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

occur nor does contraction commonly set in as a later event. In the usual form of glomerulo-nephritis, on the other hand, the degree of capillary blockage is much greater, leading to functionless hyaline glomeruli, atrophied tubules, contraction of the kidneys, and to uraemia. Lipoid nephrosis does not terminate in uraemia. In cases which do not recover, death is most commonly due to peritonitis, pneumonia, or septicaemia. The frequency of peritonitis is remarkable, as it accounts for almost half the deaths; where the responsible organism has been isolated it has been found to be pneumococcus.

There can be little doubt that the lipoid which is deposited in the renal cells, and which finds its way thence into the urine, is an outcome of the very high cholesterol content of the blood. Its constant deposition in the convoluted tubules, and to a lesser extent in the glomerular cells, suggests that an endeavour is being made to excrete the surplus. As to the cause of the cholesterolaemia we have no certain knowledge; it may be secondary to the great loss of albumin in the urine sustained by sufferers from this form of renal disease. As in diabetes, so in lipoid nephrosis, mobilization of fat from the reserves may occur in an attempt on the part of the system to feed tissues partially starved by the constant drainage from the body, in the one case of carbohydrate, in the other of protein. Of the fat so mobilized, the cholesterol fraction is stable and relatively valueless as a source of energy. It seems possible that this fraction is taken up by the renal cells, and in particular by the cells of the convoluted tubules, where it is deposited, some eventually passing away in the urine either by disruption or shedding of the cells. This process of excretion of cholesterol is analogous to a physiological process by which an isomer of cholesterol

is excreted in the normal individual: the secretion of the sebaceous gland involves a degenerative process in which ischolesterol is first laid down in the gland cells, and later, either by disruption of the cells or by their separation from the gland, is discharged and lubricates the skin and its appendages.

Finally, as to the cause of lipoid nephrosis: in view of the probability that it is in reality a chronic mild glomerulitis, one should bear in mind that two bacterial toxins are definitely known to select the glomerulus of the kidney for attack. They are the toxins of the diphtheria bacillus and of the haemolytic streptococcus. The cause of lipoid nephrosis is unknown, but there is justification for suspecting a bacterial origin. One organism, the pneumococcus, suggests itself for study. Why is it that so many of the patients die of pneumococcal peritonitis?

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INSOLUBLE PRECIPITATES IN DIPHTHERIA AND TETANUS IMMUNIZATION.

BY

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THE addition of aluminium sulphate or potash alum to a diphtheria toxoid produces a relatively insoluble precipitate which has high antigenic properties. Glenny, Pope, Waddington, and Wallace (1926), and Glenny and Waddington (1928), have shown that such precipitated toxoid immunizes guinea-pigs more readily than the original toxoid.

In view of the promising results obtained,* it is possible that the most favoured method of human immunization against diphtheria in the near future may be by means of a suspension of toxoid precipitated by alum; it appears to be of interest, therefore, to present some results of animal experiments with both diphtheria and tetanus toxoid showing the extent to which the antigenic efficiency is increased by the addition of alum. During the course of our experimental work different quantities of alum from 0.1 to 2 per cent. have been added; in some instances the whole mixture of toxoid and alum has been used; sometimes the precipitate has been separated from the supernatant liquid and re-suspended after washing in saline. It is not within the scope of this paper to deal with these differences.

The immunity index method of Glenny, Allen, and Hopkins (1923), more fully described by Glenny and Waddington (1928), forms a convenient method of testing antigenic efficiency. Table I shows the immunity index given by the injection into guinea-pigs of 0.1 c.cm. of diphtheria toxoid with and without varying amounts of alum. It will be seen that when alum had been added to the toxoid, 29 guinea-pigs out of 41 were Schick-negative when tested three weeks later, and all were immune by the fifth week. Without alum none, out of 38, was immune after three weeks, and 8 were still Schick-positive seven weeks after injection.

* Since this paper was written, W. H. Park, at the Paris Congress of the International Society of Microbiology, reported 100 per cent. successful immunizations with alum-toxoid in small groups of children.

A further series of guinea-pigs was injected with 1 c.cm. of diphtheria toxoid, and the antitoxic titre of serum was tested four to six weeks later. Of 53 guinea-

TABLE I.—Showing the immunity index of guinea-pigs injected with 0.1 c.cm. diphtheria toxoid with and without alum.

	Number of guinea-pigs giving an index of					
	1	2	3	4	5	Over 5.
With alum ...	29	10	2	—	—	—
Without alum ...	0	10	12	5	3	8

pigs injected without alum, the majority contained 0.02 unit per c.cm. of serum, and the highest value recorded was 0.5 unit; of 23 injected with alum the majority contained 0.5 to 1 unit, and the highest recorded value was 7 units per c.cm. The results of the group are summarized in Table II.

Alum has also been added to diphtheria toxin used in the hyperimmunization of horses. The average antitoxic

TABLE II.—Showing the antitoxic value of the serum of guinea-pigs four to six weeks after the injection of 1 c.cm. diphtheria toxoid with and without alum.

	No. of guinea-pigs with an antitoxic value of (per c.cm.)				
	Under 0.001 unit.	0.001-0.01 unit.	0.01-0.1 unit.	0.1-1 unit.	Over 1 unit.
With alum ...	—	—	1	9	13
Without alum	3	6	31	13	0

value of groups of 50 horses was 696 without alum; with alum 1,102.

Many experiments have also been made with tetanus toxoid and alum. Table III gives the results of an experiment on guinea-pigs injected with 0.1 c.cm. tetanus toxoid diluted to 5 c.cm. with saline, or with 0.01 or 0.1 per cent. potash alum. The injections were repeated four weeks later, and the guinea-pigs were injected with tetanus toxin two to three weeks after the second