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CONCERNING
THE CAUSATIVE FACTORS AND TREATMENT OF RENAL EDEMA

Senior Thesis
C. Paul Jeffers
1931-32

Introduction -- Definition and Proposed Contents.

Dropsy may be defined as the effusion of serous fluid into the serous cavities and the connective tissue spaces of the body, that is, into what has been called the "lacunar system" by C. Achard. (1) Edema is dropsy limited to the connective tissue; it may be localized, or involve the whole organism, when it is then known as anasarca. This problem of edema, the question of how a cell, an organism, or the body as a whole comes to hold an abnormally large amount of water is but a sub-heading of a still greater question. This is the physiological question which asks why a cell or group of cells in a plant or animal holds any water at all and why under normal circumstances this is so constant in amount.

Edema is a symptom with clinical features that have been well described for centuries, though its mode of production has been the subject of purely theoretical and largely unproductive speculation. Not until a definite function had been assigned to the serous fluids which bathe the connective tissue and fills the lacunar spaces, did it become possible to consider edema as a disturbance of a normal function. Indeed, this paper might well be titled, "Water Metabolism As Regards its Disturbance in Renal Disorders". This normal function is mainly concerned with the regulation of the body fluids which constitute our internal economy. It serves to regulate the composition of the blood, and plays a most effective part in maintaining constant its pressure and volume. The lacunar or "interstitial" fluid, owing to the ease of interchange between it and the blood, either dilutes the substances which are in excess in the blood, in its own elastic volume, or else, utilizing its own reserves, pours out into the blood stream such substances as are needed.

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Edema results from a disturbance of this function, and from an interference with the normal regulation of extravasation and absorption.

It is due to this notion that new paths of research on the pathogenesis of edema have been opened up, and both physician and physiologist have been quick to detect certain important factors in the production of this condition. These are, the retention of sodium chloride, alterations in balance of proteins and of lipoids and variations in the distribution of electrolytes. Although this problem cannot actually be said to have been solved, it can, with the aid of physical chemistry, at least be approached in a scientific manner. These views on the causation have affected treatment considerably. Of all the clinical types of edema that of Bright's disease has been the most affected by this advance in our knowledge. This is, in fact, the type of edema in which the mechanical factors of vascular disturbance plays the least part, and where, on the contrary, changes in the physical chemistry of the body fluids and of the tissues are of greater importance.

In considering, therefore, the problem of renal edema we are undertaking the study of one of the most fascinating chapters in general pathology, where is seen, at its best, the increasing tendency of normal and pathological physiology to rely upon the physico-chemical sciences for an explanation of the vast phenomena of life. Of course the task is still unfinished, and the many researches which we must pass under review are but the foundations of a structure incomplete as yet. (1) (16)

I intend in this paper to, (1) briefly review the history of renal edema from the earlier times to the present, touching on the salient features only, (2) review the principle theories as to the etiological factors of the condition, dwelling more in detail on the work of the past ten or twelve years, (3) discuss the clinical aspects of renal edema, (4) present six cases as typical as possible of the various types, (5) thoroughly discuss modern methods of treatment and (6) to briefly sum up the contents of this thesis and the conclusions I have drawn from a review of the literature.

Historical

To write the history of edema, in so far as its pathogenesis is concerned is to write also the history of dropsy in general.

The connective tissue spaces and the serous cavities both in their physiology and pathology, show a unity of function and disorder which alone justifies their inclusion into one and the same lacunar system. The ancient authors such as Erasistratus believed that all dropsy was due to disturbances of the liver. Galen, denied this, considering that dropsy was due to a disturbance of blood formation, but as he regarded the liver as the principal hemopoetic organ, he admitted that it was always affected primarily or secondarily.

Harvey introduced a new and fundamental factor into the problem by the discovery of the circulation of the blood. Henceforth dropsy became a circulatory disorder. As early as 1622, Lower had produced edema by the ligation of the inferior vena cava and the jugular veins and later, Boerhaave and Hoffman demonstrated the part played by venous disturbances(1)

Following discovery of the lymphatic circulation, disorders of this function were named as etiological factors by Pinel in the last edition of his "Nosography" (1)

The role of what might be termed blood dyscrasia was brought to light by the researches of Magendie, Valentine and Vogel, who showed that when a large quantity of water was introduced into the systemic circulation, interstitial absorption became less active and serous extravasation might occur. (1)

An hydremia was next thought of as a causal factor. Becquerel and Rodier had observed that the blood of cardiac patients contained less albumin than other cases, and attributed this to the loss of albumin through the urine. Meanwhile a new cause for this dyscrasia due to albuminuria had been discovered, and was now held to be the basis of dropsy.

Richard Bright, physician to Guy's Hospital, in 1827 and 1831 established

the connection between dropsy and lesions of the kidney. He described three types of nephropathy, though he was unable to determine whether or not they were three stages of the same disease. These were: the large white kidney, the large red mottled kidney and the indurated and contracted kidney. Previous to this Wells, in 1812, had demonstrated the presence of blood serum in the urine in a case of anasarca following scarletina, by testing with nitric acid and heat. But to Bright belongs the credit of discovering the frequent relationship between albuminuria and those changes in the kidney which constitute nephritis. Since his time, the important cause of dropsy has been the object of innumerable observations and even now the whole question still provides an inexhaustible subject for discussion. (1)

Many authors are of the opinion not only that this form of edema differs essentially from the others by reason of its greater complexity, but that actual differences in pathogenesis separate the various types of edema, and, various eclectic theories have sprung up to account for many obscure phenomena. Eclecticism, however, in explaining biological problems is often but a clever evasion and convenient way of avoiding difficulties. In the case of edema, there are of course, as far as the conditions of its appearance are concerned, obvious etiological differences. Never the less, whatever the clinical conditions, the different varieties of edema have certain features definitely in common. Edema fluid has much (not entirely in cardiac and renal cases) the same composition, it occurs in the same parts of the organism, it produces the same disturbances, and it behaves in the same way under influence of mechanical action, gravity, and excessive intake of water and salt. (1)(15)(28)

Of clearly defined physical or physico-chemical explanations two have assumed special prominence. The first, original with plant physiologists and widely adopted by animal physiologists is the osmotic theory of water absorption. Briefly, according to this theory the body cells are surrounded by a so-called semi-permeable membrane which by definition is one that is

permeable to a solvent but not to all dissolved substances. The movement of water is occasioned by differences in the concentrations of dissolved substances within and without the cell, the water being carried in the direction of the higher concentration. (16)

The second explanation of edema, the pressure theory was first proposed by Cohnheim and Lichtheim in 1877. Briefly formulated, it holds that variations in pressure of circulating liquids such as blood or lymph are chiefly responsible for the variations in the amount of water held by the tissues, in that through changes in pressure the circulating liquids are supposed to be forced through the vessel walls and into the tissues. (16)

As early as 1878 C. Bernard had hinted at the possibility of a central nervous control or brain center for governing the water content of the internal "milieu". (13)

With the advance in physical chemistry, the diminution of the proteins in the blood plasma has come to play an important part in the explanation of certain forms of edema. This part is based on the work of Starling who concluded that a rise in capillary pressure will upset the normal balance between the processes of exudation and absorption in favor of transudation and the blood will become more concentrated, while a fall of pressure will favor absorption and the volume of blood will be increased at the expense of the tissue fluids.

Widal, in 1902 first noticed that a failure to excrete water was associated with a failure also to excrete sodium chloride, in other words a sodium chloride retention. The researches of Magnus Levy and especially of L. Blum and his co-workers have shown that in the pathogenesis of dropsy sodium chloride is not retained simply as a crystalloid molecule but that it is necessary to dissociate the action of the Cl ion from that of the Na ion. (13)

New facts were added to the discussion by the study of colloids and their properties. Martin Fischer who considers edema essentially a problem of colloid chemistry in 1908 believed that the greater absorption of water

was due to a hyperacidity within the tissues, primarily caused by an insufficiency of available oxygen for the tissues.(1)(16)

Eppinger in 1913 found that thyroid extract favors the absorption of edema and since then many chapters on hormonal causes and therapy have been written.(13)(14)

Since the investigations of A.A.Epstein in 1914 it is generally known that the fundamental changes in the composition of the blood in nephrosis consist in(A) lowering of the serum proteins, affecting the albumen fraction more than the globulin, so that there is a tendency toward an inversion of the albumin- globulin ratio,(B) increase of the lipid content of the plasma. Correlated with the increase in plasma lipoids is the presence of double refractile bodies in the urine(Munk) and deposits of double refractile lipoids in the kidney tubules, shown to be esters of cholesterol.(1)(26)

The most recent work has been done by Barker and Kirk(3) and by Leiter(24)(25) in 1930-31.

Finally Kirk of Omaha has conducted a series of investigations in 1931 at the University of Nebraska, College of Medicine, Research Dept. concerning the albumen-globulin ratio,ph of the blood, nitrogen balance and water balance following the experimental bleeding of dogs.(51)

The Causative Factors of Renal Edema.

History teaches us that the views of modern times constantly revert to those points which were regarded by earlier observers as settled, then, there is ample justification for bringing old notions to view.

Calvin and Goldberg(9), in reviewing the relationship of cholesterol and edema, state that; the milky appearance of the serum in certain cases of renal disease was first noticed by Blackwell and Bostock, 1825 -27. Christison demonstrated that it is due to fat in the serum. Port and Chauffard, Laroche and Grigaut, in 1910 - 11 showed that lipid as well as fat caused a milky appearance of the serum, that a marked hypercholesterolemia may be present which is not present in cardiac edema and that patients with marked nitrogen retention had low cholesterol values in the blood. Kaiserling and Orgler in 1902 drew attention to doubly refractile lipoids in the kidneys of patients dying from certain forms of renal disease. Adami and Aschoff proved these doubly refractile lipoids to be the esters of cholesterol.

It has now been established by many different investigators that marked lipemia and lipoidemia(cholesterolemia) are practically constant observations in the nephrotic syndrome, whether in the rare true nephrosis or the more common nephrotic type of glomerulo-nephritis. The only exception is in the extremely emaciated patients. In amyloid nephroses, if patients are well nourished the lipoidemia may be marked, but as most cases of amyloidosis accompany wasting disease, the fat content is not usually elevated. As cholesterol is relatively easy to determine, it has been studied most extensively. In the nephrotic syndrome the blood cholesterol is often over 500mg.%(less than 200 being regarded as normal)

The cause of hypercholesterolemia is not as yet definitely established, there are several different theories.

1. The damage to kidney is primarily a fatty degeneration resulting in doubly refractile lipoids appearing in the tubular epithelium and urine with

resultant hypercholesterolemia.

2. A primary or secondary disturbance of fat metabolism, extra renal, resulting in lipoidemia, and the excretion of the excessive amounts of cholesterol through the kidney, the cause dependant on lipoidemia with renal damage.

3. A low amount of protein in the blood caused by excretion of albumin in the urine, and compensated by a hypercholesterolemia.

4. A primary disturbance of liver function resulting in retention of cholesterol in the blood with resulting renal damage.

Kollert and Finger showed that a reduction of kidney substance does not produce hypercholesterolemia. As the bile in nephrosis is low in cholesterol, they felt that the condition is primarily a disturbance in liver function. Less cholesterol is excreted through bile in nephrosis, indicating a retention type of cholesterolemia, according to Herrstadt(9). A definite liver damage exists as is shown by Knauer's observation on symptomless but definite hypoglycemia, found in nephritic children.

Epstein believes that in nephrosis, both protein and fat metabolism are primary disturbances and that an associated thyroid disturbance occurs with hypercholesterolemia.

Hiller and his co-workers(21) showed that nephritics can burn fat as effectively as normal individuals, and suggest that hypercholesterolemia is due to a disturbance in the mechanism for transferrance of lipoids from the blood to the tissuesdepots.

Lowenthal(9) believes that the lipemia and lipid degeneration of kidney is due to a primary disturbance of lipid metabolism and then the deposition of fat in the renal tubules. He fed rabbits with cholesterol and produced hypercholesterolemia with changes in the kidney similar to those in human lipid nephrosis. He did not produce edema however. Munk(9) stated that cholesterolemia indicates abnormal metabolism and kidney secondary injury, while excreting.

Fishberg(17) expresses the belief that hypercholesterolemia is a compensa-

tory mechanism, that rises as the blood proteins fall in an attempt to maintain colloid osmotic pressure. Barker and Kirk(3) also state that protein fall is accompanied by a rise in cholesterol.

Kollert and Finger felt that if the kidney could excrete the excess cholesterol, no edema would appear, but when lipoids were not excreted edema would follow. Lowenthal stated that lipid retention parallels the formation of edema and excretion of lipid parallels the excretion of water. Bennett and his co-workers (4) maintained that the mechanism of edema formation and hypercholesterolemia cannot be explained but cases of renal edema without hypercholesterolemia are conspicuously absent and they doubt if such conditions can occur. Murphy (33)(34) has recorded observations that the patients with chronic renal disturbance, showing edema, at autopsy had deposits of doubly refractile lipoids in the tubular epithelium of the kidneys and in the urine, while those not having edema did not. The amount of edema and degree of hypercholesterolemia were not parallel at all times. He concludes that a defective fat metabolism is the primary factor and the deposit of lipoids in the kidney is a result of a combination of factors. Maxwell(9) in a detailed study has concluded that although these two factors are usually concomitant, possibly both due to the same pathological lesion, they bear no relation to cause and effect. The most recent observations of Calvin and Goldberg(8)(9) in 1931 seem to uphold this view.

Achard(1) speaks of a lypocytic index of the tissues expressed as Cholesterol Fatty acids. He cites evidence to show that the more fatty acids present in the tissue the more that tissue resists imbibition and the more cholesterol the less the resistance to imbibition.

Senator(55) about 1895 conceived the idea that edema is largely a result of the increased permeability of the capillaries. In a monograph(55) he holds that albuminuria is due to a disintegration and degeneration of the epithelium of the uriniferous tubules which allows for the escape of albumin and globulin from the blood stream.

Many studies have been made since the time of Senator and, logical arguments both pro and con have been proposed. Loeb(28) in his monograph on edema states: recent studies of the circulation especially of the capillaries, bring evidence that the permeability of these vessels is a variable factor which in some way runs parallel to their state of dilatation in response to functional as well as pathological conditions, and that pathological stimulation may cause a still further circulatory change and may in particular call forth an increase in capillary permeability. This permeability is a graded one permitting elimination of different sized particles through the vessel walls. Thus colloid particles of various sizes may leave the vessel wall and fill the interstitial spaces around the vessels. Allevience points to the conclusion that these changes in vascular permeability are important factors in various kinds of edema.

Attempts to explain the causation of edema have nearly always been made from the point of view of local chemical and physical forces involved. The inadequacy of such explanations has become manifest to every student of this subject, especially when only one or two local forces are made to bear the whole burden of edema formation. This is illustrated in the tendency at the present time to explain the formation of edema as due to a disturbance of equilibrium between the osmotic pressure of the proteins of the blood plasma and the hydrostatic pressure in the capillaries.

With the advance in physical chemistry, the diminution in the proteins of the blood plasma has come to play an important role in the explanation of certain forms of edema. In discussing the role played by plasma protein deficit it may be well to combine the earlier works of Starling(46) and the later researches done in what might be called the "Epstein area", since 1927. In reviewing this phase of the etiology of renal edema Van Slyke et al(48) state: Evidence that plasma protein deficit predisposes to edema was first given by the physiological experiments of Starling 1895-96. He measured the osmotic pressure of the plasma proteins and found it at a level of about 30mm., between

arterial and venous blood pressures. Starling pointed out that it is presumably this osmotic attraction of the plasma proteins for water that balances in the capillaries the hydraulic pressure tending to force the fluid out into the tissue spaces, and that when the protein osmotic pressure weakens, because of decrease in protein concentration, undue amounts of fluid are likely to pass out into the tissues. He found that the edematous leg of a dog perfused with Ringer's solution remained edematous, but when perfused with serum the edema fluid was reabsorbed. The salts present, although in molar concentration many times exceeding the proteins, have relatively little effect in controlling fluid diffusion because the salts themselves diffuse freely through the capillary walls.

That proteins are scant in the plasma of many nephritic patients was noted by Bright(1836). Csatory(1891)noted that the deficiency affected the serum albumin more than it did the globulin, so that the albumin:globulin ratio, normally 1.5 to 2.0, frequently fell below 1 in nephritis. These observations have been confirmed and amplified by other authors, whose work has been reviewed by Linder, Lundsgaard, and Van Slyke(27). It was Epstein (1927), however, who connected the observation of plasma protein deficit with Starling's experimental and theoretical work to form an explanation of the cause of non-cardiac edema in nephritis. This explanation, viz., that the decreased osmotic attraction of the proteins for water permits the escape of the latter into the tissues, has been confirmed by the work of Govaerts(1924), of Schade and Claussen(1924) and of Cope(1928) who determined directly the osmotic pressure in the sera of normal subjects and of nephritic patients with and without edema.

As urea retention in nephritis is the sign of a condition leading to uraemia, so is plasma albumin deficit the sign of a condition leading to edema. As, after renal failure, edema is the complication that causes most frequent concern, so is determination of the plasma proteins, after that of the urea

excreting ability, the quantitative chemical examination to which we have come to refer most frequently in judging the condition of patients.

In a report on results from 75 nephritic patients Moore and Van Slyke (32) have shown that when the total protein content, normally averaging 7%, falls below 5.2 to 5.8%, or the albumin, normally averaging 4.3%, falls below 2.3 to 2.7%, or the plasma specific gravity, normally averaging 1.027 falls below 1.0225 to 1.0235, edema is usually present. The figure most closely connected with the edematous tendency appears to be the albumin, but as the globulin usually remains unaffected, the total proteins and the specific gravity, which reflects the total proteins, as a rule both parallel the albumin and show the same correlation with the edema.

While urea retention is a warning, and not in itself apparently the cause of uremia, there is fair proof that plasma protein deficit is an important direct cause of non-cardiac nephritic edema.

As might be expected, the relation between protein deficit and edema formation is not an entirely regular and uniform one. There are other factors which resist or reenforce the hydropigenous effect of plasma protein deficit. With plasma proteins near the level at which their deficit usually produces edema, the latter may be present or not, and may come and go in the same subject, as these other modifying factors exert their influence in one direction or the other. Salt intake is such an influence: a patient with fairly low plasma protein content and edema may lose the latter merely by being put on a salt free regime, although, as Moore and Van Slyke have shown, entire disappearance of edema is infrequent if the proteins are below the above quoted critical levels. There are other less tangible influences. In a patient with tendency to edema barely under control edema may appear after infections or operations, and disappear during recovery. In some instances fever appears to tend to make edema disappear; in others vomiting shows a desiccating effect. And in some cases on the border line edema comes and goes for no observable

reason.

In the first weeks of acute nephritis edema may occur with plasma protein level normal; this edema is due to some influence quite apart from the osmotic effect of the plasma proteins; it may arise from some toxic effect increasing capillary permeability. Again in the terminal stage of hemorrhagic or arteriosclerotic nephritis edema may occur as the result of heart failure.

With these exceptions, the accumulated data indicate that the constant and dominating factor in producing non-cardiac edema in Bright's disease is plasma albumin deficit, the effect of which is only modified in degree by other influences, and that Epstein's application of Starling's theory has been justified by the studies of subsequent investigators. The data presented

The fact that tendency to edema formation is closely related to plasma albumin deficit and relatively unaffected by globulin changes is explained by Govaerts' finding that the albumin exerts four times as much osmotic pressure per gram as the globulin.

The most recent work has been done by Leiter(24) and Barker and Kirk(3) who have conclusively shown experimentally that a low amount of protein in the blood is an important factor in the development of edema in dogs. These authors reduced blood protein by plasmapheresis, that is, the dogs were bled at intervals, the serum discarded and the cells and Locke's solution reinfused. Edema developed in dogs when the blood protein had fallen to 3% or below. The degree of edema could be varied or caused to disappear promptly by raising or lowering the blood proteins. Kirk in a personal communication states that by varying the nitrogen balance of patients in the Peter Bent Brigham renal clinic, edema could be caused to disappear and reappear also. This seems to prove without doubt the factor played by the plasma protein deficit, especially the albumin portion, is of vital importance in the etiology of renal edema.

The action of crystalloids in the causation of edema was at first as-

cribed solely to their osmotic pressure. We now know otherwise and can better define the function of the electrolytes in the exchange between the blood and tissues, and even the part they play in the permeability of the membranes.

Sodium chloride especially has been incriminated in the production of dropsy. Retention was noted in acute nephritis first in 1897 by Bohne(1). In 1902 Achard and Loeper(1) concluded that retention was not solely dependant on changes in the kidney.

In hydropigenous nephritis Strauss(1) found retention of sodium chloride without retention of phosphorous or sulphates; in cases of edema he found a decrease in diuresis after the ingestion of sodium chloride and an increase in chloride excretion when the edema disappeared.

The partisans of the theory of the renal origin of chloride retention sought to explain the edema by simple modifications in the threshold for the excretion of salt and water. In the patient with Brights disease, in accord with this theory, the renal threshold is raised after the ingestion of salt, but does not fall again subsequently. With a salt free diet however, the renal threshold becomes lowered and an excretion of the retained salt again becomes possible.

Achard(1) assumes the existance of extra-renal factors in causing the retention of salt and water -- moreover, Ambard(1) who introduced the term and the conception of a renal threshold, has recently abandoned both, and now thinks the excretion of a substance is dependant on its combination with renal albumins.

Blum(1) in a long series of papers, has emphasized the cardinal role of the Na ion, conversely it has been shown that chlorides, other than that of sodium do not produce edema(2)(23)

The distinction between the effects due to the Cl and Na ions respectively is made possible by the rather delicate study of the metabolism of Chlorides and of sodium. Blum and his co-workers(1) have shown that the ret-

ention of sodium is always accompanied by a water retention, that the loss of sodium by a water loss even in chloride retention. Moreover it soon becomes recognized that the whole mineral equilibrium must be taken into consideration.

In his recent work Ambard(1) attributes the edema of hydropigenous nephritis to be due to a hypochlorhydria of the tissues. He considers that in this affection, the iso-electric point of the albumin is displaced toward the acid zone. As a result hydrochloric acid is lost from the albumin of the blood and tissues, with a lowering of their osmotic pressure and a transudation of water into the lacunar spaces.

As far back as 1908, Martin Fischer had conceived and published ideas based on rather a radical departure from any theories at that time. Since then more work has been done to substantiate the observations of Starling and more to disprove Fischer's points, nevertheless, some of his proofs are so convincing and logical that it is impossible to omit them in a paper of this sort.

Fischers argument and subsequent proofs are briefly as follows. The absorption of water by living matter under physiological and pathological conditions is determined by the colloids contained in it and their state. Lyophilic or hydrophilic colloids are those resulting when the subdivided material is a solvent for the dispersion medium and are biologically important because they constitute the bulk of protoplasm. To discover properties of lyophilic colloids, particularly their relation to water absorption of solvent, Fischer studied the biologically important colloids, fibrin, gelatin, gluten, aleurónat and blood serum. He discovered that these colloids when placed in distilled water all swell some but swell much more in any dilute acid; absorbing in some instances 30 or 40 times their own weights.(16) Within certain limits the amount absorbed increases with the concentration of the acid. The same holds true of alkalies. Further observation showed that addition of any salt to the solution of acid or alkalies reduces the amount that the colloid swells

and this the more the higher the concentration of the salt. When equivalent concentrations of different salts are compared, some are found to be more effective than others, thus the sulphates and citrates are the most powerful. When the effects of basic radicals are compared, Mg, Cu, and Fe are the most potent. Of the non-electrolytes sugars deserve special mention because of their considerable dehydration effect. In addition to acids and alkalies, certain other substances are capable of increasing hydration capacity. Urea, pyridin, and some amines are examples. The hydration produced by these differs from that produced by acids and alkalies in that it is not reducible with salts but is readily reduced with sugars.

What has been said of solid colloids also holds for liquid colloids such as blood serum, fluid gelatin or egg white. The hydration and dehydration can be studied by noting the changes in viscosity. Fischer has further shown by the means above that the various body tissues, eye, muscle, nervous tissue, etc. behave in precisely the same manner as the protein colloids.

The problem of edema is also a problem in colloid chemistry - that of the ways by which the normal hydration capacity of the body colloids is heightened. The whole nucleus of Fischer's explanation is in his statement that the cause of edema resides in the tissues, which become edematous not because water is forced into them, but because they suffer changes which make them suck up water. This is shown by the fact that the severest grades of edema may be produced in the entire absence of any circulation, therefore in entire absence of blood pressure. (16)

An edema is induced whenever, in the presence of an adequate supply of water, the capacity of the tissue colloids for holding it is increased above that which we call normal. Any agent capable, under the conditions existing in the body, of thus increasing the hydration capacity of the tissue colloids, constitutes a cause of edema. Acid accumulation within the tissues brought about either by abnormal production or inadequate removal is chiefly responsible for this increase of the colloids. In this connection, local edemas

following insect bites are of interest. In a number of these stings, formic or other acids are carried into the tissues and by a chemical means, deprive the tissues of oxygen. It is notable that originally and during the period of the greatest swelling, the tissues are white and not red till later when the edema begins to subside. This shows that instead of the circulation determining the edema, that the edema really determines whether or not the circulation shall continue through the affected part. These weals can be mimicked perfectly in the laboratory, with a gelatine plate, fine needle and a small amount of acid.

Circulatory disturbances, generalized or local, conditions decreasing the oxygen carrying power of the blood, as the anemias, various states of inanition, the fevers, chemical changes following death as well as poisons of various kinds which are followed by edema, all represent methods by which the chemistry of the tissues is altered as to lead to an abnormal production or accumulation of acid in them.

Conditions which are capable of decreasing the hydration of protein colloids, decrease edema; while those ineffective in this regard do not do so. Thus, the edema in amputated frogs legs, laid in water are reduced by salts, and this the more, the higher the concentration. This holds for living as well as for dead frogs legs.

A number of specific problems presented by edema as it affects special organs is next considered. The edema observed in a passively congested kidney produced by the ligation of the renal vein is generally believed due to increased capillary pressure and the forcing of fluid into kidney tissue. Ligation of the renal artery with its consequent decrease in blood pressure is followed by exactly the same kind of change. Such a result is explained on the colloid-chemical basis. Whether we deprive an organ of its oxygen supply by preventing the normal efflux of blood or by preventing the normal influx the resulting accumulation of acid is the same and so the organ's colloid

hydration degree is raised, hence the swelling. The idea can be further tested on the liver which besides having a venous blood supply through the portal vein, has an arterial supply through the hepatic artery, the two streams leaving via the hepatic vein. Ligation of the portal vein does not lead to an edema while an extreme grade is produced by ligation of the hepatic artery even though there results herefrom, a fall in blood pressure. Passive congestion edema of the liver secondary to heart disease is really produced through interference with the normal oxygen supply to liver parenchyma. Pulmonary edema is essentially the same mechanism, for the lung has two blood supplies, the pulmonary circuit and arterial blood via the bronchial arteries. Interference with the pulmonary circuit scarcely leads to an edema but such is readily produced by systemic circulatory disturbance.

It remains to account for the accumulation of fluid found in states of edema in the serous cavities and tissue spaces. These accumulations represent dilute solutions of protein. The squeezing off of such dilute colloid mixtures, the transudates, by the more concentrated and solid ones, the edematous tissues, is analagous to the syneresis exhibited by colloids. When heavily hydrated solid colloids are permitted to stand, a thin colloid solution separates after a time. Such separation is not noted in slightly hydrated colloids but is marked in heavily hydrated ones and increases with time. In the same way the severer and more chronic types of edema are most likely to be accompanied by accumulations of fluid in the serous cavities and spaces.

In summing up Fischer's concept of edema it suffices to say, his ideas are that the cause of edema resides in the tissues which become edematous because they absorb free water from the fluids, blood and lymph which bathe them. This is due to the accumulation in the tissues of such products as carbonic and lactic acids which is in turn due to them being placed in a condition of lack of oxygen, in the presence of an adequate supply of water.

Few have been able to agree with the above ideas, in more than a few

details. Loeb(28), Osman(39), and Frisch, Mendel and Peters (18) have criticized Fischer recently in various ways. The general consensus of opinion seems to be that Fischer has tried to make one factor responsible for too many phenomena associated with edema, there is no evidence of an acidemia in the acidosis of nephritis, changes are small -- hardly comparable to the "in vitro" experiments of Fischer, acidosis may be due to the renal lesion and not the cause of it, edema is largely extra-cellular and can be drained mechanically. Lastly, the therapeutic steps advised By Fischer do not work any better(or as well in most cases) as exactly the opposite type of therapy.

Elwyn(13) has recently(1929) revived the role played by hormones in the formation of edema. The most important work has been based on the observations of Eppinger, which will be discussed in the section on treatment, under the thyroid treatment of Epstein's so called "diabetes albuminuricus".

Clinical Aspects

General Characteristics

Edema is manifested clinically by a puffiness or tumefaction of the soft parts, which gives rise to a greater or lesser deformity of the region affected. The skin, is generally of a dull white color, especially true in the edema of renal origin. Sometimes it has a peculiar glistening or waxy appearance and is stretched and thinned. Creases and irregularities tend to be abolished and scars when present appear to be elongated. Edema leads to the disappearance of all the hollows and prominences which give shape to the normal figure. Even in the folds of the flexures, depressions barely exist to indent the swollen integument.

The overlying skin has a more or less sodden consistence, and pressure of the fingers leaves a pit like depression which is very characteristic, and which is most easily produced over a bony surface such as the tibia, the ankles or the cranial vault. On pinching the skin in places where there is a considerable thickness of soft parts, e.g. the internal aspect of the thighs an impression of the fingers is left. This test will render an edema which is not otherwise apparent at once obvious. Where the skin is naturally very firm, such as on the palms of the hands and the soles of the feet, it remains so, and does not show any pitting. In edematous regions, sweating is often found to be diminished and the local temperature slightly lowered. Owing to the distension, striae may make their appearance; excoriations and fissures are sometimes produced, through which fluid may escape, but which serve only too often as ports of entry for infections.

Edema that is of long standing has a firmer consistence. The skin becomes hard, thick and wrinkled like shagreen leather; the orifices of the hair follicles are enlarged, and pigmented or purpuric patches are not uncommon. Pressure of the finger causes little pitting, but leaves small blanched areas, as the skin has an elastic resistance and forms a sort of carapace.

All the underlying tissues are thickened, owing to hyperplasia caused by the chronic irritation; dermatitis, eczema, and a pachydermia of the elephantiasis type often occur.

Renal edema is usually localized at first, but tends later to become generalized. It frequently starts in the face, and is shown by the puffy eyelids on waking in the morning. This has been attributed to the contraction of the orbicularis palpebrarum during sleep, with a consequent slowing of the venous circulation in the eyelids. Edema may, however, appear first in other parts, dependent on certain local conditions such as static position.

The serous infiltration is most marked in those regions where the skin is soft and the connective tissue loose and abundant, as, for example, in the eyelids, around the ankles, on the dorsum of the foot, the internal aspect of the leg, the scrotum, the prepuce, the labia majura, and the back of the hand. The edema in nephritis, having started in the face, appears at the ankles, reaches the legs, and then invades the thigh, scrotum and prepuce (or the labia majura), to spread upwards into the abdominal wall. If the patient is in bed, the lowest parts, for example, the sacro-lumbar region and the buttocks, become the most infiltrated, and form a cushion which becomes indented by the folds of the sheets.

With the progress of the disease, the edema spreads, and becomes generalized as anasarca, and effusions may then occur into the serous cavities. At other times, edema may occur into the viscera, where, if it collects rapidly and in great amount, it may lead to such dangerous complications as edema of the larynx, edema of the lung or of the brain and meninges. Anasarca is extremely common in nephritis, although sclerosis of the kidney without edema may also be observed. It is usually found, of course, in the so called hydro-pigenous nephritis. This embraces all the types of acute nephritis, in which anatomically there is a large white kidney with affection of the tubules. (1)

Special Localizations

A few of the specially localized edemas of renal origin seem deserving of some special mention, they are more rarely seen and doubtlessly are often not recognized.

One of the rarer complications of renal edema is a conjunctival edema which gives rise to chemosis.

Vomiting and diarrhoea are among the gastro-intestinal complications of nephritis. It may be questioned however if edema has any part in these incidents, as they are seen in sclerotic nephritis with hyperazotemia.

Edema of the larynx has only been described since the introduction of the laryngoscope into medicine. Most probably in this localization of the edema there is an infectious element superimposed. As a rule this is a slowly progressive edema though in certain cases it may proceed rapidly to exitus by asphyxia.

Pulmonary edema more often is observed in patients having a cardiac deficiency although there are without doubt cases of it in which the heart is normal(1)

Two types of cerebral edema have been described, dependent upon the localization: a partial edema, which produces a local and transient paralysis passing from one limb to another, an explanation which is certainly open to considerable doubt, and a diffuse edema, which is held responsible for coma and for the symptoms of so-called serous apoplexy. But it is difficult to specify the disturbances which are strictly due to intracranialdropsy, and those more particularly due to edema of the brain itself, the more so since Dickenson and Stewart(1) have described the presence of such edema without clinical manifestations.

Edema In The Clinical Types Of Nephritis

Edema does not appear in all affections of the kidney, not even when

the renal functions are most seriously compromised. Its frequent occurrence has long been recognized in those forms of chronic nephritis termed "parenchymatous" and its infrequency (at least in the absence of heart failure) in the interstitial form of chronic nephritis. Achard(1) separates nephritis into an hydropigenous(dropsy forming) and an uremigenous(uremic) form, including under the former, the greater number of the cases of the old parenchymatous nephritis, and under the latter, the majority of the cases of interstitial nephritis. Widal(1) stressed this distinction by abandoning all anatomico-pathological classification and considering only the functional disturbance. At the same time evolving a theory of the pathogenesis, he distinguished in nephritis the syndrome which he called 'chloruraemic', characterized by the retention of sodium chloride and attributable to the kidney, from the azotaemic syndrome, characterized by a retention of urea and equally of renal origin.

While it is certainly true, as has long been recognized, that a dropsical syndrome is present in certain cases of nephritis and absent in others, and if it is no less true that the dropsical syndrome is necessarily accompanied by a retention of water and sodium chloride, it still remains doubtful whether interpretations based on retention of renal origin are valid. This is a theoretical point to which we shall refer later.

Edema occurs in the acute nephritis that is most often of infectious origin, the classical example of this being scarlatinal nephritis, which is the commonest and the most important. An inflammatory edema, occurring with the exanthem at the onset and noticed in the eyelids, hands and feet, should be differentiated from the nephritic edema which appears later with the albuminuria at about the third or fourth week of the illness, i.e., during the convalescent stage, though it sometimes occurs even later. This is the post scarletinal nephritis. This delayed edema is the only kind which should rightly be included in renal edema; it is white and not roseate, unlike that which accompanies the exanthem at the onset, and may be associated with dropsy

of the serous membranes. Anasarca, after it has become generalised, disappears gradually, though a localized edema may persist for a long time, as in the face. In some forms of scarlatinal nephritis, nothing may be noticed but a slight swelling of the eyelids in the morning, or of the ankles at night. This edema causes no ⁱⁿconvenience and may be easily overlooked, but its recognition is important, as it may be the precursor of serious complications--of edema of the larynx or lungs--or of eclampsia ushered in by vomiting and headache.

There are some forms of acute nephritis where there is no edema. This is so in most cases where the nephritis is due to mercurial poisoning. In this condition, gastro-intestinal disturbances, such as vomiting or diarrhoea are very troublesome. The urine may be scanty or completely suppressed, but there is, however, no edema. Nevertheless, it is possible to appreciate in the cases that recover, that there is a retention of water and sodium chloride in the tissues of the body although there is actually no obvious edema.

Syphilitic nephritis occurring in the secondary stage is clinically of the acute or subacute type. It occurs from the second to the sixth month after the appearance of the chancre; sometimes earlier. It is mainly characterized by the hydropigenous syndrome. The onset may be sudden, with headache, nausea, vomiting, and severe lumbar pain. The urine is scanty and highly-coloured, and often contains blood. The albumen content may be high or even enormous. Edema then appears in the lower limbs and in the face; it becomes generalised, and effusions into the serous cavities also occur. In other cases the onset is insidious and progressive; the edema increases gradually and an examination of the urine reveals albuminuria. Fibro-gummatous lesions of the kidney in the advanced stages of syphilis are not ordinarily associated with edema.

Tuberculosis causes a very different type of lesion in the kidney. With tubercles of the kidney, even when caseous, there is no edema, at least during the greater part of the disease, and as is often the case, one of the kidneys functions perfectly. Acute diffuse renal tuberculosis is rare but is more or less rapidly manifested by lumbar pain, puffiness of the face, edema of the lower limbs, and turbid urine containing albumen. H

Chronic hydropigenous nephritis, in particular, is the lesion caused by tuberculosis

The edema takes on all the features of the nephritic type. Beginning in the eyelids and the dependant parts, it gradually spreads and is sometimes associated with effusions into the serous cavities. Renal permeability as tested by elimination tests is usually maintained and is sometimes even increased. The tubercular nature of these cases of nephritis is not always easily recognized.

Of the forms of chronic hydropigenous nephritis, there is one which has recently been studied by numerous investigators under the name of lipid nephrosis, a term first proposed by Muller(1) This is a lipid degeneration rather than a true nephritis, but, as Bennett(4) rightly points out, the term is ambiguous, and authors have used it in different senses. All the signs of a true nephritis may be observed--hematuria, uremia and cardio-vascular complications. In other words, nephritis may become a complication of nephrosis and vice versa. It is generally accepted now that the essential characteristics of nephrosis are, a lipid degeneration of the convoluted tubules with edema and abundant albuminuria. The cells of the tubules contain large quantities of cholesterol in the form of doubly refractive granules.(9)(21)(26).

The disease begins insidiously with a generalized puffiness and pallor of the skin. Edema then develops and spreads as anasarca, while effusions appear in the serous cavities. The urine in nephrosis is not always diminished in volume, and its specific gravity is normal. Albumen is usually found in considerable quantities. The sediment contains leucocytes, hyaline and granular casts, and lipoids which give the cross of polarization(51). The progress of the disease is slow and essentially chronic, with intervening remissions and relapses; the pure forms may go on to complete recovery. Death often occurs from some intercurrent affection. There is neither a hyperazotemia, nor an

acidosis, and the proportion of the protein is diminished; moreover, an inversion of the albumen-globulin ratio is observed. We shall return to these alterations later.

As regards the hypercholesterolemia, it must be observed that this is neither the effect, nor perhaps even the cause, of the renal lesion, for in diabetes, jaundice, and xanthoma, it may be present for many years without inducing any corresponding change in the kidneys. Some(1)(14) are inclined to think that the renal changes are secondary to a nutritional disturbance, in this favor, a lowered basal metabolism has been found, which is Epstein's (14) reason for instituting thyroid medication. Murphy(33)(34) has criticized these observations on the ground that the water retained in the tissues falsifies the value of the basal metabolism.

In the majority of the cases of chronic hydropigenous nephritis, the origin remains obscure. Edema usually appears in a slow and progressive manner~~x~~ but may appear quite early when the disease has an acute or subacute onset. Marked variations in the edema may be seen in the course of the illness; in the terminal stages it remains persistent in spite of treatment by diuretics and a salt free diet; but the administration of salt may still further increase it and expose the patient to the risk of severe complications.

Sclerotic nephritis, most nearly approximates to the pure form of uremic nephritis, the dropsical syndrome in this lesion of the kidney is inconstant, and as a rule, does not appear until an advanced stage, and even then rarely acquires any great intensity. In hydropigenous nephritis, edema exists without any failure of the heart whatsoever, but in renal sclerosis it is undoubtedly more or less directly dependent on cardiac insufficiency.

Edema is a very frequent complication of pregnancy. The cause of true renal edema in pregnancy is not known. It may be general and involve any portion of the body, but is usually limited to the lower extremities. Occasionally the vulva becomes intensely edematous. Areal anasarca, with exudation of serum in the tissues, is usually due to toxemia, renal or hepatic, and is produced

by the alteration of the constitution of the blood or capillaries or both. The accoucher is warned not to conclude too lightly that an edema is of mechanical origin or of no significance because the urinary findings are negative. Nephritis may exist without albuminuria, and eclampsia may occur with no other warning than the anasarca. (52) (53)

Case Histories.

* In writing reports of the case histories I have used illustrative cases, abstracted from the literature rather than cases I have had personal contact with.

The first case is reported by McClendon(31) and is of the pure lipoid nephrosis type in which thyroid therapy has been used.

A boy aged 8 years was admitted to the hospital after an illness of 2 months which began with an edema of the feet, legs, hands and face, some easy fatigue and headaches. The edema had been growing progressively worse. The family history was negative. The child weighed 7 lbs. at birth; teething and development had been somewhat retarded and he had been subject to frequent colds and tonsillitis. A tonsillectomy and adenoidectomy had been performed 2 years prior to entry. He had had measles and pertussis.

On entry there was marked edema of the face and the eyes were swollen shut; mucous membranes of the nose were injected, with pus in both nares and a post nasal discharge; dental hygiene was poor. There was edema of the lower extremities, marked edema of the scrotum and penis, and the abdomen was markedly distended with dullness in both flanks. There was edema of the lower chest wall with moist rales and dullness at both bases, probably due to fluid. All heart sounds were muffled, rate 88 and blood pressure $\frac{100}{60}$. The weight on entry was 89lbs. The urinary output was 300cc. in the 24 hours with 7.5% albumin, Sp.G. 1.024; no casts, pus or blood. The P.S.P. ran 70% in 2 hours

* IN communicating with Dr. Poynter he suggested that I take histories from the literature, rather than cases I had seen personally, as they would probably be worked up better, more typical and for this reason more instructive and representative.

The urea nitrogen of the blood was 12.5mg. and creatinine 1.5mg. The blood count showed R.B.C. 4,150,000, Hb. 64%(Dare) W.B.C. 10,800. The blood Wassermann was negative and the stool examination was negative. Roentgenograms of the sinuses showed a bilateral maxillary sinusitis. The basal metabolic rate was a minus 20.

For 3 months the treatment had consisted of a high protein(100gm) salt-free diet, fluid restriction to 900cc. daily; double antrotomy; ammonium chloride, merbaphen and mersalyl as diuretics; 2 blood transfusions and paracentesis abdominis one or two times weekly. There had been no noticeable changes in the blood picture or in the edema.

On entry 9 gr. of thyroid were given daily. There was an immediate increase of urinary output to 2700cc which gradually came down somewhat. In two and one half weeks the weight loss was 30lbs., albumin in the urine was decreased to 1.5%, pulse dropped to between 70 and 80 and the blood pressure remained at $\frac{100}{66}$. After 2 weeks the thyroid was decreased to 3gr. daily. The edema disappeared and fluid intake and output balanced. Six weeks after thyroid therapy was instituted the patient was dismissed with no edema, albumin 1% in the urine. He has been observed at monthly intervals. There is no edema, slight albuminuria and the boy is in school now.

In this case, thyroid therapy would appear to be the treatment par excellence, insofar as most of the other therapeutic measures had been tried.

There is no doubt that lipoid nephrosis is often seen in cases where there has been an initial inflammatory disease of the kidney, usually of the glomerulo type. And again it seems certain that many cases which are apparently primarily degenerative with the characteristic albuminuria and edema, later become complicated by glomerular inflammation. The following may be given as a case falling into this class, quoted from Bennett, Dodds and Robertson(4) as follows:

B.M., female aged 20. Measles at 2 years, "nephritis" at 6 and recurr-

ing at 15. She was then admitted to hospital three times; details unknown. In October 1925 she was admitted to Middlesex hospital under the care of Dr. R.A. Young. She had been well in the preceding March, but then began to swell in the face, abdomen and legs. Vomiting set in and continued intermittently.

On admission she had edema, ascites, oliguria and 2% albumin in the urine. The systolic blood pressure was 140 but the heart was not enlarged. Treatment consisted in a generous diet and the administration of urea. The edema subsided rapidly and considerably but on discharge she still passed considerable albumin and the systolic blood pressure remained at 140. The urine never contained more than 1.5% of urea even after urea had been given. The Wassermann was negative.

When examined 13 months later, the patient was at work and felt well except for occasional headaches. There was some edema of the ankles and she stated that the edema fluctuated considerably from month to month. The systolic blood pressure remained at 140 and there was considerable albuminuria.

Blood analyses at various dates are given below.

	On admission	6 weeks later	11 weeks later
Urea	32	94	58
N.P.N.	32	63	51
Chlorides	541	556	--
Cholesterol	517	240	375

The nitrogen retention and raised blood pressure in this case point to glomerular and interstitial changes of serious degree and make the prognosis correspondingly bad, with probable uremic termination.

Of the edema in acute nephritis of which scarlatinial nephritis is the classical example, Achard's (1) description is probably more instructive than an actual case report. He says in effect--the edema commences abruptly. One morning, to the patient's great astonishment, the face becomes puffed and the eyelids swollen, and in the space of 2 days, the edema extends to the trunk

and limbs. Occasionally, symptoms of certain other forms of acute nephritis, viz. lumbar pain and high fever are much in evidence. As a rule the fever is moderate. Albumin is present, hematuria sometimes occurs and may even precede the albuminuria. Oliguria is common and anuria may supervene.

Of the chronic type of nephritis Waterfield(50) reports a case as follows:

L.E. a white male aged 24 years, previously an attendant in a gasoline filling station. Diagnosis: Chronic Nephritis.

The patient was admitted Jan. 27, 1928, for massive edema involving most of the body, ascites and bilateral hydrothorax. In 3 preceding years, he had had 3 sudden attacks of swelling commencing in his legs and spreading up to his abdominal wall; the first 2 attacks had lasted several months and had subsided suddenly and spontaneously; the third had persisted over a year up to the time of admission. There was no history of infection.

On admission the R.B.C. was 3.7 million, W.B.C. 13,000 and the blood pressure 176 110. There were no retinal changes. The urine showed a massive albuminuria, few granular and hyaline casts and numerous doubly refractile crystals; no R.B.C., Sp.G. 1.030. The blood examination showed the N.P.N. to be 31mg.% serum protein 4.2% with an inverted albumin-globulin ratio and a high cholesterol of 410mg.% The weight on admission was 120 kilo and four months later it had fallen to 78 kilo. Still four months later he had lost 4 more kilo in weight and showed a progressive anemia. The R.B.C. at this time were 2.5 million, the N.P.N. was 45mg.% and the blood pressure had risen to 185 110. There was still massive albuminuria but in addition numerous casts and very occasional red cells were now present.

Eight months later the patient was readmitted in uremia and died.

This case well illustrates the progressive uremic type of chronic glomerulo-nephritis, with an associated tubular degeneration as is evidenced by the findings in the blood and urinary examinations.

Renal edema in pregnancy, strictly speaking, is probably rather rare(57)

I am inclined to feel that the slight swelling of the feet and ankles which is so frequently seen in the month or so of pregnancy, is more on a toxic or mechanical than a true renal basis.

Waterfield(50) has reported a case as follows:

M.L. age 42 years, an Italian housewife. Diagnosis: Anasarca, transient albuminuria; toxemia of pregnancy and nephrosis.

She was admitted April 10, 1928, one month after her seventh normal delivery, with generalized anasarca which had started to appear during the last few weeks of pregnancy.

On admission there was considerable edema of the legs with ascites. The urine showed a trace of albumin, no casts and a very occasional R.B.C., Sp.G. 1.020 and reaction acid. The blood pressure was $\frac{160}{100}$. Blood study showed N.P.N. to be 33mg%, the cholesterol content of the plasma raised, varying from 167 to 329, while the serum protein varied between 2.6 and 6.5. There was an inverted albumin-globulin ratio of .47 to .53

On a high protein diet the serum protein rose rapidly and at the same time the albumin in the urine increased markedly.

Finally the serum protein reached a normal figure, albuminuria ceased, edema disappeared and the blood pressure also fell to $\frac{118}{63}$.

Herrmann(56) reports a case of syphilitic edema as follows:

J.P. white male aged 20 years. A young, unmarried laborer was admitted to Charity hospital, complaining of weakness, swelling and cramps. A generalized edema or anasarca, especially marked over the legs and face had been present for 4 days. He had been forced to quit work three weeks previously because of pain in the abdomen, nausea and vomiting of a yellow appearing material. The symptoms were not effected by eating but he was somewhat relieved by evacuation of the bowel. There was some dyspnoea on exertion. The edema had appeared suddenly three days previously, first being noticed at the end of day and more marked in the dependent portions. It had rapidly increased, affecting the face and eyes. He had never had a similar previous

disturbance. Three months before admission he had been exposed, had contracted gonorrhoea, chancroidal infection and a painless ulcer had developed. The urine had been smoky and definitely bloody at different times two weeks prior to admission.

Physical examination revealed a young white man, who presented a conspicuous puffiness or edema about the eyelids, face and in fact all subcutaneous tissues and a marked anasarca of the feet and hands. There were rales in the bases of the lungs. The heart was normal with the exception that the aortic second sound was accentuated and it was beating forcefully and over-actively. The blood pressure was $\frac{120}{74}$. There was a hard chancre on the penis and a satellite bubo in the right groin, and a complicating chancroid at ulceration. The Wassermann reaction was strongly positive.

The urine was acid in reaction, Sp. G. 1.030, 3.5% albumin with a few casts and many pus cells. The P.S.P. test showed 100% in 2 hours. The urea clearance test was about one half normal. The blood count showed R.B.C. 3,000,000, Hb. 65%, W.B.C. 6,500, 84% of which were P.M.N. cells. Blood chemistry showed N.P.N. 50mg.%, urea nitrogen 25, creatinine 2.1, serum protein 4.9% albumin 2.3% and globulin 2.6%.

The treatment consisted in injections of Neocarsaphenamine, starting with .3gm and increasing to .45gm. at weekly intervals. The results were gratifying. The patient was also put on a low protein and low salt diet. The albuminuria disappeared after the first injection. The P.S.P test rose to over 100% in 2 hours. The patient was referred back to his own physician for continuation of the treatment.

I have been unable in the recent literature to select a suitable case of tuberculous edema. Castaigne, Landouzy and Bernard (cited by Achard(1)) have given a description which is included in lieu of a case report. The condition has ~~also~~ been discussed in the section on the clinical aspects of the disease.

Treatment

It would seem obvious at first sight that the treatment of renal edema should depend on the type of renal lesion associated with it, and ultimately upon the actual cause of the lesion.

Etiological considerations, however, rarely find any such direct application in treatment. In many cases of hydropigenous nephritis the cause remains unknown: there are many forms of cryptogenic nephritis, both acute and chronic. There are types of uremic nephritis in which the cause is known, but which are not amenable to treatment: such are scarlatinal and tuberculous nephritis, for which there are no specific remedies. On the other hand, syphilitic nephritis of the secondary stage, which is sometimes accompanied by severe edema, may be considerably benefited by specific treatment, although this must be applied with care in order to avoid an aggravation of the renal lesion. In the treatment of edema of renal origin, therefore symptomatic medication occupies the largest and perhaps the highest place, and is still of preponderant importance.

Of the forms of symptomatic treatment based on pathogenesis, diet occupies the most important place.

We know that dropsical fluid, composed chiefly of salt solution, is due to a retention of the exogenous substances, water and sodium chloride, taken into the body in the food and drink. It follows logically that dropsy should be attacked by a restriction of water and salt, and experience confirms this theoretical conclusion, not only in the case of renal edema but also of dropsy due to other causes.

The restrictions of fluids is the basis of Karrell's(1) cure. It is not only an urgency measure for dealing with threatening complications of cerebral or pulmonary edema, or of exacerbations of dropsy, but it must also be applied as a permanent and preventive measure whenever the volume of the urine falls below the volume of fluid ingested. In Achard(1) opinion many err in allowing

fluids in abundance in cases of nephritis with a hydropigenous tendency, on the assumption that, as in the healthy person, this will increase diuresis.

It is necessary to regulate the daily quantity of fluids allowed, only according to the eliminatory capacity of the individual, bearing in mind the necessity for sufficient diluent for the urinary waste products to allow of their excretion by a kidney whose concentrating power may be adversely affected. It is therefore usually sufficient to limit the quantity of fluids ingested in the twenty-four hours to 800-1200cc. Elwyn(13) however states that this is not sufficient limitation and advocates being guided by the amount of urine passed on the preceding day. It must be remembered that the restriction of fluids is less often indicated than is that of sodium chloride, because thirst is rarely keen in dropsical patients, and because the suppression of salt has in itself the effect of diminishing thirst.

Widal and Javal, in 1903, first demonstrated the value of salt restriction in renal edema. (1) In prescribing this regime, it must not be supposed that the actual cause of the renal disorder which is producing the dropsy will be affected. The deprivation of salt obviously cannot modify the lesion in the kidney. It merely suppresses or attenuates one of the effects of these lesions, an effect which is an embarrassment to the patient, and which may expose him to ~~severe~~ dangers, such as excoriations of the skin followed by infection of the edematous regions, or even to fatal complications such as edema of the lung or of the brain or meninges. In other words, the salt free diet is a method of treatment which is not directed towards the essential cause of the hydropigenous disease, and which does not definitely dispel the conditions productive of the dropsy. It is a palliative treatment only, but one capable of giving very useful results.

In all varieties of dropsy, the salt free diet gives results of three kinds, the reabsorption of the fluid, the suspended action--the fluid does not increase in volume, and the increase in the effusion, but with a decrease in its rate of progression.

This regime is particularly efficacious in the early stages of dropsy. It may arrest the anasarca of acute nephritis and the exacerbations of chronic nephritis, ~~it may even prevent~~ the edema of scarlatinal nephritis, which is, however, rarely seen now as scarlatina patients are submitted to a low salt diet. An interesting practical observation on the action of the salt free diet is that this diet is most useful when patients are able to take and digest a certain quantity of food. Patients who are submitted to a strict fast, and who are therefore best attaining a deprivation of salt and water, do not, as a rule, reabsorb their edema. For reabsorption to occur, it appears necessary for the organism to carry on the work of nutrition which is so indispensable to the play of the interchanges. It is not always sufficient to cut out salt or to give the food dry, for the patient to lose salt and water. An excretory current must be established before the excess of salt solution can be eliminated.

These observations on the application of the salt free diet tend to show that the retention of salt and water occurs whenever the body excretes less water and sodium chloride than it takes in. If it is deprived of both salt and water, it will cease to accumulate an excess of fluid, but it will not get rid of its reserves unless it has conserved its power of excretion. If it is deprived of water only, and not of salt, and if there are any causes making for saline retention, it will keep back the water necessary for the dilution of this salt. And finally, if it is deprived of salt but not of water, it will lose the excess of salt solution if there are no obstacles to the elimination of water. Otherwise, as is seen in patients with oliguria, and especially in the cardiopathies and nephritis, a certain quantity of water will be retained, and a relatively slight chloremia will be present.

The salt free diet must be applied under the supervision of the clinician, who possesses two ways of judging of its efficacy, namely by the estimation of chloride excretion in the urine, and by the weight of the patient. The latter is the method more within reach of the practitioner and suffices when one has

to deal only with chronic patients, free from acute complications, and whose nutrition is relatively stable. This control over the diet is the more desirable, as it will reveal any infringements, voluntary or involuntary, and because it avoids the necessity of unduly prolonging the severity of the cure. When the weight has become stationary, and the excretion of chloride equally steady, it is possible to try the addition of small amounts of salt to the rations, and if there is no retention, to increase it carefully. (1)

Like all systemic diets, the salt free regime is not without its disadvantages, in spite of the variety of foods allowed. For some, the deprivation of salt is a painful sacrifice. The abstinence from salt diminishes the hydrochloric secretion of the stomach, and leads to the use of other condiments which are not always harmless, for this reason it is advisable not to prolong the salt free diet beyond the time required, and to gradually increase the salt, in amounts which a judicious supervision will have shown to be permissible.

Blum(1) has called attention to certain cases of hyperazotemia which have followed upon heavy losses of salt due to profuse diarrhoea or vomiting, and in which symptoms resembling those of uremia have appeared. These disturbances were attributed to a lack of sodium chloride and were cured by the administration of salt. It is important to remember in such cases, that salt must not be given haphazardly, and that it is necessary to stop its administration when the azotemia has decreased and becomes stationary. Conversely when applying the salt free diet in cases of nephritis with hyperazotemia and salt retention, one must not over-step the mark and produce chloropenia. It is therefore advisable in these cases, while recording the variations in the azotemia, to note also those of the chlorides in the blood or in the spinal fluid. As far as hydropigenous nephritis is concerned, these precautions are hardly necessary except after the disappearance of the saline reserves which were produced by the dropsy.

Milk diet is a form of low salt diet and its use was classical in the

treatment of renal dropsy long before the salt free diet was known. Raw meat contains little chloride, and then rather more potassium than sodium chloride. As for fish, those from fresh water alone may be allowed. Of the vegetables, the farinaceous ones, because of their nutritive value, are the best given. Cereals (oatmeal, rice, tapioca, buckwheat etc.) go very well with the salt free diet. Vegetables rich in potassium and poor in sodium are particularly suitable. Blum(1) has recorded the liberating effect exercised by the K ion on the Na ion. Fruits may be given freely, especially grapes which possess a definite diuretic effect due to their high glucose content.

In choosing foods free from salt, it is advisable to be guided not only by the tastes and the digestive capacity of the patient, but also by the particular indications of each morbid state. In this way the different dietaries which are applicable in hydropigenous nephritis can be arranged to assist in the removal of salt.

The "water diet" is indicated, temporarily of course, at the beginning of the treatment of a severe case of edema in Bright's disease, or in the course of certain complications of nephritis. Water can be given sweetened with lactose or fruit juice. The milk diet is often useful as a step between a fluid and a solid diet.

The lacto vegetarian diet is the one generally preferred in chronic hydropigenous nephritis. It is easy to render it salt free, and the lack of salt in vegetables is more readily accepted by the majority of patients than it is in meat. Starchy foods, herbaceous vegetables, rice, doughy foods, creams and fruits, form the basis of a sufficiently varied diet. Eggs are generally included in the milk and vegetarian diet.

The meat diet, or what is more accurate, a mixed meat and vegetarian diet was less generally prescribed in cases of Bright's disease with edema before the institution of the salt free diet. From the earliest attempts at salt free dieting, it was recognized that meat taken without salt suited those patients who were suffering from hydropigenous nephritis.

Epstein (14) as a result of a series of observations, extending from 1917 to 1926, has devised a high nitrogen diet, combined with intensive thyroid medication, basing his conclusions on the work of Eppinger. Elwyn(13) states according to Eppinger, Thevenot was the first to use thyroid substance as a means of causing diuresis. Eppinger investigated the effect of thyroid gland on the water exchange. He found that of 300cc. of water administered by mouth to a normal dog, 184cc. or 61% appeared in the urine. The same dog was given thyroid extract for seven days beginning with .3gm on the first day and increasing to 2.1gm on the last day. The dog was then given 300cc. of water. This was followed by an increased urinary output, and in 3 hours 317cc. or more than 100% were eliminated. The thyroid extract was then withheld for four days and the water test repeated. Of 300cc. taken in, 192cc. or 64% appeared in the urine.

Eppinger then extirpated the thyroid gland and nineteen days later repeated the water test. Of the 300cc. taken in, 91cc. or only 30.3% appeared in the urine in three hours. Parallel results were obtained with a solution of sodium chloride when given by mouth.

Eppinger further experimented with sodium chloride solution given subcutaneously. The water and sodium chloride were resorbed more quickly after feeding with thyroid than before; and in twelve hours there was hardly anything of the fluid left at the site of injection. When the thyroid gland was extirpated the injected fluid remained in the form of an edema in the subcutaneous tissue after twenty-four and even after forty-eight hours.

The internal secretion of the thyroid gland has thus the effect of increasing the diuresis, and, of course, the entire water movement in normal dogs but especially in dogs with deficient thyroid secretion. Asher found that in animals kept under basal metabolic conditions, the water excretion following extirpation of the thyroid gland, sinks from day to day to a lower level.

Epstein states that the problem of treatment of chronic nephroses is three-fold. A. to replace the protein loss of the blood plasma which results from

albuminuria, and which plays so large a part in the retention of water and formation of edema. This is best accomplished by feeding 2 to 3 grams per Kilo of body weight, per day. B. To compel the tissues to utilize protein and incidentally to reduce lipoidemia. This too, is often accomplished by a liberal protein but fat-poor diet. The administration of thyroid aids in maintaining this desideratum. C. To reestablish normal metabolism. When high protein feeding fails to accomplish this, the institution of thyroid is definitely indicated. Thyroid is mainly to stimulate protein utilization, not to replace high protein feeding which is fundamental. Epstein advocates, small initial doses, one half to one grains given orally t.i.d. -- much larger doses are usually needed, therefore a rapid increase until 15 grains a day are given. If no effect the dose is doubled and tried 5-7 days. If no results are noted 5-10 mg. of thyroxin is given intravenously. If gastric distress follows the use of large doses orally thyroxin intravenously is immediately resorted to.

Epstein reports a number of cases which have cleared nicely and summarizes by stating that, the tubular degeneration is the consequence and not the cause of the profound metabolic disturbance, which he has labeled "diabetes albuminuricus". The therapeutic requirements are met sometimes by high protein feeding and in others in conjunction with thyroid or thyroxin. The response to therapy is best measured by the cholesterol content in the blood. Thyrotoxic symptoms do not occur as long as hypercholesterolemia exists. The treatment may require one or more years.

More recently, Verity(49) McClendon(31) and Bopp(6) have reported cases in which the "Epstein treatment" or with slight modifications have been used all very successfully.

Peters and Bulger(35) have made an intensive study on the nitrogen metabolism in nephritis and conclude that, A. the total urinary nitrogen is not a satisfactory measure of Nitrogen catabolism, B. the nitrogen catabolism can only be estimated from the urinary non-protein nitrogen after proper allowance has been made for changes in blood and tissue non-protein nitrogen, and var

iations in body weight due to diuresis or accumulation of edema. C. by the administration of large amounts of carbohydrates and fat it has proved possible to reduce the protein catabolism to .5 to .7gm. per Kilo per day. D. if enough protein is given to cover nitrogen catabolism plus an additional amount equivalent to that lost as albumin in the urine, nitrogen wastage may be prevented. E. most cases show evidence of previous protein deficiency, and if they are given more than enough to replace the amount lost in urine they will store the excess within certain limits, thus repairing the effect of previous nitrogen wastage. F. the protein wastage may be partly due to early dietary mismanagement. Probably the disease itself is characterized by a higher protein metabolism than normal. G. abnormally high blood non-protein nitrogen has only been observed when the nitrogen catabolism was relatively high and usually returned to the normal level as the clinical condition of the patient improved and nitrogen catabolism diminished.

More recently Barker and Kirk(3) and Kirk(51) have shown that variations in the protein content of the diet may so fluctuate the nitrogen balance as to markedly exacerbate an edematous condition or on the other hand tend to diminish it.

Achard(1) says, it naturally follows that this high nitrogen diet necessitates a constant watch being kept on the azotemia and on the excretory power of the kidneys. It is not recommended for patients in a state of urea retention and should, moreover, be salt free.

The efficacy of the nitrogen diet in lipid nephrosis is variable, failures have been recorded by Mason, Christian and Geyelin, Kahn, and Labbe(1)

Diuretic medication is often necessary to supplement the action of the salt free diet.

Theobromine is considered to be the drug par excellence for the stimulation of renal excretion. It activates the circulation in the kidney, and by increasing the blood supply, promotes the elimination of water and of dissolved substances. Moreover, it lowers the threshold of salt excretion. As Widal

and Javal(1) have shown, it is the best example of a salt and water eliminant. It is administered, not only in different forms but also in various ways. It is best as a rule to give it in large but not prolonged doses, viz. 30 grains per day for three days. Among the derivatives of theobromine, the most soluble are diuretin and allyl theobromine.

Edema may sometimes disappear very rapidly and the diuresis amount to very considerable quantities. But, there are also some cases which are refractory both to diet and to drugs, and again there are some patients who have an intolerance for theobromine and for the derivatives and substitutes that have been tried in its place. It is sometimes advisable, as in advanced cases with oliguria, refractory edema and obstinate hyperazotemia, to give it only in small and prolonged doses. Such patients must continue regularly with theobromine in the sole hope of postponing the inevitable. Caffeine, another xanthine derivative also acts on the kidney and on renal vaso-dilatation; but its principal action is on the heart.

Much work has been devoted to the possible action of caffeine, theocine and theophyllin on the imbibition of proteins. It is certain that many diuretics do cause changes in the distribution of water and salts as between the blood and the tissues, but it has not been proved that they lower imbibition of the tissue proteins. (1)

It has long been known that sugars possess diuretic properties and they are useful adjuvants in treatment. Lactose is generally preferred to other sugars, and is prescribed in doses of 2 to 4 ounces a day, dissolved in water or in infusions.

Urea has long been known as a diuretic. It should not be used in cases of edema in which there is renal insufficiency with an increase in the urea content of the blood. When this is the case the intake of large amounts of urea is apt to bring on symptoms of uremia. When there is no renal insufficiency, urea may be used in large doses; it is not effective in small doses. It may be given in doses of 5 to 10 grams t.i.d. in fruit juice. Some authors

(13) advocate as much as 80 to 100grams in twenty-four hours. The point of attack of urea is like all other diuretics in the kidneys and in the tissues. Its effect in the kidneys is due first to its not being reabsorbed in the tubules; it thus prevents a certain amount of water from being reabsorbed. In addition, according to Cushney(13) the diuresis from the urea is sometimes accompanied by dilution of the blood from increased movements of the fluids in the body, and also by increased blood flow through the kidney, and in this case the action in the tubules is reinforced by increased filtration in the capsule.

Special interest attaches to the group of diuretics which Blum(1) has proposed calling "interstitial" because their action lies in displacing the Na ion, supposed to be the principal factor in water retention, and is an effect exerted not on the kidney but on the tissues. Hence Blum has treated edema, especially the renal type, by potassium chloride and by the chloride and lactate of calcium. The salts of calcium have previously been used, and those of potassium(nitrate and acetate) for a much longer period still, in the treatment of dropsy, although usually with poor results. In order to get any appreciable results, it is necessary to give big doses, but as these are not always well tolerated, they cannot be given over prolonged periods.

In 1924 Kieth, Barrier and Whelan(22) reported two cases(the literature only contained about twenty in 1924) treated by the use of 10 to 18 grams daily of calcium chloride, in conjunction with purging, sweating and a low salt diet of 1500 calories and about 40 grams of protein. They report excellent results. If the calcium chloride is not tolerated well orally it can be given intravenously. They interpret the diuretic action to three separate mechanisms. A. the effect on the retained Na ion, the Ca being eliminated by bowel and the remaining freed Cl attaching to the Na ion and passed off in the urine. B. a change in the acid base equilibrium, causing the tissues to liberate water for the kidney, or possibly a change in the damaged renal tissue itself. and C. to the antagonistic action of the cations and possibly a specific dehydrating effect of the calcium chloride. Further work by these same three authors

showed equally good results with the use of ammonium chloride.

Gamble, Blackfan and Hamilton(31) conclude that following the injection of calcium chloride, ammonium chloride, magnesium sulphate or ammonium sulphate, in considerable amounts, the quantity of inorganic acid radicals which must be conveyed through the body fluids, is greatly increased without any appreciable accompanying increase in the amount of fixed base presenting for transport, therefore these salts are described as acid producing salts. Increased acidity of body fluids is demonstrable after ingestion of these salts. In edema much the greater part of the water removed is extra-cellular.(2)

Lashmet (23) has recently treated chronic nephritis with edema by a low protein salt poor diet with a neutral ash, to which are added acids or acid producing salts. He bases his treatment on the conclusions that, A. edema is not due to failure of the kidneys to excrete water and is independent of fluid intake, B. edema is not due to failure of kidneys to excrete chlorides -- chloride as sodium chloride increases edema but as hydrochloric acid or ammonium chloride, decreases edema, therefore the reaction is more important than the chloride content as such, C. the reaction of total ash intake is more important than the total amount in influencing edema, alkaline ash increases edema and acid ash decreases edema. He reports excellent results in three cases treated on these principles.

Fischer has on the other hand recommended the use of alkalis to counteract the acidity which he claims favors edema. Osman(38)(39) has also reported favorably on four cases in which he used large doses of alkalis(sodium bicarbonate and potassium citrate of each, doses ranging from 240 to 2100 grains in twenty four hours). He cautions however to beware of such complications as vomiting and diarrhoea.

These apparently contradictory results are to be explained, according to Stieglitz (54) , on the supposition that every change in the reaction of the blood acts as a stimulant to the renal cell, and so promotes diuresis.

The use of mercurial preparations as diuretics is very old. They date

back to Paracelsus, and later, Morgagni, Van Swieten, Hoffman, Stokes and Graves also prescribed them. (1) Elwyn (13) says, Sternberg in reviewing the history of mercury diuresis informs us that English physicians had already noted in 1790 that mercurial ointment rubbed into the skin has a diuretic effect. Mercury was used as a diuretic in the middle of the nineteenth century in England, but in other countries its use was forgotten until its diuretic effect was rediscovered by Jendrassik. In recent years mercury has again come into use as a diuretic since the discovery of novasurol and salyrgan.

Novasurol is a mercury compound and its constitution is sodium oxymercuric-ortho-chlorphenol-oxylacetate with diethylmalonylurea. It contains 33.9% of mercury. Salyrgan is a complex compound containing mercury in combination with the sodium salt of salicyl-allyl-amidoacetic acid. It contains 36% of mercury. Both of these drugs are used in the form of a 10% solution and are administered intravenously or intramuscularly at intervals of from three days to a week. The tolerance for the drug is first determined by giving .5 to .75 cc. of the solution intramuscularly and if no untoward effects are produced the dose is quickly increased to 1 and 2 cc.

Saxl and Heilig were the first to notice that the administration of novasurol in the treatment of aortic insufficiency of luetic origin with edema was followed by a marked diuresis. Since then the diuretic effect of novasurol has been repeatedly observed by them and by others.

Fourneau and Girard (1) have recently prepared a substance called Neptal, which is an addition product of mercury acetate and salicylallyl-amido-acetic acid; this is more stable than salyrgan. The diuresis obtained by these mercurial compounds is usually of rapid onset and is especially so with neptal, which seems to be the most active of these substances, but it is transient, and ceases the following day or the day after.

The elimination of salt obtained by these compounds is very pronounced, the amount excreted reaching to 30 gm. a day (1), while the concentration of chlorides in the urine is increased to such an extent that salt elimination exceeds

dehydration. An increase in the urinary chlorides may occur without any corresponding increase in the urinary volume. This happens spontaneously in the urinary crises of acute diseases. In a case of lipid nephrosis with edema, in which neptal had been tried without effect the protein osmotic pressure which at first was 26 to 28, fell to 20, and then rose to 35, while on the second occasion fell to 17. The proportion of albumins per litre in the serum varied little during this time; it would seem therefore that neptal modifies the protein composition of the blood, even in the absence of any response from the kidney. (1)

The diuretic action of mercurial compounds and even of neptal is inconstant. Failure to produce diuresis is generally a bad prognostic sign.

The diuretic action of mercurial compounds as to mode has given rise to no little discussion, some attributing it to a vaso dilator effect, others to effects on other organs and especially the tissues. (1) It is noteworthy that while large doses of mercury damage the kidney and diminish the urine, small doses stimulate it and are productive of diuresis.

It follows from these considerations that the use of mercurial diuretics is least justified in the dropsy of nephritis, as the fragility of the kidney is too great to discount any risk, however slight, of aggravating the condition by the use of such drugs. An exception can nevertheless be made in the case of syphilitic nephritis of the secondary stage, for then the drug exercises a specific effect.

Calomel is prescribed in doses of $1\frac{1}{2}$ - $7\frac{1}{2}$ grains per day; mercury cyanide in intravenous injections of $\frac{1}{6}$ grain (it has the disadvantage of causing diarrhoea frequently after a few injections). Novasurol, a white powder, is given in intra-muscular or intravenous injections of $1\frac{1}{2}$ to 3 grains every day or every second day. Salyrgan in a 10% solution is also given in doses of 1cc. every third day. Neptal is given in injections in doses of 1 to 2 cc. of the 10% solution every four days or at longer intervals. the chief defect of mercurial diuretics as a method of systematic treatment is

the transient and uncertain nature of their action. The injections must frequently be repeated and often lose their effect. An attempt can be made to assist the action of naptal by previous treatment with calcium salts, and to prolong its action by the subsequent administration of theobromine.

Calvin and Goldberg(8) in treating the nephrotic syndrome in children have used mercurial compounds as novasurol and salyrgan. They conclude that these diuretics probably affect the rate of water movement through the tissues as well as the kidneys. They find the mercurials to be more effective when preceded by several days by large doses of ammonium chloride or ammonium nitrate. The aqueous solution of bismuth sodium tartrate has been used in place of the mercurial compounds. Salyrgan is probably safer than novasusol, especially when given intra-muscularly. The mercurials are not to be used if renal function is in any way impaired because of mercurial retention and possible mercurialism, nor in the presence of moderate or severe hematuria because of the tendency to aggravate that condition.

Schelling and Tarr(41) have reported good results by the combined use of magnesium sulphate and salyrgan, when other diuretics have failed. They inject deep into the gluteal region a solution consisting of, 15cc. of 50% magnesium sulphate, 2cc. of Salyrgan and 1.5cc. of 5% novacain.

Verity(49) is of the opinion that the benefits of such diuretics as novasurol, theophyllin, metaphyllin and salyrgan are highly exaggerated.

Sprunt(45) reports nine cases in which Merbaphen(novasuro) has been used and concludes that its use is probably justifiable. The cases were all examined post mortem. In six of the cases no evidence of renal damage was apparent while in three there was evidence of pathology but the drug had been used when it was surely contra-indicated.

The kidney being the supreme organ of elimination, diuretics are undoubtedly the best means of promoting the greatest excretion of dropsical fluids. But other methods can also be used to assist elimination.

Purgative medication utilizes an intestinal side flow which may be quite

useful, especially at the beginning of treatment by other means. Emetics, rectal douches, calomel, magnesium and sodium sulphate, are the purgatives in common use.

Sudorific drugs seem to be of less value. There is nothing lost, however, in stimulating the functions of the skin by dry friction, massage, and hydrotherapy in the form of lukewarm douches and hot baths. (1)

Special attention must be paid to the complications of edema in Bright's disease. The state of the heart must be watched; any weakness necessitates the administration of cardiac tonics, and principally the digitalis preparations, which often give excellent results.

When dropsy attains a considerable volume and becomes a source of serious embarrassment to the patient, it should be removed mechanically. It is easy to aspirate the effusions of serous membranes.

Edema fluid also may be withdrawn in various ways. Superficial punctures with the point of a needle will allow the escape of quite an appreciable quantity of fluid. Since infection is the great danger of these small cutaneous abrasions, it is necessary, as of course in all other procedures, to take the most stringent aseptic precautions. The skin should first be carefully washed, painted with tincture of iocine, and then smeared with sterile vaseline to prevent maceration of the epidermis. An absorbent dressing should then be applied and frequently changed.

Incisions of the skin through to the sub-cutaneous tissue has also found its advocates, the fluid thus escaping in considerable quantity.

Southey's tubes may be used, and are quite useful (1), many however hold that this is too painful a procedure for the patient to withstand. They are narrow tubes, 5cm. long and armed with a small trocar for insertion; they are left in situ for two or more days. Along rubber tube which is attached drains the fluid away into a receptacle. Five to ten tubes are inserted into the edematous parts, and in this way, ten quarts of fluid, in favourable cases, have been withdrawn in less than two days. (1)

Comment Including Brief Summary and Conclusions.

A review of the literature has been made including the definition, historical aspects, the various etiological factors, the clinical types and treatment of renal edema.

Comment seems to be unnecessary except for the causative factors and treatment.

I have concluded that the real cause of renal edema is as yet unsolved. It is true that we are in possession of a large number of associated realities, as a result of much painstaking work and experimentation but there are many facts that do not fit with one another as well as certain observed phenomena that are totally unexplained. I feel that rather than let one factor or associated group of factors be totally responsible for the syndrome, it is better to assume that several or many mechanisms, working with one another are chiefly causative of the condition. I also think that in the not too distant future that some piece of work will definitely link up the mass of isolated truisms.

In reviewing the many treatises written on therapeutical measures I was able to form only one definite conclusion. I have noticed that many authors present a series of cases in which many varied types of treatment (sometimes of exactly opposite natures) have been employed, and each author reports excellent results, an alleviation of symptomatology, and in most instances, permanent and positive cures. We, of course have no way of knowing, but I have wondered how many times the various treatments have been tried without the brilliant results, because it is natural that only the successful cases would be reported in the literature.

I feel that there is some hair trigger mechanism, as yet undiscovered that is responsible for the sudden clearing of edema, albuminuria etc. It seems to me then, that if these various authors happened to start their treatment on the eve of one of these "pre-clearing" periods, that this, rather

than the therapeutic effect, is responsible for so many excellent cures being reported in the literature.

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Finis.

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C. Faulstich

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