FEVER AND THE WATER RESERVE OF THE BODY*

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INTRODUCTION

During the course of continued intravenous injections of glucose in dogs[1] and man[2] described elsewhere, fever was observed under certain conditions, namely, when the rate of sugar injection was sufficiently in excess of the tolerance limit to produce a marked glycosuria with its concomitant diuresis; when the rate of water administration was less than the rate of diuresis and when these conditions were sustained until the animal or man had lost a certain weight by dehydration. Chills were also observed to occur under the same conditions after the body temperature had begun to rise. Both chills and fever were seen to subside when enough additional water was administered. In the experiments on dogs, the rates of sugar administration were controlled by one motor driven pump, the rates of water injection by another pump. The urine was collected and measured continuously by a catheter retained in the bladder which emptied into a graduated cylinder. The animals lay constantly on the platform of a scales, sensitive to 10 grams. Under these conditions the water balance was subject to absolute control and gains or losses of 10 grams or more in body weight were readily detectable. In this way, fever and chills could be made to come and go at will during the course of a single experiment.

The most obvious explanation was that after a sufficient quantity of water had been abstracted from the body, there was not enough left to sustain the normal processes of cooling by evaporation through the lungs (and the skin in the case of man), and that the animals suffered a true thirst fever produced in an unusual way. The view was also expressed that the actual removal of water from the body might not be essential and that the mere presence of a sufficient quantity of extra

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1. Woodyatt, R. T.: Studies in Intermediate Carbohydrate Metabolism. Harvey Lectures, 1915-16, p. 326.

2. Sansum, W. D.: Rapid Reduction of Intraocular Tension in Glaucoma. J. A. M. A. **68:** 1885 (June 23), 1917.

sugar in the blood and tissues might serve to bind water in a physico-chemical union which would render it unavailable for evaporation at the normal body temperature.

However, various other explanations could be formulated. It might be held that during the rapid injections of glucose an increased oxidation of sugar contributed to the end result, or that the process disturbed a nervous heat regulating "center" or that the sugar set up changes of one type or another in the cells, with fever as a secondary consequence. As a matter fact, the literature of sugar and salt fevers, beginning with Finkelstein[3] in 1908, contains discussions of all these possibilities without reaching a common decision. The literature is clear, however, in showing that sugar and salt fevers disappear when enough water is administered resembling in this respect "inanition" fever of the new-born, which as Crandell[4] showed is due to thirst. The later writers on salt fever, Heim and John[5] and Peteri,[6] clearly interpret salt fever as a result of decreased evaporation of water due to the hydropigenous (or edema producing) action of salt (sodium chlorid) in the blood and tissues. Nearly all of the literature on this subject has been contributed by the pediatricians and the fevers in question have usually followed single doses of salt or sugar by the alimentary or subcutaneous route in infants. Although fever following single intravenous injections of sugar in adults[7] had been reported before our own experiments, there was, on the other hand, enough difference between the methods of producing salt and sugar fever as described in the pediatric literature and that which we describe that at first it was not clear that we were dealing with the same phenomenon. Early failure on our part to confirm the production of fever by single subcutaneous, alimentary or intravenous administrations of sugar in adult dogs or man, suggested that we were not. But it was later found that this could be done consistently in dogs if the animals were made sufficiently thirsty beforehand. The uniform success of certain pediatricians in producing salt fever in babies suggests that they also have worked regularly with thirsty animals.

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3. Finkelstein, H.: Ueber Alimentäre Intoxikation. Jahrb. f. Kinderh. **68**: 693 (Dec.), 1908.

4. Crandell, F.: Inanition Fever. Arch. Pediat. **16**: 174 (March), 1899.

5. Heim, P. and John K.: Pyrogene und hydropygene Eigenschaften der Physiologischen Salzlösung. Die Bedeutung und Behandlung Exsiccation. Arch. f. Kinderh. **54**: 65, 1910.

6. Peteri, I.: Beiträge zum Pathologischen Wesen und zur Therapie des Transitorischen Fiebers bei Neugebornen. Jahr. f. Kinderh. **80**: 612 (Dec.), 1914.

7. Bingel, A.: Ueber Salz- und Zucker-Fieber. Arch. f. exper. Path. u. Pharmakol. **64**: 1, 1910.

Our own experiments appeared to offer a very good method of producing and allaying fever in the laboratory under conditions more susceptible to control than any method heretofore used, and it was thought advisable to test its limits as a method. The experiments herein described were undertaken primarily for that purpose. It was also thought desirable to employ the method to investigate further into the mechanism of this type of fever and chills in the hope that light might be thrown on the mechanism and possibly the rational management of fevers and chills in general, particularly the toxic fevers, such as typhoid, the mechanism of which has not yet been settled. Several points bearing on these questions are elaborated in the discussion. The question presents itself as to whether all ordinary clinical fevers are not due in the last analysis to a deficit of free water in the body.

EXPERIMENTS

These were designed to determine:

1. How high the temperature of the body can be driven by the technic in question.

2. Whether or not an increased combustion of glucose is a contributing factor.

3. Whether the fever is due to a primary effect of the sugar on the water of the body or whether it is secondary and dependent in any way on a nervous "center" or nervous heat regulating mechanism.

4. Whether it is necessary actually to remove water from the body or whether molecules of sugar within the body can produce fever by their mere presence.

The experiments show that the body temperature can be driven to remarkable heights by this method. Fevers of 111 F. are readily produced, and in one case the body temperature rose to 125.6 F. Fevers of 111 F. were produced by means of salt (NaCl) and by lactose, showing that the increased combustion of glucose is not a necessary factor, which was the conclusion to be anticipated in view of the fact that diminished heat loss and not increased heat production (or supply) is known to be the determining factor in all fevers, that is to say, a great increase of heat production alone does not cause fever because normally a great excess of heat is disposed of automatically by increased cooling. The experiments show that sugar is capable of causing fever by its mere presence in the body under certain circumstances, but that no quantity of sugar which can easily be introduced will cause fever unless the water reserve of the body is for some reason sufficiently low to begin with. Finally, sugar fever can be

produced in dogs which have been rendered poikilothermic by severing the cervical cord, and therefore these fevers are in no sense dependent on a nervous heat regulating mechanism.

EXPERIMENT 1.—A female bull-terrier, weighing 9.3 kilos, was injected intravenously, with a 36 per cent. glucose solution, at the rate of 15 gms. of glucose per kilogram of body weight per hour, for a period of ninety minutes. During this time the animal received 614 c.c. of the glucose solution (containing 221 gms. of glucose) and passed 1,230 c.c. of urine, containing 68.4 gms. of glucose; a retention of 152.6 gms. The fluid output exceeded the intake by 616 c.c., or 66.2 c.c. per kilo. The temperature (vaginal), which was 102 F. at the beginning of the experiment, increased to 102.5 F. by the end of the first hour. A severe chill began twenty-one minutes later and the dog was covered with a woolen blanket. Nine minutes later violent convulsions began and the temperature was found to be 111.2 F. The convulsions became so violent that it was necessary to stop the injection. The urine ceased to flow and thirteen minutes later the dog died with a temperature of 125.6 F., the highest animal temperature that we have been able to find on record. The rise of temperature after the cessation of diuresis amounted to 14.4 degrees.

A postmortem examination was made immediately after death in the presence of Prof. H. G. Wells. The blood was turbid. The red blood cells were crenated to a marked degree. The heart was uniformly dilated to the limit of the pericardial sac. The kidneys and liver were in a state of "cloudy swelling." (Note that in spite of the loss of 66.2 c.c. of water for each kilogram of body weight, with crenation of the red cells, the parenchymas of the liver and kidneys, though dry to the touch, had the appearance of "cloudy swelling.")

EXPERIMENT 2.—The course of this experiment was similar to that of the above, except that no covering was thrown over the animal at the onset of the chills and the diuresis and temperature rise were not so marked.

The dog, weighing 16.9 kilogram, received a 36 per cent. glucose solution, at the rate of 15 gm. per kilogram per hour, for ninety minutes. During this time the fluid intake was 1,029 c.c. and the urinary output 1,470 c.c., a dehydration of 441 c.c. or 27.8 c.c. per kilogram. The temperature, which was 100.4 F. at the beginning of the experiment, rose to 109.4 F.

In previous experiments with glucose injections at the rate of 3.6 gm. per kilogram per hour it was shown that only about 0.6 gm. per kilogram is actually burned. However, the amount of combustion might increase somewhat with the higher rate of injection. Accordingly, increased combustion of glucose might be advanced as an explanation of the abnormally high temperature. We have never been able to give glucose at the rate of 15 gm. per kilogram per hour and maintain the water balance, because the heart is not capable of propelling the necessary volume of fluid. Consequently, we have not been able to determine the rate at which glucose actually burns under these conditions. But we have given 10 gm. per kilogram per hour for a period of seven hours, maintaining the water balance, without the advent of a rise of temperature. (The injection of glucose at rates above 2 gm. per kilogram per hour, will be discussed in a paper on "Intravenous Injections of Glucose at Higher Rates," now being prepared.)

We also performed two experiments, dehydrating with hypertonic sodium chlorid-sodium carbonate solutions, to ascertain how high a temperature might be obtained by employing crystalloids which do not burn in the body.

EXPERIMENT 3.—A female bull-terrier, weighing 10.4 kilograms, was given intravenously 753 c.c. of a 1.4 per cent. sodium chlorid—1 per cent. sodium carbonate solution, over a period of three hours. During this period the dog passed only 255 c.c. of urine. There was, therefore, no absolute dehydration. The temperature, which was 102.2 F. per vagina at the beginning, did not change. The concentration of sodium chlorid was therefore raised to 5 per cent. During the next two hours and thirty-five minutes the dog received 800 c.c. of this new solution and passed 1,875 c.c. of urine. During the course of the five hours and thirty-five minutes of the total injection, the dog received 1,553 c.c. of fluid and passed 2,130 c.c. of urine, a net output over intake of 577 c.c. or 55.5 c.c. per kilogram. Convulsions began and the injection was stopped thirty minutes before death. The temperature rose from 102.2 F. to 113 F. A rise of 9 degrees occurred after the cessation of urinary flow.

Excessive muscular activity during the convulsions might be suggested as a cause of the high temperature. To eliminate this factor a similar experiment was planned and the animal fully narcotized with ether at the first signs of chill, thus preventing the advent of convulsions.

EXPERIMENT 4.—A dog, weighing 10.4 kilograms, received, for a period of three hours, 718 c.c. of a 5 per cent. sodium chlorid—1 per cent sodium carbonate solution, and passed 1,005 c.c. of urine. The fluid output exceeded the intake by 287 c.c. or 28.2 c.c. per kilogram. The first slight twitchings due to a beginning chill began thirty-eight minutes before the close and were immediately stopped by the anesthetic. The temperature rose from 101.3 F. to 111.2 F.

Fever in Poikilothermic Dogs.—In order to determine whether the temperature changes during these experiments were in any way grossly influenced by a nervous mechanism, several dogs were rendered poikilothermic by sectioning their spinal cords between the sixth and seventh cervical segments. These dogs were also observed for manifestations of chills. Several experiments were made before the results were satisfactory. Following section of the cord, the body temperature adjusts itself to that of the environment and, at ordinary room temperature, it falls steadily and only becomes constant again at a deeply subnormal level. Under such conditions glucose injections may fail to start diuresis. If diuresis does occur, and it is possible to dehydrate in the usual way, the body temperature may rise materially and still the final temperature may remain markedly subnormal so that one could not then speak of having produced fever in the absolute sense. Again, if the attempt is made to keep the body temperature from falling too low by means of heating appliances, there is danger that fever may be pro-

duced accidentally by the external heat, and it requires elaborate equipment to maintain an operating room constantly at the desired temperature. The simplest method, and one that proved entirely practical, was simply to swathe the animal in cotton or blankets immediately after the operation. In this way the temperature may be kept constant for hours at a level only slightly below the normal.

EXPERIMENT 5.—The spinal cord was sectioned as described above. During the next four hours the dog cooled, spontaneously, to 83.3 F. It was then taken to a room heated approximately to this temperature, 84.4 F. During the next three hours, the dog, weighing 11.5 kilograms, received intravenously 582 c.c. of a 70 per cent. glucose solution, and passed 765 c.c. of urine. The fluid output exceeded the intake by 183 c.c. or 15.9 c.c. per kilogram. The temperature rose from 83.3 F. to 93.2 F., a rise of 9.9 degrees. Slight twitchings of the muscles of the neck and face began just before the death of the animal. Otherwise the usual outward manifestations of chill were missing.

EXPERIMENT 6.—An attempt at dehydration, in an animal whose temperature had been allowed to fall to 77 F., failed on account of the lack of diuresis. An increase in temperature of only 1.8 degree was noted.

EXPERRIMENT 7.—In this experiment the cord was severed as before. A covering was placed over the animal to prevent too great loss of heat. In the course of three and one-half hours from the time of the operation, the temperature gradually fell to 95 F., where it remained constant for four hours. During the next four hours the dog received intravenously 752 c.c. of a 61 per cent. glucose solution and passed 1,640 c.c. of urine. The fluid output exceeded the fluid intake by 888 c.c. or 71 c.c. per kilogram. The temperature rose from 95 F. to 106.7 F., an increase of 11.7 degrees. There were no external manifestations of chill and no convulsions.

These experiments prove that the fevers in question are not dependant on a nervous mechanism.

DISCUSSION

General Principles.—Because of its high specific heat, water is capable of absorbing large quantities of heat, thus preventing sudden high temperature rises in the cells.[8, 9, 10, 11] (It is a noteworthy fact that those tissues in which most heat is produced contain the highest percentage of body water.) Having absorbed heat from its sources of production, water, because of its fluid nature, is capable of distributing the heat equally throughout the body and carrying the excess to the surface where it may be given off. Water then acts as a buffer in high temperature changes, and as a vehicle of heat within the animal body.

8. Mathews, A. P.: Textbook of Physiological Chemistry, New York, 1916.
9. Henderson, L.: The Fitness of the Environment, New York, 1910, p. 80.
10. Stewart, G. N.: Manual of Physiology, New York, 1914.
11. Hunt, E. H.: Regulation of Body Temperature in Extremes of Dry Heat. J. Hygiene **12**: 479, 1912.

Rubner,[12] Wolpert[13] and Zuntz[14] have established that, in a normal body, as heat production increases, heat elimination by radiation, conduction and evaporation also increase, but that the percentage of heat dissipation by evaporation continually increases as more heat is produced. In other words, normally the loss of heat through evaporation fully compensates for that which cannot take place through radiation and conduction in order to preserve the normal temperature. In fever, however, this is not true. Krehl and Matthes[15] found that during fever, although there was usually an increase of heat elimination by radiation and conduction as well as by evaporation, the loss by evaporation was not sufficient to maintain a temperature equilibrium as in a healthy body. This failure of evaporation to compensate for the loss of heat which cannot take place through radiation and conduction would indicate that something hinders the evaporation of water in fever. Either the total supply of water runs out or the water becomes more firmly bound in the tissues and less available for evaporation.

Further investigations show that when the compensatory loss of heat by evaporation is hindered, hyperthermia results. This has been demonstrated by Sutton[16] who subjected human beings to high temperatures in an atmosphere which contained enough moisture to prevent evaporation. Similar results were observed by Haldane[17] in miners working in warm, damp mines. That most fevers are caused by increased atmospheric temperature, and moisture is of course out of the question. This is true only in cases of sunstroke, heat prostration or the like.

How then may evaporation of body water be checked in other ways? One method of accomplishing this purpose lies in the actual removal of water from the body to the extent that not enough remains to carry off the excess heat. Theoretically, if all the water should be removed from the body the specific heat of all the tissues would be reduced, and with no means left of quickly conveying it to the surface heat would accumulate in the tissues of the body and a high pyrexia

12. Rubner, M.: Die Beziehungen der Atmosphärischen Feuchtigkeit zur Wasserdampfabgabe. Arch. f. Hyg., 1890.

13. Wolpert, H.: Ueber den Einfluss der Lufttemperatur auf die im Zustand anstrengenden Körperlicher Arbeit ausgescheidenen mengen Kohlensaure und Wasserdampf beim Menschen. Arch. f. Hyg. **26:** 32, 1896.

14. Zuntz, N.: Ueber die Wärme Regulierung bei Muskelarbeit. Berl. klin. Wchnschr. **33:** 709 (Aug.), 1896.

15. Krehl, L. and Matthes, M.: Wie entsteht die Temperatursteigerung des fiebernden Organismus. Arch. exper. Path. u. Pharmakol. **38:** 284, 1896.

16. Sutton, H.: The Influence of High Temperature on the Human Body, Especially with regard to Heat Stroke. Path. and Bacteriol. **13:**62, 1908.

17. Haldane, J. S.: The Influence of High Air Temperature. J. Hygiene **5:** 494, 1905.

would result. This, of course, practically is an impossibility, for a certain amount of water must be present in order that chemical reactions may take place, but less extreme water deprivations, as confirmed by clinical and experimental evidence, inevitably lead to hyperthermias of various degrees.

The researches of Hunt[11] on the effects of prolonged perspiration indicate that there is a large reserve of water in the body tissues which is called out in emergency. Though a large amount of water may be lost without any change in temperature, this investigator believed as a result of his work, that exhaustion of the reserve water would have the same effect as prevention of evaporation by increased atmospheric moisture. So far as we are aware, he did not subject this view to direct experimental test. The present experiments do exactly this thing, and the results are in complete harmony with Hunt's conception.

Sugar Fever; Salt Fever.—This brings us to the discussion of sugar and salt fevers as described by the pediatricians. In 1899, Floyd Crandell[4] in an article on inanition fever credits McLane of New York with having first described the phenomenon of fever which develops in the new-born prior to the establishment of the regular flow of breast milk and subsides thereafter. McLane called it inanition fever, believing that the solids of the milk were what allayed it, but Crandell showed that water alone was equally effective, and that the condition was not due to inanition, but to thirst. Similar observations were made by Erich Mueller[18] concerning a form of fever which Halberstadt saw in infants undergoing changes of diet. In 1906, Schaps[19] reported that subcutaneous injections of small quantities of isotonic sugar or salt solution caused fever in normal infants reaching a crest in 8 to 10 hours to disappear within 24 hours. He reported that repetitions of the dose gave weaker results.

We have not seen anything comparable to what Schaps describes and mention it merely in passing as a type of sugar or salt fever which, if it occurs at all, is something different from that which we are here discussing,[20] but in 1908-9 Finkelstein[3] described fever after feedings of 100 c.c. of 12.5 per cent. lactose solution to infants with intestinal disorders. Other sugars and also salts produced the same results. Finkelstein's solutions were strongly hypertonic, his doses were large and his results have been amply confirmed. He made the

18. Mueller, E.: Durstfieber bei Saüglingen. Berl. klin. Wchnschr. **47**: 673, 1910.

19. Schaps, L.: Salz und Zucker Injektion beim Saügling. Gesellsch. f. Kinderh. **23**: 153, 1906.

20. The febrile reactions observed by Schaps and others with isotonic salt solutions have since come to be considered as due to the use of water which was not freshly distilled.

observation most significant in the present discussion, that these fevers could be made to disappear entirely by the administration of tea and even water alone. Thus, Finkelstein saw another kind of fever in infants which, like those described by McLane and Halberstadt, yield under water administration. However, Finkelstein was not clear as to the mechanism of his sugar and salt fevers, and ventured the opinion that they arose from "injuries to cells" caused by the physico-chemical effects of the sugar or salt. Finkelstein thought the cells were injured by physicochemical effects of the sugar or salt rather than by chemical effects, and that much is important. Following Finkelstein a number of communications on the same subject appeared which confirmed the facts but confused more than they clarified the question of mechanism, except the writings of Heim and John,[5] and of Peteri.[6] In summing up the literature in the light of his own observation, Peteri, in 1914, concluded that infection played no part, that external conditions of the atmosphere had been excluded, that the immediate causative factor is desiccation and that the height of the fever attained is in inverse ratio to the body weight. All of these conclusions are in perfect accord with our own reading of the literature, and the results of the present experiments bring proof of their correctness.

Heim and John concurred with Finkelstein's observation that sugars and salts operate to produce fever by their physicochemical effects, which is obvious, for when fever is produced by intravenous injections of lactose, every gram of the lactose given is recoverable unchanged in the urine. The lactose molecule has not been altered. It has done its work as a molecule. But Heim and John went further. Instead of saying that the sugar or salt acted in some unknown physicochemical way on the cells causing the cells in some other unknown way to produce fever, thus begging the question, they suggested that the molecule (of salt) enters the cell and increases the affinity of the cell for water and that it does it in this way. Salt molecules have an affinity for water, and if several hundred of them migrate into a cell, the cell containing them becomes endowed with an increased affinity for water just because it has more salt in it.

This is the conception which Hofmeister first expressed in explanation of the power of a salt in suitable concentration to increase the swelling of colloid jellies. Thus salt in the body holds water in the body by its "hydropigenous" (or edema producing) tendency. As a result, the elimination of water through the lungs and skin falls, cooling is retarded and the body becomes overheated by the continuance of its own metabolic fires. And, it may be added, that as the body warms up more and more, the metabolism becomes faster and faster; a vicious circle is established.

It is unnecessary in this place to delve further into the nature of the affinity of molecules of salt or sugar for water, or to discuss theories of the character of the physico chemical unions of salts or sugars and water in general. It is enough that salts and sugars generally do tend to hold water in association with themselves, and that these substances when added to a beaker of water increase its boiling point and retard its evaporation at any given temperature and pressure. The same may occur in the body. As previously pointed out, the work of the pediatricians with salt fever has been conducted on infants which were in all probability considerably dehydrated to begin with, for as Peteri noted, the heights of the fevers resulting from sugar or salt administrations appear to be related in inverse ratio to the body weight, while fluctuations of body weight are determinated largely by the water balance. Moreover, water stops the fever. Our own experiments demonstrate sharply that single large injections of sugar do not, as a rule, cause fever unless the animal is first depleted in water. Therefore, it seems clear that Hunt is right — that there is normally a reserve of water in the body; that a certain fraction of this may become bound by sugars or salts added to the body, but that this binding of water will not ordinarily exhaust the whole free water reserve and determine fever unless the water reserve has been depleted beforehand by actual removal of water from the body as by continued elimination through the lungs, skin, urine or bowels without replacement.

We believe that the discussion up to this point shows that "inanition" fever of infants, the fever seen by Halberstadt in infants during alterations of diet, sugar and salt fever in infants, in adults and in animals, are all thirst fevers due to a retarded evaporation of water caused by exhaustion of the body reserve of water available for evaporation at the normal body temperature. One cannot help asking the question: How many more of the fevers which we know in the clinic can also be drawn into the same category?

A PHYSICOCHEMICAL THEORY OF FEVER

We have entertained the following proposition:

Fever, *the symptom* as seen in typhoid, malaria, pneumonia, tuberculosis, rheumatism, measles, serum reactions, proteose intoxication and all ordinary febrile diseases, except insolation and the like, may mean a deficit of "free" water in the body. By the term "free" water we would convey the idea of water in states comparable to those of liquid water at from 20 to 40 C. and ordinary pressures. As A. P. Mathews points out in his book on Physiological Chemistry, 1915, pp. 190-191, the works of Eötvös, Ramsay and Shields and Armstrong, show that

in liquid water at from 20 to 40 C. there probably exist several kinds of molecules ranging in formula from $(H_2O)_2$ to $(H_2O)_4$. But in any case, in the present connection "free" water is used to suggest liquid water, capable of absorbing excess heat from the cells, conveying it via the blood to the surfaces of the body and there dissipating it by evaporation, all at the normal body temperature.

Over against "free" water the body contains "bound" water. By this term is meant water molecules associated in the form of hydrates with molecules of other substances such as salts, sugar, protein, etc.; also, of course, water in true chemical combination, but especially the hydration water in colloids. This would correspond to the water reserve of Hunt. It is assumed that the "free" water tends to be in equilibrium with the "bound" water, and that there is a tendency toward the maintenance of a certain "free" water concentration in the blood more or less analogous to the hydrogen ion concentration of the blood, or the blood sugar concentration. When a certain quantity of "free" water is eliminated from the body, its place is filled by more water liberated from the hydrate reserves, and when an excess of free water is taken into the body it is stored as hydrate water or eliminated from the body.

As the colloids are extremely sensitive and prone to change in their capacity to hold water in response to the subtlest chemical and physicochemical influences, it is easy to conceive how the maintenance of a uniform "free" water concentration in the blood might be susceptible to a certain degree of vasomotor nervous control. Thus, the vasomotor nerves, by constricting blood vessels in the liver and causing a relative asphyxia in the liver may increase the production of acid in that organ and so liberate more free glucose from its storage form — glycogen. In an analogous way vasomotor nerves might cause colloids to take up or release more water by causing changes of cell metabolism through variations in the blood supply as needs arose. But the same thing could be accomplished directly by physicochemical and chemical agencies without the assistance of nerves, and nerves could not regulate temperature unless there were free water and responsive cells for the nerves to influence.[21]

It is proposed that in the ordinary febrile diseases, such as typhoid, tuberculosis and others, the symptom fever is due to a deficit of "free" water resulting from an abnormal tendency on the part of the colloids of the body to bind water. The poison of the disease leads to changes of the cell colloids and increases their hydration capacities, so that they

21. The reader will note that we are discussing fever and the means of the body to prevent hyperthermia or excess of heat; we are not discussing other phases of the problem of regulation of the body temperature.

tend to take up and bind more water. The effect of this on the "free" water of the body is thus the same as that of thirst or the introduction of salt or sugar into the body from without.

It would follow from the above that if we measured the "free" water of the blood in fever, it would be found low even if the total water content of the body were high. It is known that the blood as a whole does commonly become concentrated in fever, but as yet we have no ready method of measuring the "free" water fraction, although means by which this might be accomplished suggest themselves. It would also follow that the cells should be found swollen, the secretions concentrated, etc., which, of course, is the general rule in fever (cloudy swelling of the parenchymatous organs). The thirst during fever and the sudden release of water in the form of urine and perspiration when fever ends by crisis point directly to an abnormal binding of water during the period of elevated temperature. Everyone is familiar with the remarkable emptying out of water via the kidneys and skin which may follow the crisis in a case of pneumonia. Liters of water may thus be liberated in a few hours, giving visible proof of the water retention of the febrile stage. Finally it would follow that if enough water were introduced into the body during fever to saturate the increased affinities of the colloids and provide an excess of free water, then fever should disappear entirely. Now it is possible by copious water administration to lower high grade fevers and to make low grade fevers disappear. The value of plenty of water in fever, and especially in the management of tuberculosis, is too well recognized to require discussion, but probably no one has yet daringly pushed the administration of water in fever to the ultimate limits which might be necessary to ascertain whether every fever can be made to disappear entirely if enough water is given.

The question as to whether it would be good for every patient who presents the symptom fever to eliminate this symptom by means of copious water administration if that were possible, is a question that has been raised repeatedly by friends to whom the present views have been presented. We may be pardoned, therefore, if we emphasize the fact that this question is not under discussion in the present paper. The first objective is to determine whether the symptom fever can or cannot be controlled in this way in a large percentage of cases, and the wisdom of doing so if possible would then remain to be determined by sufficiently numerous experiments in various special types of cases. It is quite conceivable that in some cases the tissues might be so badly poisoned that they would partially liquefy if sufficient water were supplied, and still leave no "free" water available for evaporation at 37 C. The administration of water might then be pushed until mas-

sive edemas or general anasarca supervened before a reserve of free water could be established, or it might prove impracticable to accomplish the desired result at all. These are questions to be answered by experiments.

Up to the present time we have conducted three experiments in pneumonia patients in all of which the body temperature returned to normal within twenty-four hours with the administration of eight liters or less of water. Several observations on diphtheria cases were indecisive, fever persisting in one case after the administration of ten liters of water. A dog poisoned with diphtheria toxin, on the other hand, ran a persistent temperature between 104 and 105 F., until given a large intravenous injection of 3 per cent. glucose solution, during which the temperature fell to normal within five hours. Other work is in progress. So far the results are considered as indecisive.

In closing, attention is invited to the recent work of Lillian Moore,[22] who repeats the experiments which have formed the entire basis for the conception that there are nervous "heat centers" in the brain which, when stimulated, may cause fever.[23] Her results were negative and she draws attention to the absence of any sound experimental support for the current teaching that ordinary fevers are due to derangements of any demonstrable nervous mechanism. She points to the need for a physicochemical theory of fever. The theory outlined above may, therefore, serve to fill a gap. It has at least the advantage that all of the factors which enter into it are concrete things that may be subjected to measurements, and it should be capable of sharp proof or disproof by well designed experiments without recourse to opinion. Whatever the outcome of such experiments, they will, perhaps, add something to our knowledge of the problem.

22. Moore, Lillian: Normal Temperature Variations and the Temperature Effects of Operative Procedures. Am. J. Physiol. **60**:24, 1918. Relation of the Corpus Striatum to the Regulation of Body Temperature. Am. J. Physiol. **46**: 253, 1918.

23. The Regulation of body Temperature. Ed. J. A. M. A. **71**:1139 (Oct.), 1918.