombin time has taken place, an increased dosage of salicylate seems to have no tendency to cause a further increase in the prothrombin time.

The question arises as to why patients taking salicylates do not all have an increase in the prothrombin time. The work of Link and his associates indicates that the level of vitamin K in the diet has a profound influence on the hypoprothrombinemic action of salicyl-

11. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: A Rational Technic, Bull. Johns Hopkins Hosp. **73**: 435-464 (Dec.) 1943.

12. Hanzlik, P. J.: Actions and Uses of the Salicylates and Cinchophen in Medicine, Medicine **5**: 197-373 (Aug.) 1926.

13. Wetzel, N. C., and Nourse, J. D.: Wintergreen Poisoning, Arch. Path. **1**: 182-188 (Feb.) 1926.

ates in rats. The difference in the intake of vitamin K might explain why only certain ones of our patients developed hypoprothrombinemia following administration of salicylates. It also would be interesting to know whether prothrombin A or prothrombin B is affected by administration of salicylates.

SUMMARY

From this study the following observations were made:

1. The administration of sodium salicylate with sodium bicarbonate in therapeutic doses to patients with rheumatic fever is followed by an increase in the Quick prothrombin time. In none of the cases reported were any hemorrhagic manifestations noted following the administration of salicylates.

2. Under the circumstances of this study, the administration of salicylates had no deleterious effect on the hepatic parenchyma.

3. A dosage of 150 grains (10 Gm.) of sodium salicylate daily is followed in most instances by a blood level of salicylate of 30 to 50 mg. per hundred cubic centimeters. When the level of salicylates in the blood falls much below these figures, one can suspect that the patient is not taking the drug.

4. In recurrent attacks of polycyclic rheumatic fever the sedimentation rate is little affected by the administration of salicylates.

5. Long continued high dosage of salicylates is followed by a slight reduction in the hemoglobin content and erythrocyte count. The leukocyte count is unaffected by salicylates, as is the urine.

STATISTICAL STUDY OF 265 CASES OF HEAT DISEASE

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AND
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MEDICAL CORPS, ARMY OF THE UNITED STATES

When work involving muscular exertion is performed by the human body over a sustained period of time in an atmosphere having a high external temperature and a high humidity, the pathologic effects of heat accumulation are frequently observed. Such a condition represents a potentially serious medical problem and one which may prove rapidly fatal in its later stages. Its proper control and treatment are highly important, especially when a large number of individuals are concerned.

This problem has been recognized and studied by many industrial plants and organizations over some years, and a great deal of progress has already been made in its management.

Modern warfare has focused further attention on heat exhaustion because of its high casualty rate in operations under adverse climatic conditions, especially in tropical and semitropical locations. Both the British and American armies have encountered the problem in training as well as in combat operations. In the Iraq campaign the casualty rate among British troops was higher from heat (8 per cent) than from all other causes (4.1 per cent).[1]

1. Marsh, Frank: Etiology of Heat Stroke and Sun Traumatism, Tr. Roy. Soc. Trop. Med. & Hyg. **24**: 257-288 (Nov.) 1930.

At this post the high incidence of heat exhaustion during the summer months has been a major medical concern. Fort Eustis is located along the southern coastline, situated on a low flat peninsula, bounded on the north and south by rivers. During the months of June, July and August there is a high external temperature with a high humidity and a low wind velocity. Troops, particularly unseasoned troops, undergoing training under such climatic conditions show a high casualty rate from the effects of heat. In the summer of 1942, 4 cases of heat stroke were admitted to the hospital in shock with pulmonary edema and terminated fatally despite heroic treatment. This experience stimulated an intensive investigation of the available data on heat disease, and the present report deals with the results of our investigation and subsequent management of the problem.

PHYSIOLOGIC CONSIDERATIONS

Man, as a warm blooded animal in contrast to a cold blooded animal, possesses certain mechanisms to maintain a constant body temperature despite the temperature of the environment. This stability of temperature represents the resultant of the balance between the mechanisms of heat production and heat loss.[2] If one of these mechanisms fails, there is a consequent gain or loss of body heat. The genesis of the condition commonly termed heat exhaustion or heat stroke usually occurs from a diminution or failure of the means of heat loss possessed by the human body.

According to Wiggers,[3] body heat is lost or dissipated by the following routes:

(*a*) Small amounts by warming the food and respired air and with the excretions (although this is not in universal agreement with all authors).

(*b*) About 15 per cent by saturation of the air in the lungs and by heat absorbed in eliminating carbon dioxide.

(*c*) The remainder (over 80 per cent) by conduction, by convection, by radiation and by vaporization of water.

The heat loss through radiation, convection and conduction depends mainly on:[4]

(*a*) Air temperature and other environmental conditions (i. e. the humidity).

(*b*) The nature and amount of clothing.

(*c*) The quantity of heat produced in the body reflected by the degree of body temperature.

It is well known that the exposed skin surface acts as a black body radiator to the direct rays of the sun and thus will absorb heat rapidly from this source. The infra-red or heat waves may however be deflected by satisfactory clothing.

It is very important to evaluate properly the part played by the vaporization of water as a means of heat loss in the production of pathologic effects from heat accumulation. Below atmospheric temperatures of 28 to 30 C. (82.4 to 86 F.) vaporization of water from the skin plays little part as a means of heat dissipation[5] (about 25 per cent and a third of this is due to loss of water by respiration).[6] While the percentage of heat loss by vaporization of water is nearly constant below this level, as the external temperature rises above it and approaches 35 C. (95 F.) vaporization of water becomes an increasingly impor-

2. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, Williams & Wilkins Company, 1943, p. 1047.
3. Wiggers, C. J.: Physiology in Health and Disease, ed. 3, Philadelphia, Lea & Febiger, 1939, p. 929.
4. Best and Taylor,[2] p. 1048.
5. Best and Taylor,[2] p. 1051.
6. Wiggers,[3] p. 932.