to the usual position of this artery. The zones on the surgical necks of the humeri again appear to us to be far too high to coincide with the normal course of the circumflex humeral arteries. Other wider zones in the shoulder region do not appear to have any possible arterial relationship. The zone in the mandible (Special Plate, Fig. 4), opposite the second molar tooth, is nearly half an inch (12.5 mm.) distant from the facial artery, as judged by the site of its pulsation. We therefore suggest that the arterial origin of Looser's zones is, at the most, only partly true, and does not appear applicable even to the narrower and tortuous zones, while some other explanation is certainly needed for the wide transverse bands.

Summary

The place of so-called "vitamin-D-resistant rickets and osteomalacia" is considered, followed by the report of the case of a woman aged 32 with osteomalacia and Milkman's syndrome. Other causes for osteomalacia were ruled out, and various metabolic investigations were then performed. Balance studies showed a high faecal calcium and phosphorus, phosphorus infusion studies showed a low tubular maximal reabsorption of phosphorus (high phosphate clearance), and calcium infusion studies showed several points of difference from the normal. The bones gave evidence of great avidity for calcium. The response to parathyroid extract was slight, delayed, and affected calcium more than phosphorus metabolism.

The effect of calciferol given parenterally in large doses was examined. On 1.2 million units per day the calcium and phosphorus absorption increased, but it was not until a dose of 4.8 million units daily was used that the serum phosphorus showed any rise. No toxic effects were seen on this dose after 14 days. The smaller dose of 1.2 million units had no effect on the tubular reabsorption of phosphate.

Finally the mechanism of production of Looser's zones is considered. The relation of some of the zones to arteries was studied by means of contrast medium introduced into the aorta. It is concluded that the zones are not in close connexion with pulsating blood vessels.

APPENDIX

The main chemical methods used were as follows. Serum calcium: Greenblatt and Hartman (1951); serum and urinary inorganic phosphate: King (1951); urinary, faecal, and food calcium: Jackson and Irwin (1958); nitrogen: micro-Kjeldahl; inulin: Roe *et al.* (1949); potassium: flame photometer (Jackson and Irwin, 1958).

The results of balance studies have been given in charts rather than tables, in order to conserve space. The exact figures may be obtained from the authors on request.

We are pleased to express our thanks to Professor J. F. Brock and Professor F. Forman for their interest and advice; to those who helped with the section concerning Looser's zones (particularly Professor R. Goetz); to Mr. B. Todt for the photographs; to the interns, the nursing and technical staff concerned, and to the dietitians. We gratefully acknowledge grants from the Council for Scientific and Industrial Research of South Africa and from the University of Capetown Staff Research Fund, which covered the expenses entailed.

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THE NEPHROTIC SYNDROME COMPLICATING MERCURIAL DIURETIC THERAPY

BY

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[WITH SPECIAL PLATE]

Mercurial diuretics are powerful weapons in the treatment of congestive heart failure. Their proper use can maintain reasonable health and activity for long periods in individuals who would otherwise be seriously disabled. It is well recognized, however, that these drugs are potentially dangerous on account of their action on the renal tubular epithelium. For this reason they are usually withheld from patients with established renal disease, though Gold *et al.* (1947) state that a mercurial diuretic may be given to patients with congestive failure "regardless of the state of the kidneys."

Isolated reports of the nephrotic syndrome occurring after prolonged administration of mercurial diuretics have appeared (Waife and Pratt, 1946; Derow and Wolff, 1947; Bruno, 1948; Siegel and Friedman, 1949; Preedy and Russell, 1953; Munck and Nissen, 1956), but we are not entirely satisfied that the renal tubular damage in all these cases should be attributed to mercury. In the patients reported by Bruno (1948) and by Siegel and Friedman (1949) the clinical and pathological findings suggest that the renal tubules had been damaged by mercury, but diabetic intercapillary glomerulosclerosis (Kimmelstiel–Wilson disease) was also present. Munck and Nissen (1956) describe the nephrotic syndrome occurring in four patients who had received mercurial diuretics, but very limited pathological data are given, and in the one case which came to necropsy the kidneys were normal. The case reported by Derow and Wolff (1947) is acceptable on clinical grounds, but post-mortem examination was not performed and there is therefore no histological evidence. In the cases reported by Waife and Pratt (1946) and by Preedy and Russell (1953), on the other hand, there is

little doubt that the nephrotic syndrome was due to mercury. In these patients there was no preceding kidney disease, and the histological findings, of lesions confined to the renal tubules, are strongly suggestive of mercurial damage.

In the past three years we have seen five cases of the nephrotic syndrome, three of them fatal, which appeared to follow the use of mercurial diuretics. We believe that this syndrome is a definite risk in long-term mercurial diuretic therapy, and that it may be more frequent than has hitherto been supposed.

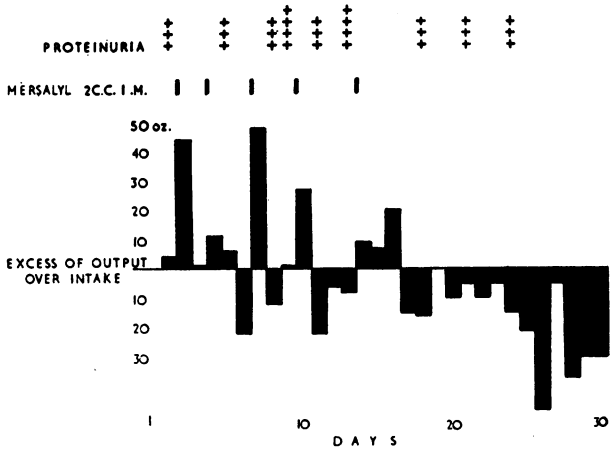
Case Reports

Case 1.—A woman aged 67 years with degenerative heart disease. When first seen she had received weekly injections of mersalyl for three years and was known to have had a low urinary output and proteinuria for three months. There was generalized oedema, but the jugular venous pressure was normal. The important biochemical findings (see Table) were heavy proteinuria, hypoalbuminanaemia, and hypercholesterolaemia. Treatment was ineffective; the blood urea rose from 53 to 135 mg. per 100 ml., and the patient died 19 days after admission to hospital.

Case 2.—A woman aged 80 years with hypertensive heart disease. Four years before death she was treated in hospital for congestive cardiac failure. Renal function at that time was normal. Weekly injections of "neptal" ("unephral") were started and continued for three years at home. The parenteral preparation was then replaced by oral "mercloran" (chlormerodrin) tablets, which were given for a further 12 months. She was readmitted to hospital on account of an attack of diarrhoea and vomiting followed by rapidly increasing oedema and oliguria. On admission there was gross anasarca, but the jugular venous pressure was normal. The urine "boiled solid" with protein and contained a few red cells, pus cells, and casts. The serum albumin was low and the serum cholesterol raised. The serum sodium and chloride levels were normal on admission, but fell during the next few days. Despite treatment she died in peripheral circulatory failure 13 days after admission.

Case 3.—A man aged 67 years with syphilitic heart disease. Three years before death he was treated for cardiac failure. When we first saw him, two years before he died, he was again suffering from congestive cardiac failure. His urine contained a trace of protein. The heart failure responded to conventional treatment and the proteinuria disappeared. During the next two years he was kept free of pulmonary oedema by the regular use of mercurial diuretics; neptal and "thiomerin" (mercaptomerin) were given at first, but later mercloran tablets were substituted because his work involved frequent trips abroad, during which he was unable to have injections. Two months before death he attended the out-patient department with oedema of the legs and left forearm; heavy proteinuria was discovered and he was admitted to hospital. The jugular venous pressure at this time was normal and the liver was neither enlarged nor tender. The biochemical findings were as shown in the Table. Despite treatment he failed to improve, and he died suddenly two months after admission.

Case 4.—A woman aged 67 years with degenerative heart disease and auricular fibrillation. This is our only case in which the condition appears to have been reversible. She was first seen five years ago, when she was treated in hospital for congestive cardiac failure. Renal function at that time was normal. Three and a half years later congestive failure recurred; she repeatedly refused to come into hospital and was therefore treated as an out-patient with the usual measures and weekly injections of neptal or thiomerin, and later with mercloran tablets. Moderate proteinuria was discovered, but it was not until eight months after this that she agreed to enter hospital. On admission the jugular venous pressure was raised and the liver was enlarged but not tender. There was pitting oedema to the mid-trunk, and other findings as shown in the Table. She was treated with a low-sodium, high-protein diet, digitalis, and mersalyl. At first a good diuretic response occurred and the jugular venous pressure fell to normal. The proteinuria, however, failed to decrease and the diuretic response diminished (see Chart). Mercurials were stopped, and she improved slowly with symptomatic treatment including high-protein, low-sodium diet. The patient was discharged free from congestive cardiac failure, but with some oedema of the ankles. She has continued to keep well at home, and the serum albumin has risen to 4.2 g. per 100 ml.



Showing response to treatment in Case 4.

Case 5.—A woman aged 61 years who had been treated for congestive cardiac failure for 14 months before her admission to hospital. She had received neptal injections twice weekly for 12 months, and mersalyl three times weekly for two months. On admission there were gross oedema of the limbs and trunk, ascites, and a raised jugular venous pressure, though the liver was not tender. Investigations showed heavy proteinuria (23 g. in the 24 hours),

Table Showing Details of Mercurial Diuretic Therapy and Biochemical Findings

Case No.	Sex and Age	Type of Heart Disease	Mercurial Diuretic and Total Dosage	Urine Protein (g. per litre)	Serum Albumin (g. per 100 ml.)	Serum Cholesterol (mg. per 100 ml.)	Blood Urea (mg. per 100 ml.)	Result
1	F 67	Degenerative	Mersalyl—300 ml. in 3 years	++++	25	800	53–135	Died
2	F 80	Hypertensive	Neptal—294 ml. in 3 years .. .. .. Mercloran—? 1 tablet daily for 12 months	++++ 15	15	470	80–130	Died
3	M 67	Syphilitic	Neptal; thiomerin—176 ml. in 3 years .. Mercloran—660 tablets in 11 months	3–16	29	440–525	28–93	Died
4	F 67	Degenerative	Neptal; thiomerin—60 ml. in 4 years .. Mercloran—112 tablets in 8 weeks	35	25–42	285–280	33–50–35	Improved
5	F 61	? Degenerative	Neptal; mersalyl—260 ml. in 14 months ..	23	18	400	60	

a plasma albumin of 1.8 g. per 100 ml., and plasma cholesterol of 400 mg. per 100 ml. With non-specific treatment the jugular venous pressure fell to normal, and the oedema and ascites diminished but did not clear. The biochemical findings remained virtually unchanged.

Post-mortem Findings

At necropsy the macroscopical and microscopical findings in the kidneys were the same in all three fatal cases. The cortices were swollen and were pale greyish-yellow in colour, contrasting with the dark-grey medullae. There was no evidence of thrombosis of renal veins or inferior vena cava.

Microscopical examination showed the glomeruli to be well preserved and essentially normal. In the renal tubules, however, striking changes had occurred—namely, necrosis and degeneration of the epithelium together with regenerative activity (Special Plate, Fig. 1). Tubular change was focal in distribution and of variable intensity, in some areas amounting to complete necrosis of the epithelium (Special Plate, Fig. 2). Elsewhere there were cloudy swelling and hyaline droplet degeneration; the latter change was often seen, with escape of hyaline droplets from the free margins of epithelial cells into the tubular lumina (Special Plate, Fig. 3). Infiltration of tubular cells with isotropic and anisotropic fat was also present. These necrotic and degenerative changes were most often found in the proximal convoluted tubules, but were also seen in the distal convoluted tubules and in the loops of Henle.

Regeneration of tubular epithelium was a striking feature in all our cases. The large, proliferating cells were irregular and often angular in shape and they had prominent hyperchromatic nuclei (Special Plate, Figs. 4 and 5). Binucleated and multinucleated cells were frequent and occasional mitotic figures were seen. The regenerated cells often did not reconstitute the tubular linings, but instead formed loose masses in the lumina. Hyaline, granular, and occasional cellular casts were seen at all levels of the nephrons; most of them gave positive benzidine reactions of varying intensity. At the sites of some of the casts the tubular epithelium was intact and normal; other casts were associated with necrosis and desquamation of tubular lining cells.

Qualitative tests for mercury were carried out on the kidneys from Cases 2 and 3, and in each gave a strongly positive result. Similarly treated material from a subject who had received mercurial diuretics without suffering any renal damage gave a weakly positive result, and material from a subject never treated with mercurials gave a negative result.

Discussion

There are good reasons for attributing the renal damage in these patients to long-term mercurial diuretic therapy. First, none of them had any previous history of kidney disease, and three of them are known to have had normal urine when treatment with mercurials was begun. Secondly, the pathological changes are similar in each of the three fatal cases, and resemble in quality those seen in acute mercuric chloride poisoning. Thirdly, an excessive amount of mercury was found at necropsy in the renal tubules in two cases. And, finally, no cause other than mercurial damage to the kidneys was found.

The significant pathological finding in these cases was necrosis, degeneration, and regeneration of renal tubules. The glomeruli were normal, which excludes such known causes of the nephrotic syndrome as Ellis's Type II nephritis, renal amyloidosis, and diabetic glomerulosclerosis, and indicates that the tubular changes were primary and not secondary to glomerular damage. The tubular changes recorded here are similar to those reported by previous authors, notably Waife and Pratt (1946) and Preedy and Russell (1953), whose patients, like ours, had no previous renal disease and no glomerular damage. They differ from the characteristic findings in acute mercuric chloride poisoning only in that the tubular damage is less diffuse and that there is no calcification of necrotic and degenerate epithelium.

It seems possible that the nephrotic syndrome is a more frequent complication of long-term mercurial diuretic therapy than the literature would suggest. Increasing oedema and increasing dyspnoea in a cardiac patient may readily be mistaken for a terminal exacerbation of chronic heart failure, and the significance of the massive albuminuria may fail to be appreciated. Two of our patients were sent to hospital with the diagnosis of congestive heart failure, though in neither was the venous pressure raised nor was the liver enlarged or tender.

Since mercurial diuretics are often used for long periods without serious incident, we have tried to determine in retrospect whether there was any unusual factor or combination of factors in our patients which precipitated the tubular damage. We have considered the total dose of mercury, the mercury compound itself, so-called "resistance" to mercurial diuretics, accessory therapeutic measures, and the presence of associated biochemical abnormalities.

(1) *Total Dose of Mercury.*—This was considerable in the three fatal cases (see Table), though many patients have had larger quantities of mercurial diuretics without showing clinical evidence of tubular damage.

(2) *The Mercurial Compound.*—An oral mercury compound, chlormerodrin, was used in three of our cases, and one of the cases recorded in the literature received "mercupurin" ("mercuzanthin"; mercurophylline) by mouth (Derow and Wolff, 1947). It is obvious that oral compounds are more easily administered than parenteral preparations, and this in itself may constitute a danger. It is also possible that oral compounds may be more toxic than parenteral preparations, though on experimental evidence this would seem to be unlikely. Moyer *et al.* (1953) found that in the dog a single large dose of chlormerodrin is completely excreted within 96 hours. According to these workers, only about 10% of ingested chlormerodrin is excreted in the urine, most of the remainder being lost in the faeces. On this assumption, a daily dose of four tablets would represent a weekly absorption of about one-third of the quantity of mercury in 2 ml. of mersalyl.

It seems certain, however, that in man the absorption and excretion of chlormerodrin is very variable. Cáceres and Stauffer (1955) describe a case of mercurialism in a patient who was treated for eleven months with only one tablet of chlormerodrin daily, and, despite this small dose, significant quantities of mercury were still being excreted in the urine two weeks after the drug was discontinued. It is clear that the excretion of these compounds in patients with congestive failure, both with normal and with impaired renal function, requires further investigation.

(3) *Resistance to Mercurial Diuretics.*—Two of our fatal cases (1 and 2) are known to have had little or no response to the mercurial diuretic preceding their terminal admission to hospital. Such absence of diuresis must be regarded as particularly dangerous, since the intratubular concentration of mercury is likely to be increased and the duration of its excretion prolonged.

(4) *Other Therapeutic Measures.*—Restriction of salt and water may, if carried to excess, impair diuresis and predispose to tubular damage by delaying excretion of mercury. In the case described by Preedy and Russell (1953) there was considerable salt depletion, but oliguria occurred only terminally; it is possible, therefore, that salt depletion alone in the absence of oliguria may facilitate renal tubular damage. In one of our cases there was terminal salt depletion, but in this instance the serum electrolytes were normal at the time of admission to hospital, when there was already clinical evidence of tubular damage.

(5) *Hypoproteinaemia.*—It has been suggested by Diengott (1953) that hypoproteinaemia may increase individual susceptibility to the toxic effects of mercurial diuretics, but

we have little evidence on this point. In only one of our cases were the serum proteins estimated before the onset of the nephrotic syndrome, and in this instance they were normal; the estimation was, however, carried out four years before the appearance of the nephrotic syndrome.

In the prophylaxis of this condition close supervision of patients treated with mercurial diuretics, including regular examination of the urine, is essential. It is noteworthy that two of our three fatal cases had no hospital supervision in the three years preceding death, and the third patient travelled round the Continent for long periods with a supply of mercloran tablets.

The principal warning signs of the onset of the nephrotic syndrome complicating mercurial diuretic therapy are: (1) Failure of albuminuria to decrease after a satisfactory diuresis. This, we think, is by far the most valuable indication of tubular damage. Case 4 undoubtedly had congestive cardiac failure, and this alone might have been responsible for the proteinuria. Mersalyl produced a satisfactory diuresis, but in spite of this the heavy proteinuria persisted (see Chart), indicating serious tubular damage. (2) Increasing oedema, especially of the arms and face, in the absence of other signs of cardiac failure. (3) Absence of diuresis after mercurial therapy. This has been ascribed to tubular damage, but in our experience it is a late and unreliable sign.

Treatment of the fully developed syndrome is unsatisfactory. BAL (dimercaprol), corticotrophin, ion-exchange resins, and decapsulation of the kidneys have all been tried without benefit.

The survival of one of our patients who received no specific therapy indicates that in some circumstances the condition is reversible. Early recognition of the condition and cessation of mercurial therapy before irreparable renal damage has occurred offer the best chance of recovery.

Summary

The nephrotic syndrome complicating congestive heart failure is reported in five patients who received mercurial diuretics for long periods.

The clinical features, and the pathological findings in three fatal cases, suggest that the renal lesion was due to mercury. Possible contributory factors are considered.

Early recognition of the condition is of the utmost importance if a fatal outcome is to be avoided.

The most useful evidence of tubular damage is persistence of albuminuria despite a satisfactory diuresis in response to mercurial therapy.

Our thanks are due to Dr. Una Ledingham and Dr. Wallace Brigden for permission to publish Cases 1 and 5 respectively.

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Middlesex had its record lowest infant mortality rate in 1957. There were 561 deaths of infants under 1 year old, giving a rate of 17.7 per thousand live births. This is 5.3 below the rate for England and Wales as a whole. As elsewhere, deaths from lung cancer increased, being 1,166, or 76 more than in 1956. Despite an excess of live births over deaths amounting to more than 9,000, the population of the county again fell owing to removal from it. At about 2¼m. the population was 2,000 lower than in 1956.

NEPHROSIS DUE TO MERCURIAL DIURETICS

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Following the work of Saxl and Heilig in 1920 on the diuretic effect of organic compounds of mercury, mercurial diuretics have been used extensively to control oedema in cardiac failure and less extensively to control oedema secondary to renal disease. At first these drugs were used with considerable caution, for it was well known that inorganic mercuric salts were apt to cause renal damage. However, these fears were soon overcome, since cases of renal damage due to mercurial diuretics have been infrequent. The first case was reported by Sprunt in 1930, although others have since come to light (Tarr and Jacobson, 1932; Rosenthal, 1933; Waife and Pratt, 1946; Bruno, 1948; Preedy and Russell, 1953). The use of mercurial diuretics is now so widespread that perhaps the danger is being overlooked. The purpose of this report is to record a case in which a mercurial diuretic is thought to have produced the renal damage, and to show by microdissection the site of the lesions, which is similar to that described for inorganic mercury.

Clinical Course

A woman of 69 was admitted to hospital on April 18, 1957, with a four-months history of progressive heart failure together with angina of effort for two months. Her health prior to this was excellent. On examination she was found to have a trace of ankle oedema. Her pulse was 85 and regular, and B.P. 140/90. The apex beat was in the fifth intercostal space 3½ in. (9 cm.) from the midline; a harsh systolic murmur was audible to the left of the sternum, maximal in the fourth interspace, and a systolic thrill was palpable in this area. Crepitations were heard at both lung bases and the liver was palpable. The urine contained no albumin.

A diagnosis of ischaemic heart disease was made and the patient was given weekly injections of 2 ml. of mersalyl. The response was satisfactory and the patient was discharged home after three weeks. The urine was protein-free on discharge.

Weekly injections of 2 ml. of mersalyl were continued at home and her condition remained satisfactory for two months. Oedema then reappeared and she was readmitted on September 15. On examination on admission there was gross oedema of the legs, of the trunk to the level of the mid-dorsal region, and of the forearms and hands. The pulse rate was 96 and regular, the B.P. 140/80. The jugular venous pressure was raised 1 in. (2.5 cm.). The systolic murmur was unchanged. There were small effusions at each base and moist adventitia in the lungs. The urine was found to contain a considerable quantity of protein, and later determinations revealed a daily urinary excretion of 11.5 to 35 g. Plasma proteins on admission were as follows: total 5.3 g./100 ml. (albumin 1.5 g., globulin 2.96 g., fibrinogen, 0.84 g.). The blood urea was 46 mg./100 ml.; sodium, 134 mEq/l.; potassium, 4.7 mEq/l.; chloride, 91 mEq/l.; CO_2 combining power, 26 mEq/l.; bilirubin, 0.2 mg./100 ml.

W. P. U. JACKSON *ET AL.*: VITAMIN-D-RESISTANT OSTEOMALACIA

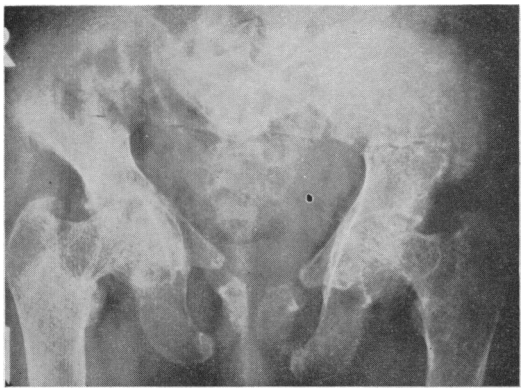

FIG. 1.—Radiograph of pelvis. Note wide symmetrical Looser's zones in pubic and ischiopubic rami, and narrow zones running from angle of brim of pelvis.

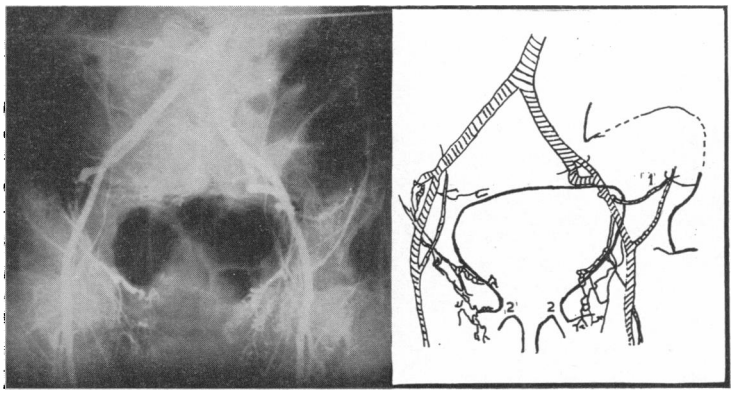

FIG. 2.—Aortogram to show relation of arteries to Looser's zones. In tracing, continuous line indicates pelvic outline. Note that superior gluteal artery (1) appears to be in fairly close superimposition over one zone, whereas no arteries are to be found near wide pubic zones (2).

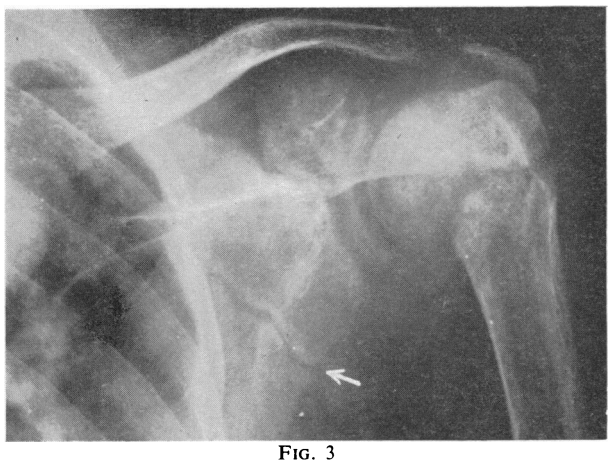

FIG. 3

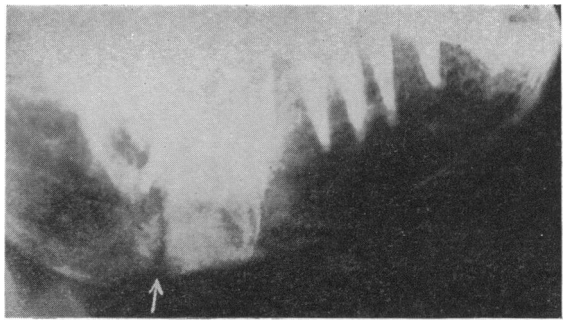

FIG. 4.—Looser's zone close to last molar tooth. Incidentally lamina dura around teeth has largely disappeared.

FIG. 3.—Left shoulder girdle. Note Looser's zones at surgical neck of humerus, in scapula close to glenoid cavity, and traversing greater wing from lateral border.

M. RIDDLE *ET AL.*: NEPHROTIC SYNDROME COMPLICATING MERCURIAL DIURETIC THERAPY

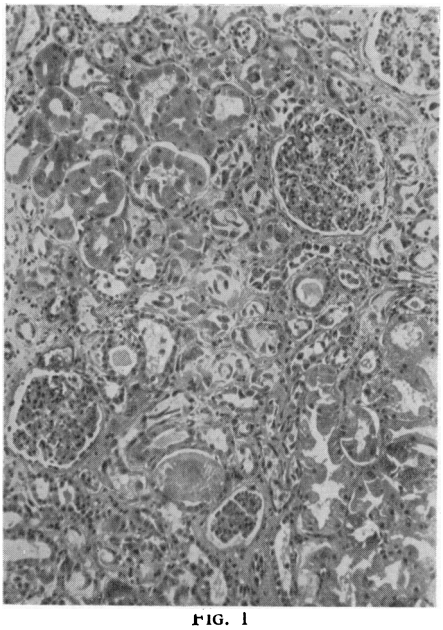

FIG. 1

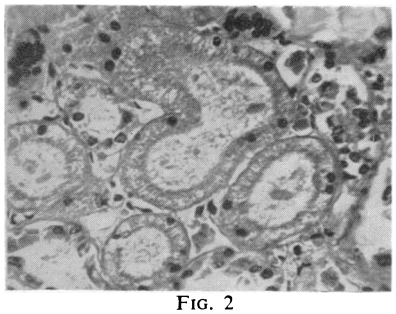

FIG. 2

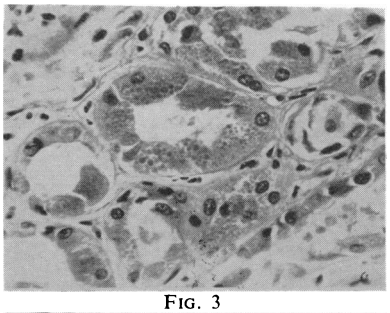

FIG. 3

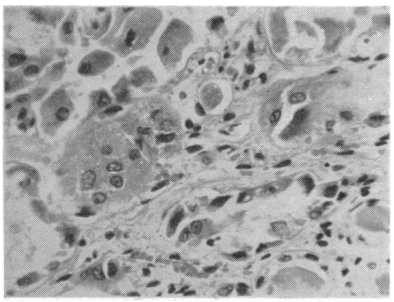

FIG. 4

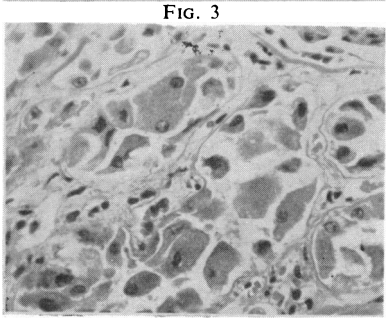

FIG. 5

FIG. 1.—Epithelial degeneration and necrosis in proximal convoluted tubules (top left and bottom right), with regeneration of tubular epithelium (centre). (H. and E. ×75.)

FIG. 2.—Proximal convoluted tubules showing epithelial necrosis with vacuolation of cytoplasm and nuclear pyknosis. Brush borders are preserved. Cellular debris in tubular lumina. (H. and E. ×200.)

FIG. 3.—Proximal convoluted tubules showing hyaline droplet degeneration. (H. and E. ×200.)

FIG. 4.—Tubules showing epithelial regeneration. A binucleate cell is present (lower centre). (H. and E. ×200.)

FIG. 5.—Tubules showing regeneration. A mitotic figure can be seen near top left-hand corner. (H. and E. ×200.)