PYRETOTHERAPY IN LEPROSY.

BIOCHEMICAL CHANGES RESULTING FROM EXPOSURE TO AN AIR-CONDITIONED HYPERTHERM[1]

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A great deal of work is being done at present to evaluate artificially induced fever as a therapeutic procedure. Since 1929 especially, numerous methods of producing fever have been described, such as the injections of foreign protein in the form of typhoid vaccine, malaria inoculation, physical energies such as radiant heat, radiotherm and diathermy, and hydrotherapy in the form of hot baths. There are vast differences of opinion as to the action of these various forms of hyperpyrexia, but evidence is fast accumulating attesting the superiority of the physical means of producing therapeutic fever over some of the forms of protein therapy; hence the study of the biologic effects produced by these energies has opened a wide field for investigation.

The chronicity of leprosy and its almost invariable tendency towards a progressively unfavorable course except in a small number of cases in which it is spontaneously or otherwise arrested, have through the centuries stimulated the therapeutic trial of a great variety of medicaments and methods, few of which have survived. Small wonder, then, that pyretotherapy, with the large amount of favorable lay publicity given it, has stimulated a desire among leprous patients at Carville for experimental treatment.

The knowledge that leprosy tends to become a deep-seated chronic infection, with bacterial invasion of nearly all body tissues, and the tendency of leprous persons to succumb from cardio-renal or pulmonary disfunction, caused considerable hesitation in administering pyretotherapy. This apprehension was emphasized by the knowledge that the heat disseminating mechanism of the average leper is impaired in direct proportion to the temporary or permanent destruction of the sweat mechanism. In order to determine by experimentation whether pyretotherapy has a field

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in the treatment of leprosy, five patients showing gradations of involvement from early lesions to late leontiasis were selected from a large group of volunteers, on whom careful investigations were carried out to determine particularly renal, cardiac and hepatic normality.

EXPERIMENTAL WORK

The experiments were planned to determine the physiologic and chemical alterations in lepers resulting from hyperpyrexia produced by the Kettering air-conditioned hypertherm.

Physical apparatus.—The Kettering hypertherm (10) consists of an insulated cabinet in which the nude patient lies, with his head extending outside the cabinet. The patient lies on an air mattress, supported by a box-like bed, which is rolled in and out at will. Sponge-rubber insulation is utilized in the neck region to permit him to shift his position. In the rear of the cabinet is a small insulated, fire-proof compartment in which the air-conditioning apparatus is housed. The dry-bulb air temperature is controlled by a thermostat. The wet-bulb temperature, which governs the relative humidity, is controlled by a humidistat or by a wet-bulb thermostat. The air velocity within the cabinet is controlled by blowers of fixed speed. Dry-bulb and wet-bulb temperatures within the cabinet are indicated on large dials, equipped with warning pilot lights, on the top of the front end of the cabinet, where they may be constantly observed by the nurse-technician. The temperature-humidity factors may be controlled by the turning of a single knob.

The average set of air conditions to which the patient's body is subjected is as follows: dry-bulb air temperature of from 130 to 150°F., relative humidity of from 35 to 50 percent, and air velocity of 425 cubic feet per minute. The elevation of the rectal temperature to 105°F. is ordinarily accomplished in from forty minutes to one hour. The air is constantly conditioned by continuous passage through the air-conditioning compartment. The safety and comfort of the patient are greatly enhanced by the accurate control of the relative humidity.

The mechanism of fever induction with the Kettering hypertherm depends primarily on heat transfer by conduction from the circulating heated air. This factor, combined with prevention of the normal rate of heat loss from the body by radiation and evaporation, is responsible for the elevation of the body temperature and its maintenance at any desired level.

With this apparatus, the average loss of sweat was between one to five liters during a five hour treatment at 105-106°F. This loss of fluid was partially replaced during treatment by the oral administration of from one to three liters of 0.6 percent iced sodium chloride solution, alternating with water and coca-cola when the patient experienced nausea from the salt solution.

Three courses of weekly treatments were given: the first course consisted of eight treatments; the second, after a rest of seven weeks, of six treatments; and after a rest of twenty-six weeks a third, of six treatments. During each treatment the rectal temperature was elevated to 105-106°F., with an average of 105.8°F. This temperature was sustained for five hours in Cases 684, 610, 774 and 698, and for one to three hours in Case 899. One patient (Case 698) refused the third course.

The general procedure in this experiment was to collect approximately 35 cc. of blood from a cubital vein before and after each of the first eight sessions of treatment, five weeks after the eighth session, one week after the second course of treatments, one week before the third course, and three weeks following the third course. No food was taken for twelve hours preceding each treatment. In order that the results might be uniform all blood was collected before the patient was placed in the cabinet, when his temperature was normal, and from one to two hours after he had been removed from the cabinet, at which time his temperature ranged between 100 and 100.7°F.

For the pH and carbon dioxide determinations the blood was drawn with a minimum of stasis and collected in a special tube containing heavy paraffin oil and a small amount of sodium oxalate. Determinations were made within one-half hour after the sample was obtained. The blood for the calcium, inorganic phosphorus, total proteins, albumin and globulin was centrifuged and determinations were carried out on the serum within twelve hours. Oxalated blood was used for all other analyses, determinations being completed within three hours.

Capillary blood was used for the leucocyte and differential counts. Because of the thickened ear lobes and the marked induration of the hands of two of the patients, venous blood, unoxalated, was used for the cell volume, hemoglobin, and red-cell counts of all five patients after they had had their first febrile treatment. The diluents were added within two minutes after the blood was taken.

Cell volumes were determined in duplicate with the Van Allen (13) hematocrit, using 1.6 percent sodium oxalate as an anticoagulant and diluting fluid. Readings were made after centrifugalizing for one-half hour at 3,000 revolutions per minute. The erythrocyte sedimentation rate was estimated according to the method of Linzenmeier (12). For pH, the colorimetric procedure of Cullen (3) was used on plasma. The values were determined at room temperature and corrected to 38°C., using the calculation $pH\ 38° = pH\ t° + 0.01\ (t° - 20°) - 0.23$, in which t° represents the observed temperature. Carbon dioxide was determined by the method of Van Slyke and Cullen (14). The analytical procedures for cholesterol, total proteins, albumin, globulin, calcium and phosphorus that were used have been described in previous papers from this laboratory (2, 19). Nonprotein nitrogen, urea nitrogen, sugar and creatinine were estimated by the Folin-Wu technique (4). Chlorides were determined by the Whitehorn method (17). The Sahli method was used in the estimation of hemoglobin. The complement

fixation test by Kolmer's quantitative method was done in parallel with Kahn's precipitation test.

RESULTS AND COMMENTS

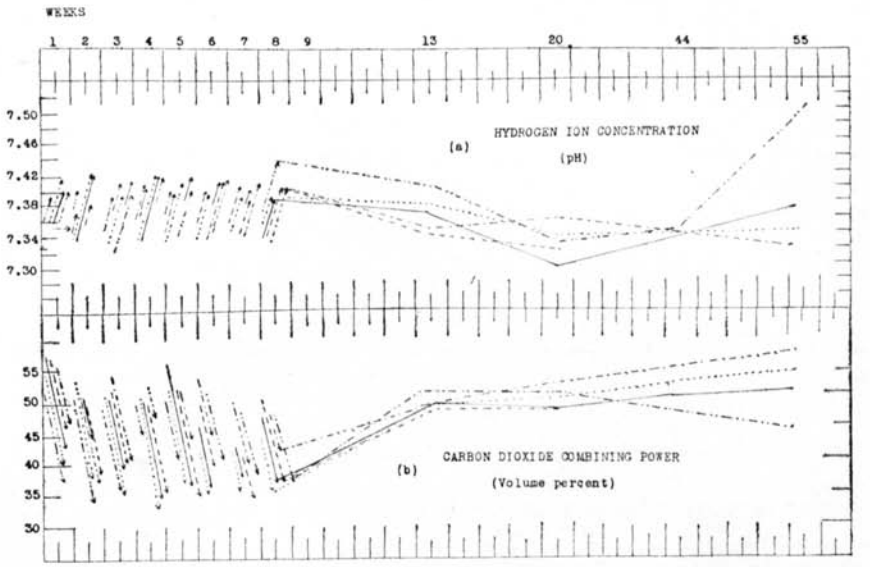
The total number of experiments that were carried out in the cases of leprosy, together with the experimental data obtained, is indicated in the charts. For comparison, we analyzed concurrently the blood and sera of three nonleprous cases of gonorrhoea and two of syphilis, subjected to the same form of pyretotherapy; the data of these cases are not incorporated in this report.

Acid-base equilibrium.—There was an alteration in the pH of the blood towards the alkaline side in all of the cases studied, including the five nonlepers used for a comparison (Text-fig. 1). The maximum rise was from 7.34 to 7.42 pH, a change of 0.08. In Case 899 the pH rose above the normal maximum (normal range 7.33 to 7.40) in five of the eight treatments, in Cases 774 and 684 in four instances each, and in Case 698 in one instance. In Case 610 there was no increase beyond the normal range during the entire course of treatments, and the same is true of the group used for comparison. Our controls, which consisted of fifteen apparently normal individuals, gave readings within the normal range mentioned. In the entire series the pH showed an increase of 0.01 to 0.08. Though this variation seems slight, it must not be forgotten that a slight variation in pH means a very great variation in H ion concentration, for the pH value is an exponent of 10. Thus if the pH of blood changes from 7.40 to 7.30 it means an increase in H ions of 25 percent (8).

The rise in temperature caused an appreciable fall in the CO_2 capacity of the plasma in all of the cases (Text-fig. 1). After the first treatment there was a tendency for the CO_2 capacity to remain at a low level before exposure as well as after. In the entire series the loss in CO_2 ranged from 5 to 22.6 volume percent. The fall was not as marked in the nonleprous cases.

The above changes in CO_2 and pH show an uncompensated CO_2 deficit. This condition, caused by ventilation in excess of that required to maintain the usual relationship between $NaHCO_3$ and H_2CO_3 in the blood, has been noted as the result of oxygen deficit of hot baths, of exposure to dry hot air and of fevers due to various causes (1). Peters and Van Slyke (9) state in substance that the occurrence of a primary CO_2 deficit in hyperpyrexia can be accounted for on a taleological basis by assuming that the deman s for increased oxygen supply and for cooling are suffi-

ciently important to cause the organism to accelerate respiration for these purposes despite the fact that a certain degree of alkalosis from CO_2 deficit results.



TEXT-FIG. 1. Changes in the hydrogen ion concentration (pH) and carbon-dioxide combining power of the blood plasma during the treatment experiments.[1]

This hyperventilation was sufficiently marked in 14 instances (Case 899, five instances; Cases 774 and 684, four instances each; and Case 698, one instance) to cause an alkalosis that resulted in distressing symptoms such as cyanosis, dyspnea, muscle and abdominal cramps and extreme restlessness. These symptoms persisted after the patient had received the usual sedation of sodium amytal grs. vi, orally, when placed in the cabinet, and morphine sulphate gr. $\frac{1}{4}$ hypodermically, at the onset of restlessness. At the cessation of the eighth treatment Case 684 developed moderate tetany, with periodic muscular cramps and spasms and spasmodic contracture of the toes. The pH in this case ranged

[1]NOTE: The determinations shown in this and all other graphs for Weeks 1 to 8 were made before and after each of the first eight febrile periods; that shown for Week 9 was made one week after the eighth treatment; that for Week 13 was made after a five-weeks rest, immediately before the beginning of the second course of six treatments; that for Week 20 was made one week after the second course; that for Week 44 was made one week before the third course of six treatments; that for Week 55 was made three weeks after the third course. The individual cases are indicated in all of the graphs as follows: No. 774····, No. 899—, No. 698– – –, No. 610–·–, No. 684–···–.

from 7.37 to 7.44 and the CO_2 from 46.7 to 34 volumes percent. The tetany persisted for approximately seventy-two hours. During this period calcium gluconate (10 cc. of a 10 percent solution) was given intravenously every four hours.

Alkalosis is not the only possible etiological factor of the tetany; other conditions operating concomitantly may have been responsible. This patient was extremely nervous and restless, had dyspnea, nausea, vomiting, burning of feet, knees, shins and hands, during the entire course of the treatment before the actual tetany developed. These symptoms were not relieved by the administration of morphine sulphate grs. $\frac{1}{4}$, two such doses hypodermically, caffeine sodium benzoate grs. $7\frac{1}{2}$ hypodermically, ephedrine sulphate grs. $\frac{3}{4}$, orally, and two intravenous injections of a 10 percent solution of calcium gluconate, 10 cc. each. The serum calcium content was below the physiological limits (8.6 mgm. per 100 cc. serum) before treatment, but after the febrile period it increased to 9.8 mgm., which would exclude the possibility of a hypocalcemic tetany. This patient also developed an acute but transient nephritis with a high initial nonprotein and urea nitrogen of the blood.

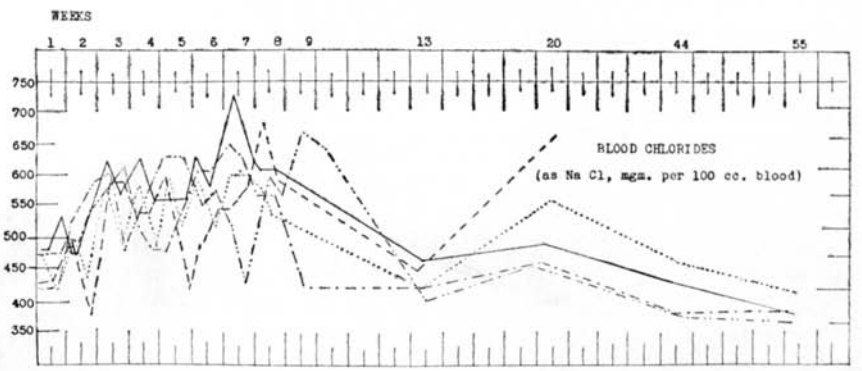
It is probable, however, that the symptoms noted in the other thirteen instances resulted from alkalosis even though there was diminution in the serum calcium content. Similar symptoms were noted in several of the cases used as a comparison, their blood also showing a shift towards the alkaline side, yet the serum calcium content remained within the physiological limits, a slight increase being noted in several instances.

Bazett (1) found that hot baths produced hyperpnea which lowered the CO_2 tension and increased pH to such an extent that tetany resulted. Similar changes due to rise of body temperature during acute fevers and hot baths were observed by Koehler (5). He found an uncompensated alkalosis in a great majority of the cases; two cases developed incipient symptoms of tetany.

The pH and CO_2 contents of the plasma returned approximately to their original levels five weeks after the eighth febrile period. After the second course of treatments (tests made one week after the last treatment), the pH was slightly below the normal range in two cases, and the CO_2 content of the plasma was slightly below the normal range in three. Following the third course (tests three weeks afterward) the pH and the CO_2 content were normal in three cases, one case developing an alkalosis with a pH of 7.52 and a CO_2 content of 43 volumes percent.

Blood chlorides.—The blood chloride changes were somewhat variable after each of the first eight sessions of fever (Text-fig. 2).

In 18 instances there were noted decreases ranging from 11 to 149 mgm. per 100 cc. whole blood; in 10 instances there were increases ranging from 1 to 65 mgm.; and in 11 instances there was no change. During the first two weeks of treatment the chloride content fluctuated within the approximate normal range in Cases 899, 698, 774 and 610, but after that there was decided hyperchloremia, which persisted throughout the remainder of the first course. The same phenomena occurred in Case 684 after the first treatment, and persisted for three weeks after the eighth one. The blood chloride changes in the majority of the cases used for comparison either remained stationary or showed a slight decline after the febrile periods.



TEXT-FIG. 2. Changes in the blood chlorides.

Simpson et al (11), in a study of the blood chemistry of patients subjected to hyperpyrexia treatments, found that the blood chloride values exhibited an average decline of 40 mgm. percent at the end of the febrile period in approximately 80 percent of the patients. The sweat had an average sodium chloride content of 650 mgm. percent. The authors state; "It became apparent that from 20 to 26 grams of sodium chloride were being withdrawn from the blood and tissues during each treatment." On giving liberal quantities of 0.6 percent sodium chloride solution by mouth during treatment they found that the replacing of chlorides lost in the sweat produced an apparently beneficial influence upon the blood chloride content, the majority showing no appreciable change in blood chloride values during or after treatment.

In leprosy the relationship between the sodium chloride intake during treatment and the blood chloride values after it was variable. In six instances (Case 610, three instances; Cases 684,

698 and 774, one instance each), with no sodium chloride intake during treatment, the blood chloride values showed no change after the febrile period. In four instances (Cases 698 and 899, one instance each; and Case 684, two instances), with no chloride intake, there was an increase ranging from 11 to 50 mgm. In eight instances (Cases 899, 610 and 774, one instance each; Case 698, two instances; Case 684, three instances), with no chloride intake, there was an average decline of 65 mgm.

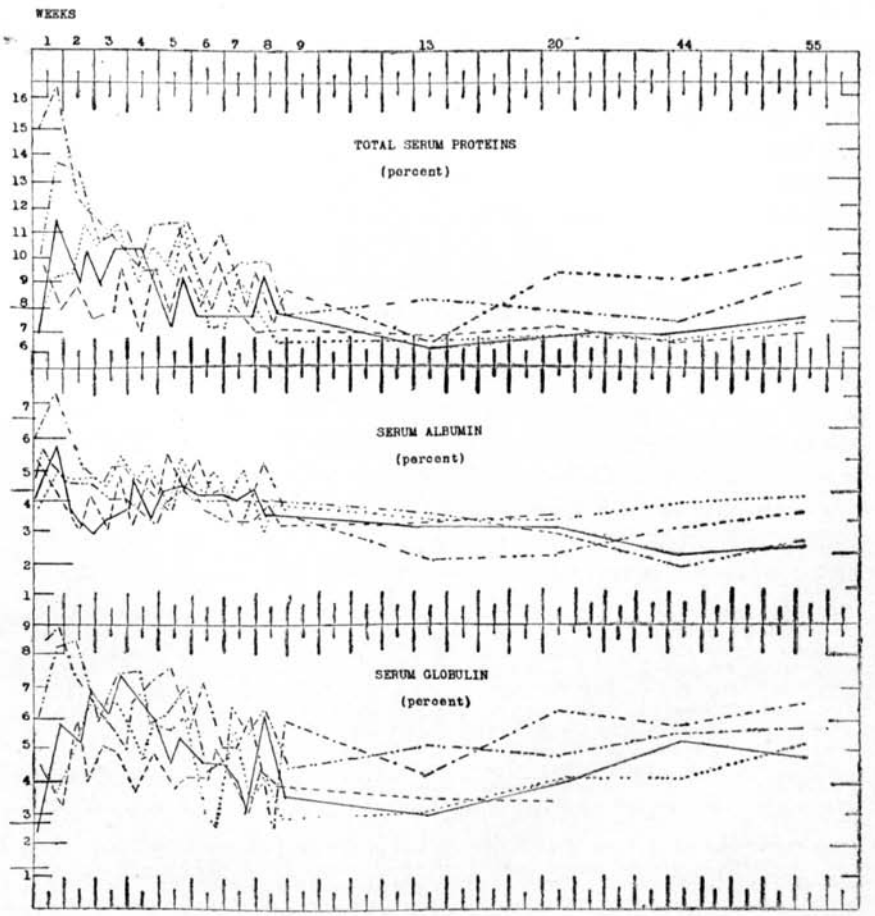
The regulating factor in the adjustment to high temperature is obviously the very heavy excretion of sweat. In leprosy there is impairment of the functioning of the sweat and sebaceous glands, probably due to tissue destruction. However, the patients lost from one to five liters of sweat during each febrile period.[2] A peculiar distribution of the sweat was noted; the upper part of the body may be bathed in sweat, while the limbs may remain dry. In Cases 684 and 610 the secretion was completely suppressed over the surfaces of many diffusely thickened patches, while the surrounding skin sweated freely. After the third febrile period and during subsequent treatments general sweating occurred in all cases. According to the blood chloride analyses the sweat loss was apparently chiefly a water loss. It would be difficult to tell to what extent retarded sodium chloride excretion was due to tissue retention or to a diminution in the salt excreting capacity of the kidneys. Neither the chemical analysis of the sweat nor the urinary chloride output was determined. It seems hardly necessary to add that a tissue will function better under normal conditions than under abnormal ones, as is the case in lepers.

It seems evident that there was an abnormal blood chloride metabolism in these patients during the course of the hyperpyrexia treatments. This phenomenon was apparently a transitory one, since five weeks after the completion of the eighth treatment the blood chloride values were found to be slightly below the normal range in the majority of the cases. After the second course the values were above normal in two of the five cases, but following the third course they were below the normal range in all of them.

Serum proteins.—The findings with regard to the total serum proteins were variable (Text-fig. 3). An increase after the febrile period was noted in 19 instances, a decrease in 13 instances,

[2] The difference in weight, plus the fluid intake, minus the urinary output was taken as the amount of sweat. No deduction was made for the amount of water lost through the respiratory channels.

and no change in 7 instances. No appreciable change was noted in the albumin-globulin ratio in the majority of the cases; the albumin and globulin declined equally. The same changes were observed in nonleprous patients.



TEXT-FIG. 3. Changes in the total serum proteins, serum albumin and serum globulin.

Previous to the hyperpyrexia treatments the total proteins were found to be extremely high in three cases (Nos. 610, 684 and 698). Cases 899 and 774 were within the normal range; after the first treatment they showed an increase. As the number of treatments increased there was a gradual decline in all cases, and at the eighth treatment all values were within the normal range. After the second course the total proteins were normal in four

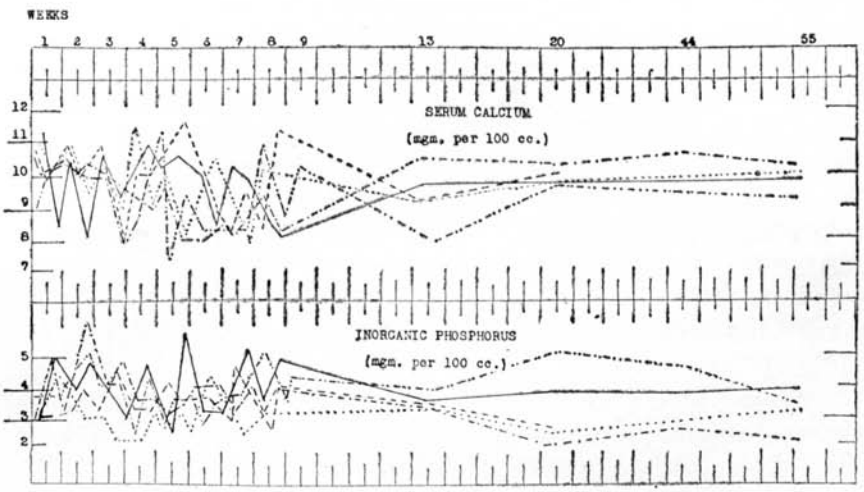
cases, an increase being noted in one. After the third course a slight increase was noted in two of the cases. In all of them the albumin-globulin ratio was abnormally low before treatment and remained practically the same throughout, the ratio averaging 1:0.9.

In a previous study of the protein metabolism in leprosy (19) it was found that certain definite changes in the serum proteins existed. A low albumin-globulin ratio was associated with retrogression, with suggestions that clinical improvement was generally accompanied by a decrease in the percentage of globulin with a corresponding increase of the ratio. Though the marked fall in the total proteins observed during the course of the fever treatment was favorable, yet it seems logical that any improvement in the infection should have been accompanied by a decrease of the globulin fraction. Little or no improvement was noted in the clinical manifestations of the disease at the end of the treatments. It is realized, however, that not enough time has elapsed to allow us to make deductions as to the value of therapeutic fever in leprosy. It is hoped that the induced febrile reactions will have a direct inhibiting action on the growth and development of the invading organisms, thus decreasing infection and tissue destruction and reducing toxemia.

Serum calcium and inorganic phosphorus.—The serum calcium content was appreciably altered after each febrile period, the majority of the cases showing a tendency towards a decline, though in a few instances an increase was noted (Text-fig. 4). In 13 instances the values dropped below the physiological limit of 9 mgm. per 100 cc. serum—7.5 mgm. was the lowest value obtained. Calcium lactate, grs. x three times a day, orally, was administered to all of the patients during the intervening days between treatments. In the nonleprous cases the calcium values fluctuated but remained throughout within the physiological limits 9 to 11 mgm.)

In an investigation of the serum calcium of lepers (18) a diminution in the diffusible form and a rather high concentration in the nondiffusible form was found, although the total content was within the physiological limits. Radiographic studies of the bones of the hands and feet of 48 of the cases showed bone atrophy in 44, the condition manifesting itself either as decalcification or absorption. From a subsequent study (19) it was thought that possibly the bone changes were due in part to a

lack of transference to the tissues of the functionally available and diffusible calcium, and it was suggested that the disturbance in the protein balance noted may in some way affect the degree of diffusibility. Although the diffusible serum calcium was not determined in the present study, no correlation between the decrease in serum proteins and the total serum calcium content was noted. The serum calcium loss may represent an altered distribution in the tissues of the body due to changes in the acid-base equilibrium, a possible factor being the deposition of greater amounts of calcium in the bones.



TEXT-FIG. 4. Changes in the serum calcium and inorganic phosphorus.

Warren (15), in a study of the effect of artificial fever upon hopeless tumor cases, noted marked recalcification of the pelvis and other bones in cases of osteogenic sarcoma, multiple myeloma and endothelioma of the bone marrow. He states, concerning a case of endothelioma of the bone marrow: "The most striking effect from the fever treatment seems to be found in the deposition of calcium in the bony skeleton." Chemical analysis of the serum calcium was not reported.

The changes in the inorganic phosphorus (Text-fig. 4) were somewhat variable. Although hyperphosphatemia was noted in a great many instances, no definite relationship was found between increase of this element and decrease of the calcium, as would be expected in view of the mutual interdependence of the two ions.

In cases of nephritis that present gross retention of nitrogenous waste products in the blood, the phosphorus values are high (9, 16). During the course of febrile therapy the results for inorganic phosphorus and nonprotein nitrogen ran a somewhat parallel course (Text-figs. 4 and 5), which suggests the possibility of a transient impairment of the renal function. A high initial nonprotein nitrogen and a slight increase of the inorganic phosphorus was noted after the first febrile period in all of the nonleprous cases. After each subsequent treatment both constituents fluctuated within the approximate normal range.

Nitrogenous constituents of the blood.—The general effect of the febrile treatments was to bring about an increase in the *nonprotein nitrogen* of the blood, which remained at a high level for three subsequent weeks in four of the cases (Text-fig. 5). After the fourth, fifth and sixth treatments an increase was noted, but the values returned to the approximate original figures before each subsequent treatment. The results of the seventh and eighth treatments were variable, nonprotein nitrogen retention being noted before the seventh or eighth. During the eighth treatment Case 684 developed acute nephritis which persisted for five weeks.

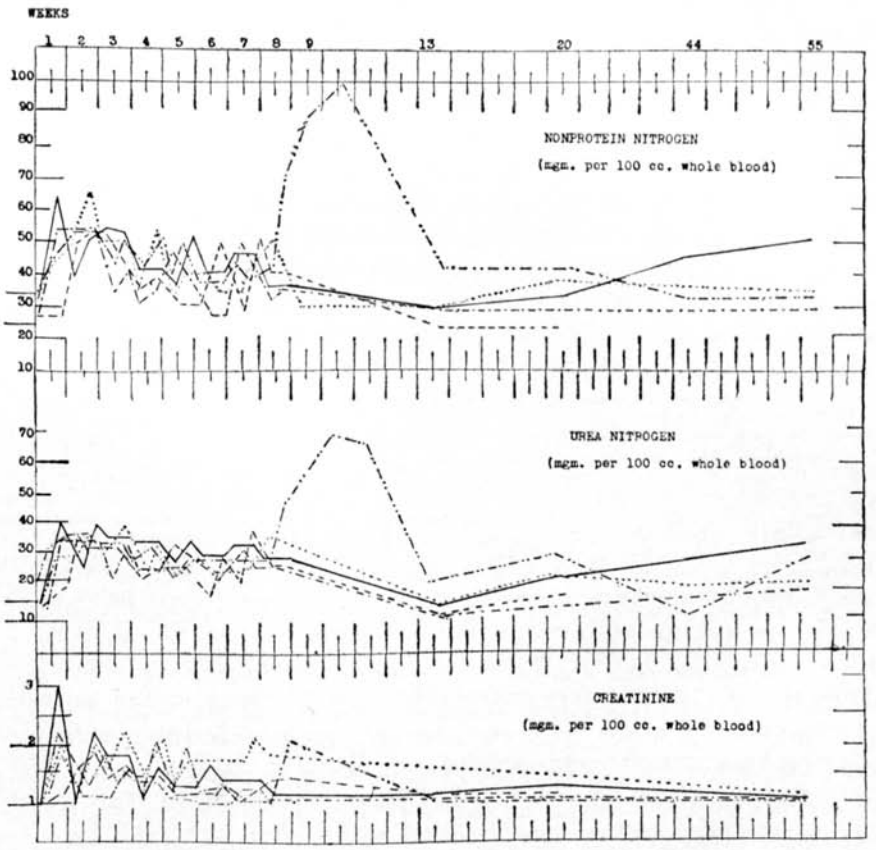
Albuminuria (from 1 to 4 +), hyaline and granular casts (from 1 to 4 +) were noted in four of the cases the day following the febrile period, from the third treatment on; in the fifth case these abnormalities were not noted until after the seventh and eighth periods. In eight instances the urinalyses showed albumin and casts before and after the febrile periods.

The *urea nitrogen* of the blood increased somewhat parallel with the nonprotein nitrogen. The *creatinine* values showed an increase after the febrile periods. In four instances the increase was slightly beyond the maximum normal range.

In all of the nonleprous cases an increase in the nonprotein nitrogen, with a parallel increase of urea nitrogen and creatinine, was noted after the febrile periods. However, in all but one instance the values returned approximately to their original levels before each subsequent treatment. In a few instances albuminuria and casts were found on the days following the febrile periods, but the urinalyses were negative before each treatment.

The increase in nonprotein nitrogen, urea nitrogen and creati-

nine after each febrile period may be due in part to an increase of metabolism resulting from the rise in temperature and the relative oliguria. It was thought possible that the high level of the circulating nitrogen noted during the first three weeks of the treatment occurred as a result of the catabolism of proteins noted during the same febrile periods. On tabulating the results

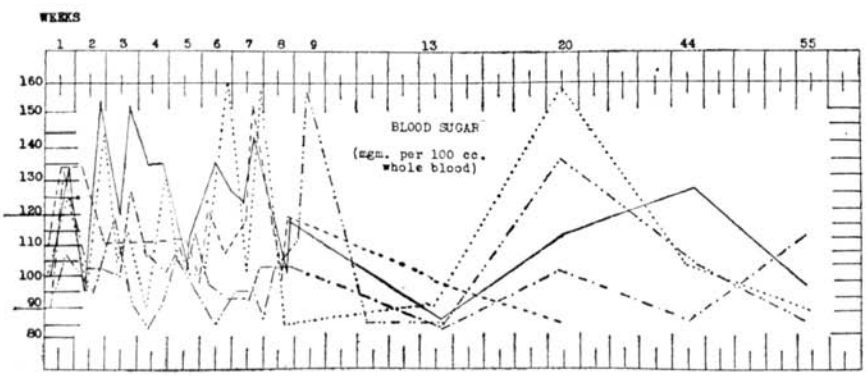


TEXT-FIG. 5. Changes in the nonprotein nitrogen, urea nitrogen and creatinine of the blood.

no parallelism was found to exist between the decrease in serum proteins and the increase in the nitrogenous constituents. Presumably the nitrogenous retention noted was due to inability of the kidneys and the skin to excrete properly the waste products of nitrogenous metabolism. All values returned approximately to their normal figures five weeks after the eighth period. After the second course all values were found to be within the approxi-

mate normal range. After the third course the value was above normal in one case.

Blood sugar.—The blood sugar content showed considerable variation (Text-fig. 6), a marked increase being noted after the first febrile period in all cases, including nonlepers. The values fluctuated within the approximate normal range after each subsequent treatment in Cases 610 and 684. Hyperglycemia was noted in Case 684 for three successive days following the eighth treatment, this patient having developed acute nephritis. Glycosuria was not noted. Marked increase in the blood sugar was noted in Cases 774 and 899 after most of the treatments. The values returned approximately to their original levels before each subsequent treatment. In Case 698 there was a marked increase after the first and seventh febrile periods, fluctuating within the approximate normal range during the intervening treatments. After the second course hyperglycemia was noted in two cases, but after the third course all values were within the normal range.



TEXT-FIG. 6. Changes in the blood sugar.

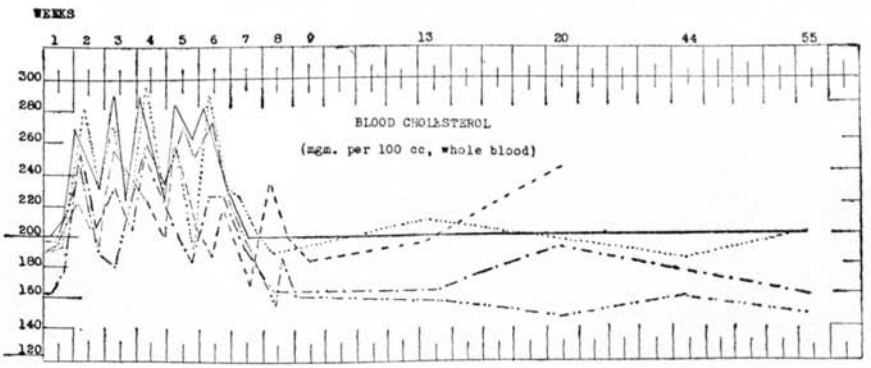
The increase in blood sugar during the first eight sessions of treatment was apparently due to the increase of metabolism resulting from the rise in body temperature. The hyperglycemia noted after the second course is probably due to a defect in the carbohydrate metabolism. Changes in blood chemistry have been ascribed to blood concentration (7, 11), but, because the change for each constituent in our experiment is not constant, this explanation does not seem tenable.

Part of the fluid intake during the treatment periods consisted of one to two bottles (180-360 cc.) of coca-cola. It was thought that

the increase of blood sugar noted afterward was possibly due in part to the ingestion of carbohydrate in this beverage, each bottle containing approximately 18 gm. of sugar (6). It was found, however, that no definite relationship existed between the carbohydrate intake and the blood sugar content.

Blood cholesterol.—Although the results for cholesterol were variable after each febrile period, definite hypercholesterolemia was noted during the intervening days (Text-fig. 7). This condition persisted for six weeks in the majority of the cases, a decline being noted before and after the seventh and eighth treatments. After the second course hypercholesterolemia was noted in one case.

In nonlepers the results were variable, but the fluctuations were within the approximate normal range.

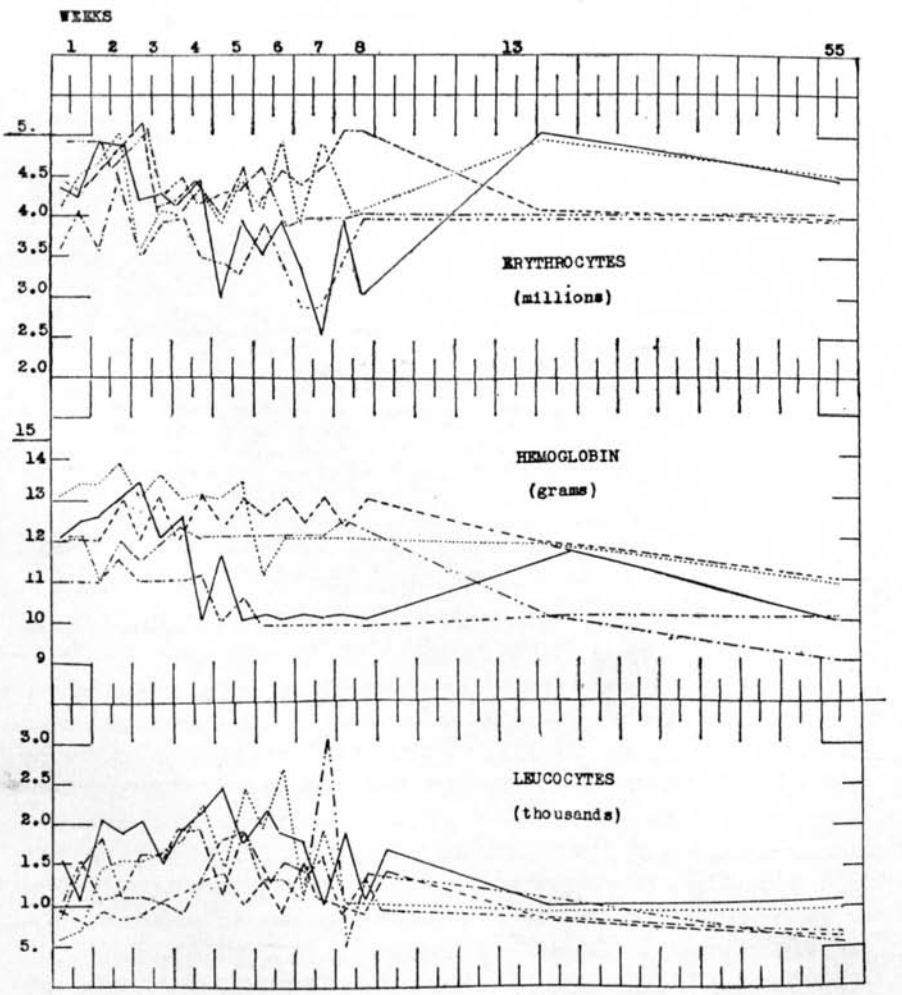


TEXT-FIG. 7. Changes in the blood cholesterol.

In a previous study of the cholesterol metabolism (2) it was found that the cholesterol esters averaged considerably higher in lepers than in normal individuals, with suggestions that these changes were the result of a widespread disorder of function of the body tissues, involving the skin, sweat and sebaceous glands and probably the internal organs. Although the cholesterol esters were not determined in the present experiment, the retention noted in the total cholesterol may be in the ester fraction due to the partial suppression of the excretory function of the skin, or it may be due to a generalized disturbance in the cellular lipoid metabolism due to the increase of metabolism resulting from the rise in temperature, thereby unloading a large quantity of cholesterol into the blood.

Erythrocyte sedimentation time and the numerical and morpho-

logic changes in the blood.—The erythrocyte sedimentation time was determined before each febrile period. All values were low before the treatments were started—20 to 26 minutes, the normal time being 360 minutes. A decline was noted in all of the cases, averaging 10 to 30 minutes during the entire course of treatments. Five weeks after the eighth period one case (No. 774) returned to the original time, 60 minutes. After the second and third courses the times ranged between 15 and 30 minutes in all five cases.



TEXT-FIG. 8. Changes in the erythrocyte counts, hemoglobin and total leucocyte counts.

In nonlepers the sedimentation time averaged higher (90 to 300 minutes). As treatment progressed the sedimentation time corresponded with clinical improvement.

A slight increase was noted in the number of red blood cells and in the hemoglobin content after each febrile period, while during the intervening weeks there was a gradual decline (Text-fig. 8). It is possible that this decline was due to lack of sunshine and exercise consequent upon confinement of the patients in the isolation wards during the entire course of treatments.

The leucocytes tended to increase after the febrile periods, although in a few instances a decrease was noted. There was increase in the neutrophiles, chiefly in the staff cells and occasionally in the juveniles, probably due to circulatory stimulation. The eosinophiles, lymphocytes and monocytes decreased.

The blood Wassermann and Kahn reactions remained negative in two instances, became negative in one instance (2+ Kolmer and 3+Kahn at the outset), and became less positive in one instance (a 4+ Kolmer to 3+, and 4+ Kahn to 1+); in the fifth case a 2+ Kolmer was reversed to negative and a negative Kahn to 1+. While we are encouraged by the serological improvement noted, we realize that the number of cases treated is too small to justify drawing any conclusions.

SUMMARY AND CONCLUSION

A study of the physiological and biochemical changes resulting from the production of artificial fever in an air-conditioned hypertherm was made on five lepers with different grades of involvement by the disease. For comparison, similar studies were made on three nonleprous cases of gonorrhoea and two of syphilis.

Marked changes in the acid-base equilibrium were noted, resulting in an uncompensated CO_2 deficit, one case developing a moderate alkalotic tetany. There was diminution of serum calcium, not noted in nonlepers, with suggestions that the loss may represent an altered distribution in the tissues of the body due to changes in the acid-base equilibrium, though a possible factor may be the deposition of greater amounts of calcium in the bones. The increase of inorganic phosphorus did not parallel the decrease of serum calcium.

There was a marked reduction of the total proteins, which were unusually high before the febrile treatments were started. Both the serum albumin and serum globulin were decreased

equally, the ratio averaging 1:09 in all of the cases during the entire course of treatment. In nonlepers the total proteins, albumin, and globulin fluctuated within the approximate normal range.

There was a definite retention of the nonprotein nitrogen, urea nitrogen, blood chlorides, and cholesterol, accompanied by albuminuria, hyaline and granular casts. In the nonlepers albuminuria and casts occurred after the febrile periods, but no retention of the blood constituents mentioned. It is suggested that there was impairment of the renal function, with partial suppression of the excretory action of the skin during the course of febrile therapy. Phenolsulphophthalein renal function tests failed to show evidence of damage to the kidneys as a result of the treatments.

The erythrocyte sedimentation time remained practically the same during the entire course of treatments, averaging 10 to 30 minutes in all of the cases, the normal time being 360 minutes.

The hemoglobin and red blood cells showed a gradual decline during the course of the treatment. It is possible that this decline was due to lack of sunshine and exercise consequent upon the patients' confinement in the isolation wards. There was an increase of the polymorphonuclear leucocytes.

The changes observed in the nitrogenous constituents of the blood and in the chlorides, inorganic phosphorus and cholesterol during the first course of treatments were transient phenomena, since all values returned approximately to their original levels five weeks after the eighth febrile period. One week after the second course of treatments blood chloride retention was noted in two cases, hyperglycemia in two cases and hypercholesterolemia in one case. Obviously these changes become important if treatment is pushed close to the limits of physical endurance. The various conditions in which there is a definite contraindication to the use of fever therapy in leprosy are too numerous to list here. However, progression of leprosy to the point of depletion of physical resistance would, it seems, be one of the contraindications because such a patient would be unable to withstand the vascular changes brought about by this treatment. Other contraindications would be renal insufficiency, extensive scarring of the skin surface and destruction of the sweat glands. The treatment being strenuous, it is necessary to use caution in the selection of cases. It is suggested that a careful physiological and biochemical study

should be made on the patient before such treatment is undertaken, and that the blood urea nitrogen, blood sugar and blood chlorides should be determined at intervals during its course.

It is desired to make acknowledgments to Surgeon O. E. Denney, former Medical Officer in Charge of the National Leprosarium, and Senior Surgeon T. B. H. Anderson, former Medical Officer in Charge of the U. S. Marine Hospital, New Orleans, for suggesting the work here reported; to Doctor Sam H. Black for making the renal function tests, and to the laboratory staff of the U. S. Marine Hospital, New Orleans, for making the leucocyte counts, erythrocyte counts and the urinalyses.

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