Remarks

ON

RENAL FUNCTIONAL DISTURBANCE IN ACUTE AND SUBACUTE NEPHRITIS*

BY

J. SHAW DUNN, M.D., M.Sc.

ST. MUNGO (NOTMAN) PROFESSOR OF PATHOLOGY, UNIVERSITY OF GLASGOW; PATHOLOGIST, GLASGOW ROYAL INFIRMARY

The efforts of the morbid anatomist to comprehend and classify derangements of structure in disease, in order to have practical value, must find their completion in attempts to correlate these changes with the disturbances of function with which they are associated. The attainment of such a desirable end by one individual from the fruits of his own observations is nowadays virtually impossible. In the investigation of renal problems in particular very many different methods of investigation must be employed—clinical, biochemical, pathological, and experimental. All have their separate and individual fields, each requires special training and opportunities and is pursued in time-consuming practice, while each differs somewhat from the others in immediate aim and outlook. It thus ceases to be possible for one worker in any sphere to attain the same intimate knowledge and balance of judgement on all aspects of a complex problem, and completion of knowledge must be sought in combined and closely correlated observations by experts in different fields, a form of association from which, indeed, much valuable information has proceeded in the past. Even so there may arise important matters for decision on which an agreed opinion cannot be readily achieved owing to the contradictory nature of facts resulting from the different methods of analysis. Questions may be asked whether antagonism of view is the result of non-recognition of facts, or of imperfect interpretation of them, or of improper correlation of correctly interpreted facts in the varying fields. Hence the desirability for an occasional "taking of soundings" in the form of an open discussion, giving each side an opportunity to put forward its case.

In acute and subacute nephritis, the subject that we have elected to discuss, several main phenomena of renal functional disturbance are presented at various times and with varying significance. There can be no question, however, that the most baffling problem, and the one on which uniformity of view is furthest from being achieved, is renal oedema. It is to this that I propose to devote my main attention, referring, however, to other phenomena as may be necessary in elucidation of the whole.

EXTRARENAL ORIGIN

In earlier times, before the finer methods of chemical analysis of fluids had been elaborated, it was assumed that in nephritis the special type of oedema was the result of ineffective excretion of fluid by the diseased kidney, leading to accumulation of the fluid in the tissues. It cannot be gainsaid that there were excellent general grounds for this belief in ordinary physiological and clinical observations. The kidney is an important organ in the disposal of excess fluid from the body, and it responds with great exactness and within wide limits to increase or decrease of fluid intake. Also, it is just in the types of nephritis where oliguria occurs that oedema is prominent, while in chronic nephritis, with an extreme degree of renal lesion, oedema is usually absent and polyuria is the rule. In recent years, however, there has

been a considerable recession from the conception of oedema as the direct effect of the renal disability, both in acute and in subacute nephritis. The reasons for this departure differ to some extent in the two stages, and it may be said as regards subacute nephritis that, while various authorities agree that there are extrarenal causes, they disagree as to the nature of these causes, and their reasons are not always compatible. This may be regarded as an encouragement to attempt to find some unifying principle which will unite all forms and stages of renal oedema in one comprehensive classification.

MECHANICAL ANURIA

There is, of course, one fundamental objection to the view that renal oedema can be of the nature of retention of fluid resulting from failure of a renal function—namely, the absence of oedema in complete anuria resulting from blockage of both ureters or extirpation of a solitary kidney. Many cases have been recorded in which fluid continued for ten days or more, yet no trace of oedema was noted, though food and water were consumed; in some instances there was no vomiting. A few such cases do present some oedema (Fromme,¹ Myers²), showing that the occurrence is not impossible; but these are rare. A very important point, however, which appears to have escaped the general observation of commentators, is that while oedema is usually absent there is also lack of evidence that the body weight undergoes any increase. Cahill and Gyle³ describe one case showing emaciation in a twelve days' anuria. This would apparently signify that in the peculiar circumstances of total mechanical anuria the intake of fluid is, for some reason, nearly balanced by extrarenal loss through intestine, lungs, and skin, so that no extra fluid is disposable which might give oedema. In oedematous nephritis, on the other hand, the state of affairs is entirely different. It has been well known since the observation of Widál and Javal⁴ that in subacute nephritis there is a rise of body weight—which in an adult may amount to 12½ lb. above normal—before the clinical appearance of oedema, and that this continues increasingly as oedema sets in. In acute nephritis the existence of over-retention of fluid has been made apparent most usually by considerable loss of weight (20 lb. in ten days, H. MacLean⁵), with diuresis during the period of recovery. Some of this loss might be attributed to emaciation, but Kaliebe's⁶ charts of very early cases of war nephritis revealed a rise of body weight amounting to about 4 lb. in two days while oedema was increasing, thus proving a genuine retention of fluid. It appears possible to say, therefore, that the usual absence of oedema in mechanical anuria is not the complete argument against the retention origin of renal oedema that it has sometimes been represented to be.

VARIETIES OF HYDROPIGENOUS NEPHRITIS

Another important difficulty in the way of accepting fluid retention by the diseased kidney as the common cause of all renal oedemas has been the diversity of renal lesions described in the group of nephritis which exhibit this symptom, and especially the predominance of tubular changes in some, whereas excretion of water appears to be most likely a glomerular function. This variation in lesion is probably less wide than was at one time believed, but it still appears considerable. The main characteristics of the various forms of nephritis in which oedema is common may be sketched here only very briefly.

(a) In acute diffuse glomerulo-nephritis the lesion is a partial blockage of the tuft capillaries by excess of endothelial cells, accompanied by leakiness of the capillary walls for blood protein. The tubules, though they sometimes exhibit changes, are frequently of normal aspect in cases ending fatally within a week or ten days of onset (Dunn and

* Made in opening a discussion in the Section of Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Dublin, 1933.

McNee).⁷ The rise of blood pressure, which continues through the oedema period, is confirmatory of the view, based on histology, that there is some obstruction to the circulation through the kidneys.

(b) In subacute glomerulo-tubular nephritis the above lesion of glomeruli persists more or less, and is probably often a more effective obstruction to blood flow, as some tufts may be entirely ablated. With this there are often hypertrophy of the left ventricle and continued high blood pressure, but the rate at which these appear varies widely in different instances. There are also here much fatty deposit and other degenerative appearances in tubule cells, while catarrh and atrophy of tubules may be prominent if the glomerular lesions are severe.

(c) In nephrosis, so far as that term is applicable to a disease characterized by high albuminuria and obstinate oedema without nitrogen retention or raised blood pressure, the glomeruli differ from those of typical subacute nephritis in that the capillaries appear mainly patent. I would, however, agree with Bell⁸ and Gray⁹ that minute stigmata which frequently occur have the significance of an earlier primary inflammatory lesion of the tufts, and are not, as Fahr¹⁰ and Bennett¹¹ have suggested, secondary to tubular changes. The capillary walls, at any rate, are abnormally pervious to protein, as in nephritis. The absence of hypertonus is no doubt to be correlated with freedom of blood flow through the tufts. The tubules often, but, I believe, not invariably, show much appearance of degenerative change as in subacute nephritis, but usually no catarrh or atrophy.

(d) In amyloid kidney, where oedema sometimes occurs, the main changes are amyloid disease of the glomerular capillary walls associated with leakage of protein but with little occlusion of lumina. Here again the blood pressure is usually low. The tubular changes are as in subacute nephritis.

(e) The nephritis of pregnancy has frequently been described as a degenerative tubular lesion, though not on the basis of very critical examination. It is probable, however, that its morbid histology is that revealed in fatal eclampsias by the careful observations of Fahr¹² and Bell.¹³ They find a lesion of the tufts which has some points of resemblance to glomerulo-nephritis but with less evidence of obstruction to capillaries. I have recently had the opportunity, with Dr. Dugald Baird, to confirm the occurrence of a diffuse lesion of glomeruli, and we definitely regard it as a variety of glomerulo-nephritis. We have observed that in cases which are known to have been oedematous the glomerular change is frequently unaccompanied by any definite degeneration of tubule cells.

It will be noted that the main features in which the above five conditions differ among themselves are: (1) the state of the tuft capillaries as regards blockage of their lumina, the latter being absent in nephrosis and amyloid disease, intermediate in nephritis of pregnancy, and marked in glomerulo-nephritis; and (2) the appearance of degenerative change in tubular epithelium, this being often absent in early acute nephritis and nephritis of pregnancy, but marked in the other three. The main features which all exhibit are diffuseness of lesion, all the nephrons being involved, the permeability of tufts to protein, and the persistence in bulk of tubular tissue, though degenerative changes are more or less in evidence: at the same time these degenerative appearances are often unassociated with death or desquamation of cells, and the frequently good concentrating power for urea suggests that the cellular alterations noted are of less lethal import than their extent might imply. The group differs on the one hand from non-oedematous acute nephritis in that the glomerular lesions are diffuse, not focal, and on the other from chronic glomerulo-nephritis or interstitial nephritis without oedema in that the latter show extensive atrophy of tubules and usually variable lesions in surviving tufts. The distinction that can be made of the oedematous group as a whole no doubt requires a broad basis, but the symptom of oedema has had to be supported on an even broader basis of functional disturbance.

OEDEMA OF ACUTE NEPHRITIS

An important question that must be dealt with is the question of whether oedema can have the same underlying cause in all the types of nephritis, or whether, as some suggest, entirely different forms of pathological function are represented. In regard to this, the occurrence of continuity between stages and the appearance of linking forms have some significance. The oedema of the acute stage may extend without interval into that of subacute nephritis. Again, the oedema and other clinical features of some cases which are ultimately proved to be subacute glomerulo-nephritis so closely resemble those of what is called nephrosis that no certain differentiation is possible during life. This might be interpreted to mean that, even if a group of genuine nephrosis can be identified by skilled histological examination after death, as Leiter¹⁴ has concluded in his admirable review, the difference during life between them and some cases of subacute glomerulo-nephritis is so slight as to be immaterial.

A theory which has obtained wide currency is that the oedema of acute nephritis is of the nature of an inflammatory oedema due to injury of the tissue capillaries by the same agent as damages the renal glomeruli (Beckman¹⁵). This view is based mainly on the relatively high protein content of the oedema fluid. This may undoubtedly be high—1.12 to 2.15 per cent., as compared with that in nephrosis of 0.03 to 0.04 per cent. or that in cardiac oedema of 0.25 to 0.7 per cent. (Beckman¹⁵)—but apparently it is not invariably so high, as the two cases of acute nephritis of Fischer and Fodor¹⁶ gave only 0.4 to 0.6 per cent. On the other hand, in acute nephritis oedema is generally less in amount and the fluid is less easily collected without serum contamination than is the abundant transudate of nephrosis. Furthermore, Beckman has himself observed in the resolution of cardiac oedema that the protein content of the fluid may rise well above the mean of that observed in acute nephritis as the fluid diminishes. The same occurrence was noted also in his case of acute nephritis, where successive observations were made—that is to say, the high protein content, supposedly an indication of inflammatory injury to capillaries, became greater as the lesion improved. The protein content of oedematous fluids of known inflammatory origin is usually much higher than in the oedema of acute nephritis—4 per cent. or more (Hoffman¹⁷). Also it is noteworthy that in subjects with large local inflammatory exudates, as in poisoning from war gas or in acute pleural effusion, the blood is concentrated owing to loss of fluid. In acute nephritis, on the contrary, as will be shown, the blood contains an excess of water. The evidence for the inflammatory character of the dropsy in acute nephritis therefore appears less significant than other features, which point to its origin from retention of fluid by the kidneys. In further discussion it will accordingly be considered along with the other forms as part of a general problem.

THEORIES OF RENAL OEDEMA

Widal's¹⁸ view was one of retention by the diseased kidneys, not of fluid, but of common salt; the water was judged to be held secondarily in order to preserve the isotonicity of the tissues. It is proper to say that while this view, as it stood, is not now generally accepted, it contains a large element of truth that has never been completely contradicted. It does make some attempt to account for the well-known influence of salt intake in many cases of nephritic oedema, and it seems possible that if Widal had maintained a retention by the kidneys of physiological saline solution rather than of the salt itself his argument would have been less open to criticism. The main grounds for objection to Widal's theory are,

first, that very marked salt retention, up to 1 per cent., may occur in the blood without oedema resulting, as in chronic interstitial nephritis; although here there is no tendency to fluid retention by the kidney. The second objection is that which was first put forward by Volhard¹⁰—namely, that in some nephritic oedemas, and especially in nephrosis, the blood shows no increase of water or salt but may actually be concentrated. Volhard attributed this fact to damage, by toxic substances absorbed from degenerate renal epithelium, of the capillary walls throughout the body. Owing to this toxic injury these became unduly permeable, and the consequent escape of fluid in large amount from the vessels produced the oedema and at the same time rendered the blood unduly concentrated.

Volhard thus initiated the theory of extrarenal causation of the oedema, and he considered that in such cases also the appearance of impaired water and salt excretion by the kidneys was due rather to this organ receiving these substances at too low a level in the blood than to an essential inability of the renal tissues to excrete them. The fact of low blood water and low blood chloride in nephrosis has been repeatedly confirmed (Veil,¹⁹ de Wesselow²⁰), but variously interpreted as due to injury of vessels or of the tissues (Beckman,¹⁵ and Fischer and Fodor¹⁶). Nonnenbruch²¹ has observed its occurrence even in acute nephritis, though only exceptionally. In acute and in subacute glomerulo-nephritis hydraemia appears to be the general rule (Veil,²² Fischer and Fodor¹⁶), and this, so far as it goes, is in keeping with the idea of retention of water by the kidney so that the blood becomes diluted and subsequently the excess escapes to the tissues.

The facts regarding salt and water distribution in oedematous nephritis are, however, somewhat complex. In the early stages of acute war-nephritis with oedema the blood almost invariably contained an excess of water and salt (H. MacLean,⁵ Thannhäuser²³). As this was associated with marked oliguria and a known acute renal lesion it was interpreted as significant of retention of fluid by the kidney. But in protracted cases of the same type MacLean observed concentration of the blood, not hydraemia, though oedema was still present. He attributed this to loss of fluid from blood to tissues, partly dependent on damage of vessels and partly on low colloid osmotic pressure of the blood from loss of plasma protein. These cases, which might be considered early subacute glomerulo-nephritis, are very important as linking the oedema phenomena of this condition to those noted in nephrosis. De Wesselow's²⁰ observations in cases of nephritis tested by salt dosage are also of much interest. He concluded that in a mixed group of oedematous nephritis, including acute, subacute, and nephritis of pregnancy, where the plasma chloride rose after a dose of salt, there was evidence of renal retention. On the other hand, in typical parenchymatous nephritis with ascites (nephrosis type), the absence of rise of blood chloride and the probable existence of blood concentration pointed to abnormal permeability of capillaries which would permit of escape of salt and water into the tissues. As F. C. McLean²⁴ has pointed out, however, in controversy of the latter view—Volhard's, which is shared by de Wesselow—the capillaries cannot well be more permeable to water and salt than they are normally, while the extremely low protein content of the oedema fluid in nephrosis would suggest a less degree of permeability of the vessel walls than normal.

EXCRETION FROM ARTERIAL BLOOD

An important series of facts which do not appear to have received sufficient attention in relation to this vexed question of blood and tissue exchange, and of renal

participation in retention, refer to the general arrangement of the circulation and the opportunities for addition to, or removal of, fluid from the blood at various points. Samples of blood which are clinically available for examination are almost invariably venous blood returning from the tissues, where, in an oedematous case, more or less water and salt may have been given up, thus causing some degree of concentration. But the blood which goes to the kidney, and from which any deduction of fluid and salts is made for the purpose of elimination, is arterial. Now arterial blood is of uniform composition, like that in the right ventricle, which mingles, in addition to blood from the periphery, with hepatic vein blood bringing absorbed fluid from the intestine and also lymph from the thoracic duct. In oedema there is no reason to suppose that the tissue fluid is absolutely static, and the lymph may well be more abundant than normally. Therefore we may assume that frequently, especially in oedema, the arterial blood will contain definitely more water and salt than a peripheral venous sample. This will be the case even when the venous blood is hydraemic so long as oedema is on the increase: it seems even more certain to be the case when the venous blood is definitely concentrated as in nephrosis.

On the other hand, when oedema is undergoing resolution the venous blood accessible to examination will contain more water than the arterial, as it is helping to remove fluid from the tissues. Veil²² has noted a further dilution of venous blood during resolution of oedema in subacute nephritis. Kylin²⁵ also, who has actually examined arterial and venous samples taken at the same time from oedematous cases, has found that, while oedema is increasing, the colloid osmotic pressure of arterial blood is lower than that of the venous blood, but during resolution of oedema the reverse is the case, owing to dilution of the latter by absorption of fluid from the tissues. On these grounds it is possible to suggest that the low salt and water values in the venous blood of nephrotic cases are no fair indication of the arterial blood content, yet it was largely on this assumption that the theory of extrarenal genesis of nephrotic oedema was originally based.

SALT DOSAGE IN NORMAL SUBJECTS

In attempting to appreciate how readily salt and water retention by the diseased kidney may occur and how this may lead to subcutaneous oedema, it is useful to refer to the results of test doses of salt in normal subjects. Thus Veil¹⁹ has found that if 20 grams of common salt are ingested in a moderate amount of water there is an immediate diuresis, but only half the salt is excreted. By the following day the blood chloride and water are nearing normal, but the extra salt continues to be excreted till the third day, the evidence being that salt has been temporarily deposited in the tissues. In such experiments there may be a rise of body weight owing to retention of fluid with the salt; but in Veil's experience this was a variable occurrence, depending not only on the amount of fluid ingested but on the state of salt and water plethora of the body at the start of the experiment. Baird and Haldane,²⁶ ingesting larger doses of salt (38 grams), also observed much retention in spite of initial diuresis, and they found that the deposition of salt in the tissues was accompanied at times by definite oedema.

An abnormal accumulation of fluid in the tissues in the normal subject is apparently more difficult to secure than that of salt. It is of interest to note, however, that while a large dose of plain water produces rapid and copious diuresis, the ingestion of the same amount of physiological saline solution often has no such effect (Meyer,²⁷ Crawford²⁸). This suggests that the kidneys part with these two substances less readily, if they are brought to them

near the proportions in which they occur in normal blood. What apparently must happen in test dosage experiments is that as extra salt is absorbed through the portal system it brings the content of the arterial blood above normal concentration. As this is distributed over the body the amount that can be excreted from that passing through the renal arteries is, in spite of the diuresis produced, too small to keep pace with the intake from the intestine. As the salt content of the arterial blood still rises some is deposited in the tissues, probably because, as McLean²⁴ points out in connexion with water, the maintenance of a fairly constant volume and constitution of the blood appears to be a paramount physiological desideratum. In the meantime diuresis depletes the blood of water, thus interfering with the removal of salt from the tissues until fresh supplies of fluid have been taken in.

These facts might be said to indicate that the retention of excess salt in the normal subject is due to extrarenal factors; but this is so only in a sense, for the accumulation in the body is due to the inability of the normal kidney to excrete more than a certain amount of salt per day with the aid of any known amount of fluid intake. In nephritis, however, oedema begins on the ingestion of amounts of water and salt determined by natural choice, and such amounts are dealt with easily by the normal kidney so that no retention occurs. The difference appears to be that in nephritis the kidneys cannot excrete the proper amount of salt and water, so that these accumulate first of all in the blood, but, in accordance with the above-mentioned law, they are soon transferred to the tissues. A fundamental problem of oedema is that of regulation of volume, including that of the blood and the tissue fluids (F. C. McLean²⁴).

LOW COLLOID OSMOTIC PRESSURE OF PLASMA AND OEDEMA

A still different theory of nephrotic oedema is that developed mainly by Epstein²⁹ on the basis of Starling's observations on the osmotic pressure of plasma proteins. In these chronic oedemas the plasma proteins are much diminished owing to loss by albuminuria, and the colloid osmotic pressure of the plasma may be even lower than the low total protein would indicate, owing to the greater diminution of albumin than of globulin. The power of the blood proteins to hold fluid in the capillaries, against the hydrostatic pressure which tends to drive it out, is much lessened: accordingly, we have a basis for a greater passage of fluid into the tissues than normally, and for less being drawn back at the venous ends of the capillaries, where hydrostatic pressure is lower. This view has been accepted by some as a complete explanation of nephrotic oedema, and, as will be seen, it is only indirectly the result of the renal disability. The theory has not, however, escaped important criticism. Some have observed that the degree of oedema does not always correspond with the amount of decrease of plasma protein (Linder, Lunds-gaard, and Van Slyke³⁰); while Leiter,¹⁴ in the main adhering to Epstein's view, does not apparently entirely discount this claim. Kylin²⁵ also has noted resolution of oedema occurring in a nephrosis without the antecedent rise of colloid osmotic pressure in the blood that one would expect. Another difficulty is that the low colloid osmotic pressure of the blood does not apparently interfere with absorption of water from the intestine as might be anticipated; not does it render more effective the separation of fluid from the blood by the kidneys. This important blood change must no doubt be a significant contributory factor in allowing escape of fluid from the vessels into the tissues, thus giving oedema and also concentration of the venous blood. There is as yet, however, no evidence that it can account for the large

retentions of fluid in the body which characterize nephrotic oedema.

FLUID RETENTION AS A RESULT OF DISORDERED REABSORPTION IN THE KIDNEY

A consideration of much of the literature dealing with this subject would suggest that one reason why extra-renal explanations of renal oedema have been sought out and adhered to is that the kidney has been regarded as a secreting organ after Heidenhain's theory. According to this view the water and salt appearing in the urine represent all of these substances which have been filtered from the glomeruli, while most other constituents, like urea, have been secreted into this current by the tubule cells, thus attaining a high concentration. On this view oliguria would be explained simply by lessened filtration. Very few workers, apparently, have attempted to apply Ludwig's theory of large filtration and reabsorption, in its modern form as expressed by Cushny³¹, to the problem of renal oedema, though Mayrs³² has developed its application to the explanation of oliguria. Obviously these two theories of physiological mechanism would provide very different interpretations of the phenomena observed in disease as in the normal. The application of the secretion theory to the interpretation of the known facts in acute glomerulo-nephritis and in nephrosis shows great difficulties in the way of securing reasonable and concordant explanations in the two cases. In acute nephritis the suggestion would be that, owing to blockage of capillaries in the tufts, the amount of filtration was insufficient to secure adequate disposal of water and salt, while the tubules, intact at first, would still secrete sufficient urea to keep the blood urea down, as it is in the early period when oedema is already well marked. But if the glomerular blood flow were so much reduced by capillary blockage as to cause retention of water and chloride we would expect to find urea retained even more markedly. As Huber's³³ analysis has finally shown, all the blood which reaches the renal tubules has first to pass through the glomeruli, so will be correspondingly diminished. Here the low concentration, 30 mg. per cent. of urea, as compared with sodium chloride, 600 mg. per cent. in the blood, gives much less opportunity for getting rid of the former than the latter at a low rate of flow. In the case of nephrosis the blood flow through the tufts and to the tubules is probably not diminished, and the capillary walls are sufficiently permeable as they leak albumin, yet here it is salt and water which are retained while urea is concentrated and often excreted efficiently though some of the main morbid appearances are in the tubule cells.

The filtration-reabsorption hypothesis is not without its difficulties also, but it appears on the whole to offer more chance of an explanation in all cases of retention of an undue amount of fluid and salt while urea is dealt with efficiently. On this view, in the normal working of the kidney, a moiety of protein-free plasma with all soluble constituents is filtered by pressure from the blood passing through the tufts. In passage down the tubules water, chloride, and sugar are reabsorbed to an extent which leaves urea and other purely excretory substances highly concentrated. By this theory the amount of filtrate is very large in proportion to the amount of urine formed, but it is not large in proportion to the amount of blood passing through the kidney—probably round about 10 per cent. (Dunn, Kay, and Sheehan³⁴). The amount of fluid reabsorbed by the tubules is almost equally large—say 59/60 or 90/100 of the filtrate, so that the kidney acts in respect of water and salt as an organ of conservation rather than of excretion. In this process, going on continuously, it will obviously require very exact

adjustment to secure that neither too much nor too little water is reabsorbed, and a small error by way of excess in reabsorption throughout the day will result in a real retention of water and salt in the body so long as sufficient quantities of these are taken in.

The effects of this view of functional activity may be matched in a general way with the anatomical features which the hydropigenous nephritides possess in common—namely, diffuseness of lesion and the persistence in bulk of tubular or reabsorbing tissue. Considered more in detail, it fits in very well with the three conditions showing some degree of blockage of glomerular capillaries, especially for the stage most difficult to explain—namely, where there is already oedema and water and salt retention, but sufficient excretion of urea. Here we may suppose that, owing to partial blockage of capillaries, the tufts can no longer produce a sufficient amount of filtrate by working in relays as normally, but all have to be perfused continuously, possibly with the aid of increased blood pressure. A normal total amount of filtrate with a sufficient total amount of urea is thus being produced, but it is distributed to all the tubules instead of to the smaller number, a third or a fourth, corresponding to the number of tufts normally functioning at a time. The opportunity for reabsorption is thereby increased. With a worsening lesion of the tufts this system would still carry on with a rise of blood urea, for a greater percentage of urea in the original filtrate would mean an equal total elimination from a less amount of fluid. Ultimately, however, definite urea retention would show, as it often does, in later periods of acute and subacute glomerulonephritis. This may be regarded only as a type of explanation, and is by no means necessarily the correct one: it would not apparently apply to the elucidation of conditions in nephrosis. On the other hand, in nephrosis the anatomical fact of apparent freedom of circulation seems to demand excessive reabsorption as the likeliest explanation for the oliguria, especially with urea excreted normally. The imbalance of reabsorption and filtration may well be produced on some less obvious principle.

The account which has been given in opening this discussion is doubtless open to the charge of bias in favour of a renal retention origin of renal oedema. It would, however, have been difficult in the time available to do justice to all the more important theories, and at the same time convey an idea of the need for reconsideration of certain important dicta. It is hoped that some of the arguments brought forward will be accepted as justifying the view that some reconsideration is possible. As a minor form of excuse for attacking the purely extrarenal theories, it may be urged that while these have been highly developed and made to assume great probability, they are diverse and probably cannot all be correct, while none of them produces a principle applicable to all stages of the oedema. In the end, when it is desired to remove the pathological accumulations of fluid, it is to the kidney that appeal has to be made, and if diuresis cannot be established the condition remains essentially unchanged.

REFERENCES

- ¹ Fromme: *Deut. klin. Woch.*, 1914, xl, 780.
- ² Myers, W. A.: *Journ. Amer. Med. Assoc.*, 1925, lxxxv, 10.
- ³ Cahill and Gyle: *Ibid.*, 1928, xci, 1970.
- ⁴ Vidal and Javal: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, third series, 1903, xx, 733.
- ⁵ MacLean, H.: Medical Research Council, Special Report Series No. 43, 1919.
- ⁶ Kaliebe: *Münch. med. Woch.*, 1917, lxiv, 1086.
- ⁷ Dunn and MacNee: *British Medical Journal*, 1917, i, 327.
- ⁸ Bell: *Amer. Journ. Path.*, 1929, v, 587.
- ⁹ Gray: Medical Research Council, Special Report Series No. 178, 1933.
- ¹⁰ Volhard and Fahr: *Bright'sche Nierenkrankheiten*, Berlin, 1914.
- ¹¹ Bennett, Dodds, and Robertson: *Quart. Journ. Med.*, 1930-1, xxiv, 239.
- ¹² Fahr: *Zentralbl. f. Gynäk.*, 1920, xlv, 991.

- ¹³ Bell: *Amer. Journ. Path.*, 1932, viii, 1.
- ¹⁴ Leiter: *Medicine*, 1931, x, 135.
- ¹⁵ Beckman: *Deut. Arch. f. klin. Med.*, 1921, cxxxv, 39.
- ¹⁶ Fischer and Fodor: *Zeit. f. Ges. Exper. Med.*, 1922, xxix, 465.
- ¹⁷ Hoffmann: *Deut. Arch. f. klin. Med.*, 1889, xlv, 313.
- ¹⁸ Vidal and Lemierre: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, third series, 1903, xx, 678, 785.
- ¹⁹ Veil: *Biochem. Zeit.*, 1918, xci, 267.
- ²⁰ de Wesselow: *Quart. Journ. Med.*, 1925-6, xix, 53.
- ²¹ Nonnenbruch: *Deut. Arch. f. klin. Med.*, 1921, cxxxvi, 170.
- ²² Veil: *Ibid.*, 1914, cxiii, 225.
- ²³ Thannhäuser: *Zeit. f. klin. Med.*, 1920, lxxxix, 181.
- ²⁴ McLean, F. C.: *Physiol. Rev.*, 1925, v, 618.
- ²⁵ Kylin: *Zeit. f. Ges. Exper. Med.*, 1931, lxxvii, 289.
- ²⁶ Baird and Haldane: *Journ. of Physiol.*, 1922, lvi, 259.
- ²⁷ Meyer, L. F.: *Ergeb. d. inn. Med. u. Kinderheilk.*, 1919, xvii, 563.
- ²⁸ Crawford: *Quart. Journ. Med.*, 1927-8, xxi, 71.
- ²⁹ Epstein: *Amer. Journ. Med. Sci.*, 1917, cliv, 638.
- ³⁰ Linder, Lundsgaard, and Van Slyke: *Journ. Exper. Med.*, 1924, xxxix, 887.
- ³¹ Cushny: *The Secretion of Urine*, second edition, 1926.
- ³² Mayrs, E. B.: *Quart. Journ. Med.*, 1926, xix, 273.
- ³³ Huber: *Cowdry's Special Cytology*, 1927, i, 662.
- ³⁴ Dunn, Kay, and Sheehan: *Journ. of Physiol.*, 1931, lxxiii, 371.

AUTOLYSED YEAST PRODUCTS IN THE TREATMENT OF ANAEMIA

BY

L. S. P. DAVIDSON, B.A.CANTAB., M.D.
F.R.C.P.ED.

The number of publications which have appeared within the past two years regarding the value of vitamin B preparations, especially those derived from yeast, in the treatment of anaemia is evidence of the interest which the problem has aroused in the minds of clinical haematologists and laboratory workers alike. In view of the scientific and practical importance of the subject, and the fact that considerable divergence of opinion exists regarding the therapeutic efficiency of such products, the time appears ripe for a review of the whole problem.

YEAST PRODUCTS IN THE ANAEMIAS

I. HYPOCHROMIC ANAEMIA

(a) The milk anaemia of rats. Parsons¹ has shown that when yeast is added to the milk diet the anaemia is cured, growth proceeds satisfactorily, and reproduction may occur. The progeny, however, develop anaemia. This can be prevented by supplying iron as well as yeast to the pregnant mother rat.

(b) Nutritional anaemia of infants. Although the hypochromic anaemia of milk-fed rats and infants appears to be similar, since iron deficiency is the essential feature, Parsons found that yeast products generally failed to influence the nutritional anaemia of infants, which, however, responded to adequate doses of iron. In a few resistant cases the supplemental effect of adding yeast or copper, or both, to the iron ration appeared to produce beneficial results.

(c) Iron-deficiency anaemias of adults. In 1931 I published the results of my investigations² into the therapeutic value of yeast preparations in the treatment of hypochromic anaemia in adults, particularly of the type associated with achlorhydria. Marmite was found to be as useless as liver extract in the treatment of hypochromic anaemia, a point on which all workers in this field agreed.

II. HYPERCHROMIC MACROCYTIC ANAEMIA

Wills³ showed that the tropical macrocytic anaemia of Indian women responded to small doses (12 to 30 grams) of autolysed yeast product (marmite), by showing a