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NOTE ON A CASE OF LIPOID NEPHROSIS.

PART I.—CLINICAL AND BIOCHEMICAL.

BY

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THE term nephrosis was first suggested in 1905 by Friederick Müller¹; it is usually employed nowadays to distinguish a bilateral degenerative and mainly tubular diffuse renal lesion in contrast with nephritis, which is limited to diffuse inflammatory and proliferative kidney changes. Valuable contributions to the problem of nephrosis were made from 1913 onwards by Munk,² Volhard and Fahr,^{3,4} Epstein,⁵ Elwin,⁶ and others. In 1914 a special lipoid form of nephrosis was described by Volhard and Fahr, and has since received a good deal of attention, the following characteristics being defined.

Lipoid nephrosis has an insidious onset, but some think it may follow a comparatively mild or unnoticed attack of acute nephritis; its course is chronic; there is marked albuminuria, oliguria, decreased blood protein with relative globulin increase and reversal of the normal albumin-globulin ratio, lipaemia, hypercholesterolaemia, normal renal function tests, oedema, and no retention in the blood of nitrogenous waste products. In the urine are found casts and double refractive lipoid droplets, but no erythrocytes. The blood pressure is normal, and the basal metabolic rate is frequently below the normal. With regard to the basal metabolic rate, it should be noted that most determinations in the published cases were made when the patient was oedematous, and that the increase in body weight due to water retention tends in itself to lower the rate, which would have a higher reading were the patient oedema-free.

The main lesion in lipoid nephrosis is supposed to be a degenerative one chiefly affecting the renal tubules, but its occurrence is very rare. Very few necropsy findings of pure lipoid nephrosis have been recorded, partly because of the infrequency of the condition, and partly because the patients exhibiting this syndrome usually live for a considerable time, or die of intercurrent infections, or progress into chronic nephritis with glomerular as well as tubular changes. Thus, sometimes the clinical syndrome of nephrosis is present, but at necropsy the changes characteristic of nephritis are found as well as those of tubular degeneration.

Generally speaking it may be said that, while we have

no pathological classification of diffuse degeneration or inflammation of the kidneys which may be used clinically to predict accurately the nature of the kidney lesions, nevertheless it appears that the clinical syndrome of nephrosis does exist. It must be remembered also that the physiological unit of architecture of the kidney is in itself a complex structure, consisting of glomerulus, proximal convoluted tubule, loop of Henle, and distal convoluted tubule which empties into a collecting tubule; that this tubular system is lined by a layer of epithelial cells which are of different types in the different parts; and that between the afferent glomerular arteriole and the efferent tubular venule a double system of capillaries exists. It is reasonable to expect that if this complex secreting structure is injured in any part, its other parts may become secondarily affected, either functionally or structurally. It is thus readily realized that a diffuse renal lesion seldom follows a simple course, but that one type of lesion frequently merges into another. The view is gaining ground that, while the most obvious early kidney lesion in lipoid nephrosis is a degenerative one affecting the tubules, changes may be found also (and possibly at an early stage in the development of the disease) in the glomeruli; these glomerular changes at first may be slight, and may require special pathological methods for their demonstration. Lipoid nephrosis is regarded by some as a particular form, or development in the course, of Bright's disease, but others think that it may be primarily due to a special type of disturbance of the lipoid-protein metabolism. At any rate, its position as a *clinical* entity is doubtless established.

The work of Barker and Kirk⁷ is interesting in this connexion. These authors decreased the blood proteins in dogs by repeated bleedings, but returned the corpuscles to the circulation; when the serum protein was diminished to a certain degree by this procedure oedema appeared, and its amount seemed to be more closely related to the level of the serum albumin than to that of the total serum protein. At the time of the appearance of the oedema, albumin, fat droplets, and casts appeared in the urine, and the basal metabolic rate fell; pathological study of these dogs showed definite degeneration of the renal tubules, and later, with progression of the disorder, glomerular changes. In other words, the clinical picture of nephrosis was experimentally produced.

Christian's⁸ views are of importance. This investigator believes that the majority of cases of nephrosis are mixed cases in which, clinically and pathologically, there are evidences of both nephrosis and nephritis, and that as they progress they tend to lose the clinical evidences of nephrosis, and to gain the clinical features of nephritis. He seems to consider the protein loss through albuminuria of considerable significance, and points out the necessity of liberalizing the protein of the diet to replace the protein lost from the blood through the albuminuria. He believes that the source of the albuminuria is in the passage of albumin through the walls of blood vessels, most probably glomerular capillaries, because of functional changes. He considers nephrosis as simply a form of chronic nephritis, and thinks that the name should be used merely to describe a clinical syndrome, since it does not imply that a definite and single form of pathological lesion will be found in the kidney.

Report of Case.

A man, aged 34, was admitted to the Mater Misericordiae Hospital on January 10th. His weight was 151½ lb. and height 5 ft. 7 in. The previous history is irrelevant. From six months before admission he had oedema of the legs and face, and he first noticed oedema in the legs on the day after he had marched in a procession for several hours. On admission to the hospital the legs and lower part of the back were considerably oedematous, and the face was puffy and pasty pale. Albumin was abundant in the urine, which also showed hyaline and fatty casts and a few leucocytes, but no erythrocytes. The blood pressure was 170/100, and the pulse rate 70 per minute and regular; there was slight accentuation of the aortic sound at the base of the heart. X-ray examination by Dr. J. Geraghty revealed pyorrhocal absorption of the alveolar borders of most teeth present, but Professor Edward Sheridan stated that, owing to recession of the gums, there was almost complete absence of pockets, and consequently only a small area of infection at the time of examination. The nose, accessory sinuses, and throat were normal (Dr. P. Dempsey). There was dullness on percussion, and diminished breath sounds over both pulmonary bases. X-ray examination of the lungs by

Dr. Geraghty revealed small bilateral basal pleural effusions. There was achlorhydria and a mild secondary anaemia. The patient was on a low protein diet for about a month previous to admission.

Function Tests and Blood Chemistry.

The total protein, albumin, and globulin determinations were performed on plasma, by the combined methods of Howe,⁹ Wu,¹⁰ and Kock and McMeekin,¹¹ as described by Hawke and Bergeim¹²; blood cholesterol was estimated as described by Myers and Wardell,¹³ blood phosphorus by the method of Benedict and Theis,¹⁴ and blood calcium by the method of Clark and Collip.¹⁵ The Roth-Benedict portable spirometer was used for estimating the basal metabolic rate.

The phenolsulphonphthalein excretion test gave a figure of 60 per cent. in two hours; 600 c.cm. of urine was excreted in four hours after ingesting 1,000 c.cm. of water. The fixation test of the urine showed no inability of the kidney to concentrate. The following blood values per 100 c.cm. were obtained shortly after admission:

Urea, 28 mg.; uric acid, 2.5 mg.; creatinin, 1.4 mg.; non-protein nitrogen, 30 mg.; cholesterol, 600 mg. (normal about 180); calcium, 8.9 mg.; and phosphorus, 1.4 mg. The plasma chloride content was 456 mg.

The basal metabolic rate was +12 per cent. at a period when the oedema was slight, and apparently confined to the shins and ankles. The differential blood count was normal. The urea concentration test gave 2.12 per cent. of urea in the first hour and 2.53 per cent. in the second. The blood serum was milky. The total amount of albumin excreted in twenty-four hours was 44.8 grams. On admission there was oliguria (about 800 c.cm. in the twenty-four hours), but later the urine volume became about normal in amount, in correspondence with the fluid intake.

The erythrocytes numbered 4,000,000 and the leucocytes 6,000 per c.mm. The haemoglobin percentage was 60. The blood Wassermann reaction was negative.

Blood Protein Determinations. (Grams per 100 c.cm.)

	Jan. 2.	Jan. 8.	Jan. 20.	Mar. 12.	April 7.	Normal Figure.
Total protein ...	2.5	2.2	2.3	5.58	5.8	6.5 to 8.2
Albumin ...	1	2.1	2.5	3.7	3.1	4.6 to 6.7
Globulin ...	1.4	0.7	0.56	0.18	2.6	1.2 to 2.3

This table indicates that the case before treatment showed reversal of the normal albumin-globulin ratio, and marked diminution of the total protein. Double refractive lipid globules were found in abundance free in the urine, in the casts, and in desquamated renal epithelium, by Dr. R. A. Q. O'Meara (see Part II). The retinal arteries showed a slightly increased light reflex, and there was evidence of compression of the retinal veins under the arterial crossings (beginning arterio-sclerotic changes); these findings were confirmed by Dr. D. O'Donoghue, assistant ophthalmologist to the hospital.

It is interesting to note that, after a profuse diuresis induced by ammonium chloride and salyrgan, the oedema practically disappeared, the blood pressure fell to 144/94, and the basal metabolic rate was +5 per cent.

Treatment.—The diet consisted of 120 to 140 grams of protein, about 60 grams of fat, unlimited carbohydrate, moderate restriction of salt, and about 1,200 c.cm. of fluid per day. Thyroxine was given for a few days; dilute hydrochloric acid and iron were administered. Periods of a few days on ammonium chloride were followed by a few single intramuscular doses (2 c.cm.) of salyrgan to control the oedema, and there were occasional exhibitions of digitalis. The duration of observation was about five months. The patient was only confined to bed for the first few days, and thereafter was allowed exercise in moderation.

Result.—Great improvement in the general health ensued, with disappearance of anaemia and of the pleural effusions, lowering of the blood cholesterol from 600 to 270 mg. per 100 c.cm., increase of the serum proteins as shown in the table, and lowering of the body weight from 151½ lb. to 124½ lb., due apparently to almost complete disappearance of the oedema and the pleural effusions. The blood pressure on discharge was at about the same level as on admission, the fall after the previously mentioned diuresis being transitory.

The patient is probably beginning to develop arterio-sclerotic changes, as is evidenced by the elevation of the blood pressure and the slight changes in the retinal arteries; this may possibly be due to involvement of the glomeruli

in the pathological kidney process. The case is interpreted as being one of impure lipid nephrosis.

It is a pleasure to acknowledge the efficient assistance of Dr. K. Malley, the house-physician, and Mr. M. Moriarty, M.Sc., the resident student, in the study of this case.

PART II.—PATHOLOGICAL.

BY

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LIPOIDURIA is an almost constant finding in lipid nephrosis. It was regarded by Munk² as pathognomonic of the condition. This view, however, has been challenged, since lipoids, similar in characteristics to those found in the urine in lipid nephrosis, are found in other conditions as well. Not only do they occur in the urine in different types of renal disease, but also in certain chronic intoxications and metabolic disorders, associated with increased blood cholesterol, such as diabetes. In lipid nephrosis, however, they are usually present in abundance.

When seen with the ordinary microscope in a urinary deposit from a case of nephrosis they appear as fatty globules, either free in the casts or in renal epithelium. The polarizing microscope, however, reveals the fact that many of the lipid globules possess exceptional properties. When viewed with the aid of this instrument, the Nicol prism being crossed, many of them are seen to present a remarkable appearance, showing up brightly as Maltese crosses of light against the dark field. While the Maltese cross is the predominant pattern, other less striking patterns are also to be seen. One of these resembles a cross of light the centre of which has been blacked out; another a ring of light encircling a dark centre.

The physical properties of the globules, which are responsible for these appearances, are summed up in the adjective anisotropic; by virtue of their anisotropism they are doubly refractive. In a sense they are unique, since anisotropism is a property of crystalline solids. The globules, however, are fluid, and their discoverer, O. Lehmann, has called their physical condition the liquid crystalline state of matter. Chemically they are esters of cholesterol, but not in the pure state, since esters of cholesterol alone are not doubly refractive. The work of Aschoff, Windaus, and others shows that they are admixed with free fatty acids, fats, or phosphatides.

In the urinary sediment from Professor Moore's case, anisotropic lipoids were present in profusion, and were well demonstrated in photographs taken with the polarizing microscope. One of these photographs showed a cast in which the crosses of light, large and small, are apparent. In the neighbourhood of the cast could be distinguished the shadowy forms of renal cells which likewise contained anisotropic globules; other globules were free.

What is the pathology of the condition which gives rise to these bodies in the urine in lipid nephrosis? Is the condition primarily a metabolic disease with secondary involvement of the kidney, or is it primarily a disease of the kidney from which the other phenomena of the condition follow? An extensive critical review of the literature of the condition, combined with personal study of a number of cases was given recently by Bell,¹⁶ who discusses in detail the clinical features of the disease and the post-mortem appearances in cases which terminated fatally. Using a modification of Mallory's aniline blue connective tissue stain, he has been able to demonstrate that the endothelial cells of the glomeruli of the kidney are increased in both number and size, and that there is in addition some thickening of the basement membrane. The endothelial cells may or may not contain lipid droplets. The convoluted tubules are constantly the seat of lipid deposition, and coarse hyaline droplets may be found in the tubules. There is no tubular atrophy.

Lipoid nephrosis may therefore be regarded as a form of glomerulo-nephritis or glomerulitis in which the glomeruli are damaged, but their capillaries are only partially obstructed by the increase in number and size of the endothelial cells. This is very important, since they continue to function, and tubular atrophy does not usually