CHANGES IN BLOOD CONCENTRATION WITH SPECIAL REFERENCE TO THE TREATMENT OF EXTENSIVE SUPERFICIAL BURNS*

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Among the nutritional requirements of the body that of water holds a prominent place. Normally, the capacity of the organism for storing water is very great. The body usually possesses an available store of water which exists for the most part in the muscles and skin although all tissues undoubtedly share in this function. When for any reason water is withheld or withdrawn from the body the different tissues and organs vary markedly in their water loss. Thus, the fatty tissues, the brain, heart, and bony structures lose relatively little water as compared with the muscles and skin. More than one-half of the water lost is given up by the muscles without apparent injury to either structure or function. The same is probably true for the skin.

On the other hand in water loss the condition in the blood is quite different. It is an axiom in physiology that the composition of the blood is constant. Comprehended in this statement is the recognition of small fluctuations in either direction induced probably by the organism in its attempt to maintain the equilibrium of the circulating medium. Under normal circumstances the stability of blood composition is remarkable. This constancy of blood composition may be regarded as one of the most fundamental requirements of the organism in its endeavor to safeguard the environment of the cell. As proof of the general proposition just cited one has only to think of the constancy of blood sugar content, of the urea of the blood, of uric acid, of the stability of the acid-base equilibrium, and of the small variations in inorganic constituents, as calcium, magnesium, sodium and potassium.

Attention, however, is particularly called to an entirely different aspect of blood composition. Normally, the water content of the blood constitutes one of the body's constants. Attempts to alter the water content of the blood by introduction of even large volumes of fluid have failed to change appreciably blood composition. The water regulating mechanism is adequate to make the proper compensation quickly. It is only when this mechanism is overwhelmed either experimentally or as a result of disease that marked changes in blood concentration occur. Either dilution or concentration effects may then be observed, although, in general, from studies thus far carried through concentration is more commonly encountered than is dilution.

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The literature on the subject of blood concentration has been reviewed under the title of Anhydremia by Marriott W. McKim: Physiol. Reviews, 1923, vol. ii, p. 275.

In the blood, concentration to even a moderate degree results in recognizable symptoms. The first indication noted is impairment of the circulation. When water loss becomes great the circulatory deficiency is magnified. The thick, sticky blood finds difficulty in its passage through the capillaries. It becomes an inefficient oxygen carrier, resulting in partial asphyxiation of the tissues. In consequence, there may be alteration in the metabolic processes, and when blood concentration has reached a certain high level a disturbance in the heat-regulating mechanism occurs: the temperature, at first, elevated, falls and vital activities are suspended.

Before discussing further the problem of blood concentration it may not be out of place to consider the question how to measure changes in blood concentration. Of all the constituents of the blood only the red corpuscle fails to pass rapidly through the capillary wall. From this viewpoint it would appear that the measurement of hæmoglobin content should serve as an excellent indicator of changes in blood concentration. This procedure, however, is not entirely free from possible sources of error since in various diseased conditions it is well recognized that hæmoglobin content varies greatly especially over extended periods of time. Moreover, even in short time intervals new corpuscles may be poured into the blood stream or masses of corpuscles may be held in certain restricted areas. Again, " when a condition of severe anhydremia has lasted for a number of days a decrease in the concentration of hæmoglobin and of serum protein occurs even though the body weight and the blood volume determinations may indicate a further loss of water (Lust, Marriott). This may be taken as indication of destruction of blood corpuscles and of serum protein. The experiments of Gürber on frogs, of Utheim on rabbits and Keith on dehydrated dogs shows a decrease in the total number of red blood cells in the circulation, when the diminished total blood volume is considered in connection with the cell counts and protein concentration. As a result of this destruction of the blood constituents an abnormally low cell count, hæmoglobin and serum protein contents of the blood are often observed following a restoration of the blood volume of fluid administration. It is thus seen that determination of the cell count, hæmoglobin or serum protein may at times fail to indicate accurately the degree of anhydremia. The same may be said of the determination of total solids. The measurement of blood volume taken together with the determination of the other constituents mentioned supplies the necessary data for the estimation of the degree of anhydremia."

On the other hand, where it is desired to follow changes in blood concentration at frequent intervals the usual blood volume methods are inadequate or too cumbersome to fulfill the experimental conditions. A consideration of this problem over a period of years has convinced the writer that for the purpose of observing blood concentration changes during short intervals of time the hæmoglobin method is unsurpassed by any other method yet proposed, provided experimental conditions are adequately controlled, that small fluctua-

tions are disregarded, and that due consideration is given to possible changes in the number of red corpuscles.

Clinically, severe blood concentration may be encountered when water is refused for prolonged periods as exemplified in cases of mental derangement. Individuals exposed to the high heat of the desert or subjected to the heat of boiler rooms or mines (Haldane) often show marked blood concentration. Vomiting induced by any cause may be productive of severe blood concentration. This is especially true for infants with pyloric stenosis since little water is absorbed from the stomach and relatively little reaches below the pylorus. High intestinal obstruction leads to the same result.

In persistent diarrhœa much water may be lost to the organism through the stools. In Asiatic Cholera and certain forms of diarrhœas in infants such loss is peculiarly marked and may be productive of blood concentration to a degree sufficient to lead to death. In infants especially severe blood concentration is likely to occur, partly, from the fact that they have a high water requirement which may not be covered since they are dependent upon others for their water supply, and, partly, for the reason that infection may induce refusal of food, vomiting and diarrhœa with a subsequent concentration of the blood. In cases of infantile toxemias, so-called, it is generally exceedingly difficult to determine whether concentrated blood initiates the clinical symptoms or whether concentrated blood must be regarded as secondary to some other change in metabolic processes. Certain it is, however, that in many of these cases if blood concentration can be restored to the normal level the condition of the infant is usually greatly improved and soon regains the normal state.

It is well recognized that in war gas poisoning the outstanding feature of the pathological state is the markedly concentrated blood. In certain fulminating cases of influenza a similar condition is presented and in extensive superficial burns concentrated blood may be chiefly responsible for the clinical symptoms evoked. In eclampsia and in surgical shock the blood is generally concentrated above the normal level.

Experimentally a concentrated blood may be induced by restriction of water intake, by sweating, by the action of certain drugs, as pilocarpine, cantharides, saline cathartics, by proteose, histamine, by administration of sodium chloride or urea by mouth or by the intravenous injection of sodium chloride, urea, glucose, saccharose or lactose.

The composition of the blood when highly concentrated shows various changes such as increased viscosity, and the non-protein nitrogen is generally augmented which may be explained in part by the functional disturbance of the kidney induced by the dehydrated blood and in part by an increased destruction of protein. Sugar of the blood may also be above normal. This finding is a common occurrence in other conditions associated with a lowered blood volume as in shock (Cannon). It may also be induced under a variety of circumstances in which there is vaso-constriction or a diminution in the oxygen-carrying capacity of the blood (Araki). Acidosis, as indicated by

diminished alkali reserve, carbon dioxide content and bicarbonate combining power, is a prominent feature of a highly concentrated blood, which, however, rapidly disappears when the blood volume is restored to the normal level. Acidosis therefore must be regarded as a secondary manifestation induced without doubt by the failure of the circulation. When the kidneys are affected acid phosphates may be retained which is undoubtedly an additional factor in the production of acidosis.

With a highly concentrated blood there may be evidence of a distinctly impaired functional capacity of the kidney. The kidney only occasionally shows structural changes. All evidence of renal impairment disappears with the restoration of a normal water balance. This fact leads to the conclusion that the renal insufficiency is purely functional, probably the result of the inability of the kidney to separate a normal urine from a concentrated blood.

The blood pressure may be high or low; usually, however, it is well maintained. In shock, of course, and in Asiatic Cholera it may be very low. One reason why dehydration of the blood does not cause a significant fall of pressure is perhaps because the increased viscosity prevents that condition which might be expected to occur with a decreased blood volume.

In most of the published discussions relative to changes in blood concentration apparently little attempt has been made to differentiate these changes and correlate them with the types of reactions calling them forth. For example, in conditions of clinical anhydremia no distinction is made between the state existing in water starvation and that induced by extensive superficial burns and yet there must be a vast difference in the significance to be attached to the two conditions. This is especially prominent when attempts are made to restore the blood to a normal level of concentration. In the case of anhydremia induced by water deprivation simple administration of water rapidly restores the blood to its normal condition whereas in anhydremia from superficial burns the restoration to normal is much more difficult. It would appear that in the two examples cited fundamental differences exist in the mechanism leading to the anhydremia. There are at least two ways in which blood concentration may be induced. In the first place one may imagine that a fluid, nearly simple water, or a dilute salt solution, in composition, leaves the blood-vessels in response to the proper stimulus, resulting in a more concentrated blood, a dehydration, a desiccation as it were. Or again by a different type of mechanism, or perhaps as a result of a different form of stimulus, fluid of the nature of dilute plasma rather than of salt solution passes through the vessels leaving behind a blood concentrated above normal. That both these two types of change occur will be pointed out later.

The impetus for our own studies in changes in blood concentration came from experience with war gas poisoning in which it was shown that the intensive irritation of the respiratory tract by the gas called forth a massive œdema which is associated with very marked blood concentration. The intensity of blood concentration under these circumstances became so great that the heart was unable to push the thick viscid blood through the capillaries at a rate

sufficient to aerate properly the tissues, resulting eventually in tissue asphyxiation, fall of temperature, circulatory failure, and death. Death was ascribed to the change in blood concentration rather than to pulmonary œdema. From a wide experience the impression was gained that within certain well defined limits concentrated blood, although not compatible with proper nutrition, is not necessarily a serious condition. Beyond these limits, however, life can be maintained for only a short interval. To put it differently—blood concentration up to 125 per cent. of the normal value is not serious but when 140 per cent. has been reached danger enters and life is not possible for long if this limit is maintained. These relatively wide variations which may occur without serious consequences may be regarded as another example of the factors of safety resident in the organism. That death is due to blood concentration rather than to pulmonary œdema can be tested experimentally by gassing two animals with the same concentration of gas for equal periods of time. Both animals will develop pulmonary œdema to the same degree and both will present the same blood concentration picture. If one is treated so as to maintain blood concentration below the danger level recovery will follow, whereas the untreated animal will die. In neither case does the treatment materially change the lung condition, at least during the critical period.

Another striking example of this type of blood change is seen in certain cases of influenza, the alteration of concentration of the blood being invariably associated with a fatal outcome. From the standpoint of pathology these cases of influenza present a lung picture difficulty distinguishable from that of gas poisoning. From these two facts, together with the similarity in the manner of death, one may be perhaps warranted in concluding that the mechanism called into play in the two instances is either the same or else closely related.

It seems a far cry from gas poisoning and influenza to superficial burns and yet in the latter instance the blood may be markedly concentrated and if sufficiently so undoubtedly plays a large contributing rôle to a fatal outcome. The proof for this statement lies in the fact that if by any means blood concentration can be prevented or abolished the chances of recovery in any of the conditions cited are very materially increased.

Our experience with the treatment of the systemic effects of superficial burns was gained as a result of observations carried through on more than twenty victims of a theatre fire in New Haven.

The patients were admitted into the New Haven Hospital † in the early evening and at once received first aid treatment and were sent to the various wards. Blood concentration estimations were made at once. From the clinical standpoint the patients were divided into two groups (a) those seriously burned (b) those not so seriously burned. The blood concentration of the first group was above the danger level, namely, more than 125 per cent. Those

† Through the courtesy of Dr. Samuel C. Harvey, Surgeon-in-Chief in the New Haven Hospital, opportunity was afforded to us to conduct this investigation. (The details of the work are published in the Archives of Internal Medicine, 1923, vol. xxxii, p. 31.)

less seriously burned were below this level. The correspondence between the severity of the clinical picture and the blood concentration was perfect. In the first group all patients were placed upon the danger list, in the second none were included in this list. The first point of significance in this investigation is that the determination of blood concentration which takes only a few moments serves as an indication of the gravity of the patients' condition and also points out definitely the type of treatment necessary.

In our opinion the serious condition in burn cases is the concentration of the blood and treatment should be directed to reduce this concentrated blood to a more fluid state. The systematic treatment of these burn cases consisted simply in the forcing of fluids, water by mouth when possible, when the patient could not coöperate because of unconsciousness, fluid was injected under the skin, directly into the blood, by the rectum, etc. The quantity of fluid taken in varied from four to eight litres daily.

In a day or two on this treatment the blood concentration fell gradually and the patients' condition steadily improved. All patients so treated recovered although of the group of those severely burned the vast majority could be regarded as poor risks.

"Although from figures and other data relative to these observations one is apparently justified in concluding that restoration of blood concentration is of prime significance in burn cases, nevertheless, to the sceptically inclined there are at least two points at which the above conclusions may be attacked. In the first place, one may assume that fluid intake has only an inappreciable influence on blood concentration, that fluid is excreted from the body almost as rapidly as it is ingested. All the available literature on the subject supports such an assumption. One point, however, must be emphasized, namely, that in nearly all instances in which this hypothesis has been put to the test the organism employed was that of a normal person. Herein lies the crux of the whole matter. It is utterly fallacious to predict the behavior toward water administration of an organism suffering from lack of water from observations made on an organism with a sufficiency of water supply. It is quite true that partaking of large volumes of water by normal man or dog does not perceptibly alter the concentration of the blood. So long as the water regulating mechanism of the body is normal such a result is to be expected. On the other hand, when an animal has been deprived of water for a sufficiently long period, blood concentration becomes markedly increased. Water administered under these circumstances causes a rapid fall in the concentration of the blood. The experiments by Keith and by Underhill and Kapsinow cause us to reiterate the statement previously made that it is fallacious to draw conclusions relative to the abnormal organism when these inferences are largely based on observations on normal persons, and they furthermore dispose of one of the points of attack cited above.

A second point of attack centres in the query, " Did the fluid intake in these cases actually influence blood concentration or would blood concentration have returned to the normal without such aid?" To answer this question

absolutely control experiments would be necessary. Such a control, however, is obviously lacking. The question receives a partial answer from the experiments of Keith and our own cited above together with our experience with war gas poisoning. Death may follow, but blood concentration is not restored to near normal limits under conditions of water lack unless sufficient fluid has been introduced. We believe, however, that the question is fully answered by our experience with one burned patient treated outside the hospital. A victim of the same fire, this patient was cared for at his home by his own physician. Special attention to forcing of fluids was lacking. This case was especially badly burned and presented the typical signs and symptoms characteristic of intoxication from burns, chief among which was an active delirium, it being necessary to take measures to keep the patient in bed. This was succeeded by a period of collapse and unconsciousness, death being anticipated. After a period of eight days, consultation with the physician resulted in the active forcing of fluids. Previous to fluid administration (two litres of 0.7 per cent. sodium chloride solution subcutaneously) the hæmoglobin value was 163 per cent. A few hours after the salt solution had been given the patient regained consciousness, became rational, and was capable of coöperation in taking of fluid. Blood concentration fell rapidly and the patient went on to recovery. The point to be emphasized here is that this patient on the eighth day after being burned still had a blood concentration equal to that in some of our own serious cases on the first day. The presumption is valid that if this patient's blood concentration would have returned to normal of itself it should have done so within a period of eight days, an interval during which none of our own treated patients maintained such a concentration.

From such data it would appear that water intake is responsible for the decrease in blood concentration observed in our cases, and it is quite safe to assert that without such water introduction blood concentration would not have taken the decided fall observed in every case. We believe, therefore, that the observations recorded justify the conclusion that water introduction in sufficient quantities to restore blood concentration to within normal limits is of paramount importance in the treatment of burned cases. As a result of this type of treatment, it may be stated that only two patients gave any evidences of symptoms characteristic of intoxication in burns. In these cases unconsciousness at first prevailed; this, however, disappeared after restoration of the normal blood concentration. In all the other cases, the patients presented no untoward symptoms, such as delirium, unconsciousness, gastro-intestinal disturbance, hæmoglobinuria, albuminuria, etc. Whether such facts are to be interpreted from the viewpoint that restoration of blood concentration prevented the development of conditions responsible for these symptoms or that fluid introduction caused prompt elimination of toxic material so diluted as to be innocuous or both, remains a problem the solution of which can be determined only in the future. At any rate, from either viewpoint it would appear that fluid introduction is a rational method of treatment for extensive superficial burns."

Since the initial experience gained from the victims of the theatre fire we have had occasion to treat a number of burned cases in the New Haven Hospital and have been consulted on cases in various parts of the United States and in general the results obtained from the treatment have been very encouraging.

How is it that the same type of mechanism is called into play in two such diverse pathological conditions as war gas poisoning and superficial burns? A little thought will show that the difference is apparent rather than real—the seat of action is the factor which makes the apparent diversity.

In a consideration of the development of pulmonary œdema in gas poisoning I wrote the following—" the lethal war gases are all substances eminently irritant to living tissues and it must be accepted that the irritation produced by a gas is the initial step in the development of œdema. In response to the first irritative stimulus tissue fluid finds its way to the injured area in an apparent attempt toward repair or alleviation of the injury. It is conceivable that if damage to the tissue is only slight such a procedure would result in the passage to the damaged area of only a small quantity of tissue fluid. According to this view the degree of response with respect to the local deposition of tissue fluid would be in direct ratio to the extent of injury. On the other hand, it is equally plausible to assume that this reaction may reach a breaking point at a certain degree of stimulation whereby the whole mechanism governing the exudation of tissue fluid is thrown out of control so that the response to the stimulation becomes overwhelming. Under these conditions a reaction which in its initial function may be regarded as beneficent eventually becomes a direct menace to continued existence on the part of the mechanism as a whole, merely by interposing difficulties in the way of respiration and circulation." If in this quotation one substituted for war gases, heat as the irritative stimulus playing upon the skin the mechanism is entirely similar. With burns, fluid rushes to the skin, resulting, if the skin is unbroken, in either œdema of the part affected or blisters; or if the burn is more severe fluid drips from the raw surfaces. Our experience in burned cases leads one to believe that the quantity of fluid lost in this way during the first few hours after the injury may be very large, in fact sufficiently great to account for the rapid blood concentration which occurs.

Other abnormal conditions which produce a marked concentration of the blood are Asiatic Cholera; shock, whether arising spontaneously from trauma or toxemia, or evoked experimentally by peptone or histamine; dysentery; acute arsenic poisoning and peritonitis.

If one analyzes these pathological states it must be quite evident, that the one underlying factor common to all with the exception of shock, is that an extensive inflammatory reaction is prominent, acting usually upon a more or less restricted area, as the respiratory tract, the skin, the alimentary canal, the peritoneum, etc. All are areas plentifully supplied with capillaries.

In order to understand the nature of the mechanism producing the blood concentration a word as to the character of the fluid lost from the blood is

essential. From my own observations on gas poisoning it becomes apparent that this fluid partakes of the nature of plasma, diluted plasma, as it were, containing somewhat less protein than plasma, but otherwise of practically the same composition. The fact that significant quantities of proteins are present and indeed the blood proteins, particularly fibrinogen, leads to the view that the irritant factor has changed the character of the capillary wall. In ultimate analysis therefore one may conclude that the direct cause of blood concentration, in the pathological states under discussion, is due to a changed permeability of the capillary wall.

In most of these instances actual loss of fluid to the body has occurred sufficient in amount to account for the concentration of the blood. With shock, however, where no loss of fluid to the body takes place the explanation of the mechanism is not so obvious. Under shock conditions increased capillary permeability may also explain the mechanism involved since the fluid leaving the vessels is plasma (Bayliss, Dale). The toxic substance responsible for the condition acts more or less specifically upon the capillaries resulting in a pouring of fluid into the tissue spaces of the body, thus provoking an exceedingly rapid and marked blood concentration.

From our experience and conception of the mechanism involved in the loss of plasma from the blood a change in capillary permeability is essential—in the loss of salt solution no such alteration is necessary. We believe that any irritative or inflammatory reaction upon any extensive area of mucous membrane may, if sufficiently acute, cause a rapid loss of plasma resulting in blood concentration. In general it is this type of blood concentration which is likely to prove disastrous to the organism. We shall return to this point later.

Blood concentration induced by loss of water and presumably salts only, results in a concentration by a process of dehydration or real desiccation. This is what occurs when sufficient fluid is not introduced as by experimental water deprivation of animals, or clinically in the dehydration of infants. Again intense secretion induced by pilocarpine or purgation by the saline cathartics will cause a rapid blood concentration. It is significant, however, that this process in general does not proceed to the point where a dangerous degree of blood concentration is attained. The concentration approaches the danger line but is not maintained. This, however, is only a general statement and is particularly applicable to the saline cathartics and to pilocarpine. If actual water deprivation is pushed for a sufficiently long period blood concentration steadily mounts and death follows. Such a result, however, can be called forth only by drastic measures.

Blood concentration of this type is obviously of an entirely different nature than that induced by an inflammatory reaction. This becomes quite apparent when attempts are made to restore the blood to its normal concentration. In the former case administration of fluid is all that is essential. With the concentration induced by an inflammatory reaction administration of fluid alone although helpful is not strikingly successful. Why? Because in the latter instance the capillary wall has been modified so that it is no longer

capable to the normal extent of retaining fluid. In other words, in the one type of blood concentration the capillary wall is involved, in the other it is not, at least to an extent capable of measurement.

The potency of the agencies which may play upon the mechanism governing blood concentration are determined in large measure by the fluid content of the body at a given moment. Thus, when an animal has been deprived of water to the point where blood concentration becomes significant even though still within safe limits, the saline purgatives no longer cause purgation. With sodium sulphate and Rochelle Salts no immediate symptoms are in evidence. When magnesium sulphate is employed complete anæsthesia takes places and unless treatment is given immediately death follows. This fact may have a certain clinical bearing in the indiscriminate use of Epsom Salts both before and after operation. The administration of plenty of fluid both before and after operations is in most instances a wise procedure. From this viewpoint if a cathartic is to be used it should be one which by its action does not draw fluid from the blood.

It is also quite probable that shock may be much more easily produced in an organism in which the blood is concentrated than in one when the fluid reserves are normal, for in peptone shock the blood concentration curve is distinctly modified and the poison appears to be more potent.

Another point of considerable clinical significance is the fact that it is much easier to prevent marked blood concentration than it is to change it once it has become established. For the prevention of blood concentration large volumes of fluid are essential administered more or less continuously. In certain instances venesection tends to keep down concentration acting as it were as a stimulus upon the reserves of the body to maintain constancy of blood concentration. In attempts of the past to maintain blood concentration the error in procedure has been that only a single intravenous infusion has been made or repeated infusions at infrequent intervals. The relief afforded has been only temporary since the fluid quickly left the vessels. Administration of fluid should be more or less continuous and it is essential only to attempt to reduce the concentration to the safe limits. This reduction of concentration by administration of fluid or by venesection plus fluid need be practiced for relatively short periods only—it carries the individual over a critical period—a period necessary for restoration of the normal permeability of the capillary wall—in other words the capillary wall repairs itself which takes from twenty-four to forty-eight hours. It is during this period that fluid must be pushed continuously.

In the treatment of burns, therefore, the essential object is to keep the blood concentration near a normal level until the blood capillaries in the skin injured by the heat have had an opportunity to repair themselves and again become capable of holding within themselves the fluid of the blood in a normal manner.