Clinicopathological Conference

A Case of Renal Cortical Necrosis with Dystrophic Calcification

DEMONSTRATED AT THE POSTGRADUATE MEDICAL SCHOOL OF LONDON

Clinical History

Dr. C. NEWMAN: This patient was a child aged 4 years at the time of death. He was admitted on 12 March 1964, having been off colour during the first week of March. He had a history of not eating well and was off his play. On 7 March he vomited. This was followed on 8 March by further vomiting and diarrhoea two or three times a day, with some central abdominal pain. On 9 March he complained of pain in the back, intermittent at first but becoming continuous. On 10 March the pain in the back continued in the lumbar region and he vomited again. He was pale and looked yellowish. The bowels were not open. Micturition was normal. On 11 March he was lethargic and ill. He had repeated vomiting and was probably anuric; his bowels were still not open. He was admitted to St. John's Hospital, Chelmsford, where his blood-pressure was found to be 150/90 mm. Hg; there was tenderness in both loins and his blood urea was 200 mg./100 ml. The following day anuria was definitely established, with drowsiness and a blood urea of 310 mg./100 ml. Serum potassium was 6.8 mEq/litre after the patient had been given resonium A. Haemoglobin was 87%, and the white cell count 24,000/c.mm. Platelets were normal. There was slight pyrexia. The patient was transferred to Hammersmith Hospital.

On examination the patient was alert and co-operative. There was no pallor or jaundice and no oedema. He was very tender over both kidneys; the kidneys themselves could not be felt. The heart was normal. Blood-pressure was 130/70 mm. Hg; there was no purpura. The C.N.S. was normal and fundi were normal. He had passed no urine.

Blood examination showed a haemoglobin of 68% with a white cell count of 7,000/c.mm. and platelets of 164,000/c.mm. The blood was normal. Blood urea was 295 mg./100 ml.

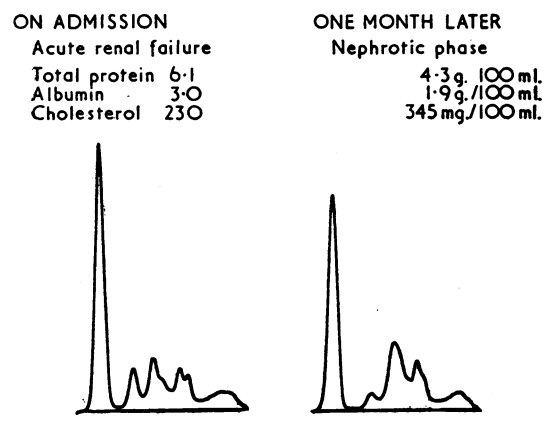

FIG. 1.—On admission (and again in the terminal phase) serum electrophoresis on cellulose acetate showed the raised α_1 and α_2 globulins usually found in acute renal failure. The γ-globulin was normal, not raised as is usual in acute post-streptococcal nephritis. One month later the serum pattern resembles that found in mild nephrotic syndrome, with a reduced albumin and raised α_2 globulin and cholesterol, indicating that any recovery of the renal cortex was only partial.

Serum potassium was 6.5–9.6, sodium 128–147, bicarbonate 14, and chloride 97 mEq/litre. Serum protein was 6.1 g./100 ml., with albumin 3 g./100 ml. (Fig. 1). Anti-streptolysin titre was 75 units.

X-rays of chest and abdomen were normal, with normal kidney outline. There was no spinal abnormality.

Bilateral renal stones were at first suspected, but a bilateral instrumental pyelography was normal. The patient was then thought to have acute glomerulonephritis, and peritoneal dialysis was started. This was continued for eight weeks and the blood urea fell to 100 mg./100 ml. Dialysis was kept up satisfactorily except for pyocyanea infection.

On 26 March he began to pass very small quantities of blood-stained urine, rising to 200 ml. a day. A maculo-papular rash appeared. He was given prednisolone, 40 mg. daily, which was tailed off over the next six weeks.

On 10 May the peritoneal dialysis was stopped because of technical difficulties. His urine volume rose to 400 ml., with a blood urea ranging between 200 and 300 mg./100 ml. Blood-pressure was 150/110 mm. Hg under control by methyldopa, 500 mg. daily. Resonium A was given to control potassium excretion.

During April and May the daily excretion of urine varied between 50 and 700 ml. a day. Blood urea varied between 95 and 350 mg./100 ml. On two occasions his serum potassium rose between 6.2–7 mEq/litre, reduced by resonium A. In June he had an unexplained attack of diarrhoea and developed a pericardial effusion. Another attack of maculo-papular rash occurred on the face, chest, and abdomen. By July he was sufficiently well to be discharged home, but he returned two weeks later with oedema and relapse of the pericardial effusion. In August he was sent home again.

On 2 September he was readmitted in a state of venous congestion with diarrhoea, dyspnoea, generalized oedema, and oliguria. There was a pericardial effusion and blood-pressure was 145/120 mm. Hg. The liver was enlarged and his veins were engorged.

His blood urea was now 365 mg./100 ml. Serum potassium was 7.6, sodium 141, bicarbonate 6, and chloride 106 mEq/litre. Serum protein was 7.5 g./100 ml., with albumin 3 and globulin 2.3 g./100 ml. Serum bilirubin was 0.3 mg./100 ml. Serum alkaline phosphatase was 13 King-Armstrong units/100 ml. His haemoglobin was 48% and the white cell count was 6,000/c.mm., with 60% polymorphs. Serum cholesterol was 230 mg./100 ml.

The urine volume was 50–90 ml. daily. It contained sodium, 62 mg./100 ml., and potassium, 12.7 mg./100 ml. Urine chloride was 43 mg./100 ml., and urea 600 mg./100 ml. Urine protein was 700 mg./100 ml. His blood-pressure was 160/110 mm. Hg.

The pericardial effusion was tapped (300 ml.), with little result. He lapsed into stupor, with diarrhoea and twitching. The urine output fell, as did the blood-pressure, to 100/40 mm. Hg. The blood urea, however, did not rise in spite of oliguria. He died on 21 September 1964.

Post-mortem Findings

Dr. M. J. R. DAWKINS*: The child was well nourished and weighed 22.5 kg. There were keloid scars over the lower abdomen.

The *kidneys* were extremely small (R. 5.5 × 2.5 cm., weight 15 g.; L. 6 × 2 cm., weight 18 g.), and showed gross reduction in the width of the cortex (1–2 mm. wide), with irregular calcified nodules scattered throughout the cortex (Figs. 2 and 3). There was an area of relatively normal cortex at the lower pole of the left kidney, and the medulla was quite well preserved. The renal arteries and veins were patent, but the main divisions of the renal arteries showed slight calcification of their walls. Histological examination showed virtually complete destruction of the renal cortex with calcification and fibrosis (Fig. 4). There was a surviving rim of tubules and an occasional glomerulus in the subcapsular region. A few glomeruli were present at the cortico-medullary junction and showed a variety of degenerative changes but no evidence of glomerulonephritis. The remaining viable tubules were grossly dilated and contained protein and cellular casts. Elastic and van Gieson stains showed intimal proliferation of the arcuate arteries; interlobar arteries could only be identified as distorted fragments of elastic tissue. The appearances were typical of renal cortical necrosis.

The *pericardium* contained at least 200 ml. of turbid fluid and showed a fibrinous pericarditis. The *heart* (135 g.) showed moderate left ventricular hypertrophy (outflow tract thickness 15 mm.), and histological examination showed focal necroses with calcification (Fig. 5). Both pleural cavities contained small effusions, and there was a fibrinous pleurisy. The *lungs* were overweight (L. 210 g., R. 205 g.), and the subcarinal lymph nodes were large and oedematous. Histological examination revealed fibrinoid material over a thickened pleura, many alveolar siderocytes which stained strongly by the Prussian blue reaction, a few "hyaline membranes," and areas of basophilic calcifying exudate (Fig. 6).

The alimentary system showed no evidence of uraemic gastritis or colitis, but an area of focal necrosis with calcification was found in the muscle coat of the sigmoid colon (Fig. 7). The *liver* (830 g.) showed chronic passive venous congestion. *Pancreas* and *spleen* were normal. *Brain* (1,450 g.) was overweight and oedematous.

The *endocrine glands* were normal apart from the parathyroids, all of which were enlarged. Histological examination showed chief cell hyperplasia. Examination of ribs and vertebrae showed increased osteoclastic activity and fibrosis around bony trabeculae.

Pathologist's Diagnosis

(1) Renal cortical necrosis with dystrophic calcification.
(2) Uraemic lung with dystrophic calcification of exudate.
(3) Uraemic pericarditis and pleurisy.
(4) Left ventricular hypertrophy.
(5) Secondary hyperparathyroidism.
(6) Focal necrosis with calcification of myocardium and muscle coat of sigmoid colon.

Discussion

Dr. NEWMAN: Did you see any evidence of vascular obstruction to account for the focal necrosis of the heart muscle?

Dr. DAWKINS: No.

Dr. NEWMAN: Then this must have been of a different aetiology from the focal necrosis of the kidney.

Dr. J. R. HOBBS: I have just checked through the results of the biochemical tests—185 in all. There were 72 serum potassium results and none of these were low, so it was not due to low potassium.

Professor RUSSELL FRASER: However, the case suggests a common factor, doesn't it, between the calcification in the pituitary and the colon muscle? Do you think it might be a high serum potassium that was the cause of this condition?

Dr. DAWSON: Allen[1] does describe a case with focal necrosis of the myocardium associated with hyperkalaemia. Disorders of cardiac function are often found with hyperkalaemia, but necrosis is usually associated with hypokalaemia.

Origin of Calcification

Professor R. E. STEINER: The pulmonary calcification—was this calcification or ossification?

Dr. DAWKINS: It was calcification of exudate which had not yet become ossified. I suppose it might have become so if we had kept him alive longer.

Professor STEINER: It could be closely allied to the type of thing we see in mitral heart disease with interstitial oedema, where you get ossification.

Dr. D. J. EVANS: Could I ask Dr. Dawkins why he rejects the possibility that this merely represents a metastatic calcification such as one not infrequently sees with renal failure, possibly associated with hyperparathyroidism? Surely these might be multiple focal necroses which have subsequently calcified? It seems to be a simpler explanation than the one he postulated.

Dr. DAWKINS: I don't reject the possibility—I am sitting on the fence about that one. This may well be a mixed picture of dystrophic and metastatic calcification, but the usual pattern of metastatic calcification of the alveolar septa and blood vessels of the lung is not present here; neither is there metastatic calcification in the stomach.

Professor FRASER: The distribution of this calcification throughout looks more ischaemic than what you see in metastatic calcification. I don't know whether Dr. Wrong agrees.

Significance of Serum Calcium

Dr. O. WRONG: The pattern is unusual for a metabolic calcification. However, I would be interested to know what his calcium and phosphorus were during his last few weeks of life, because it is believed that the tendency towards soft-tissue calcification in renal failure is related to the product of those two concentrations.

Dr. HOBBS: Calcium was 5.4 and phosphate 2.8 mN.

Dr. I. MACINTYRE: Not very abnormal.

Professor FRASER: No, it is not. On the other hand, we commonly see metastatic calcification in much older subjects, possibly because of the age of their arteries.

Dr. HOBBS: I should stress that the calcium of 5.4 mN is associated with an albumin of 2 g./100 ml.

Professor FRASER: So that is quite high.

Dr. MACINTYRE: What do you suppose is the explanation of his high calcium? If this calcium represents a high level of ionized calcium how can we explain this?

Professor FRASER: Possibly secondary hyperparathyroidism? What do you think, Dr. Macintyre?

Dr. MACINTYRE: Well, I don't think that is a very good explanation, because secondary hyperparathyroidism is produced by the stimulus of a low plasma calcium acting on the parathyroid gland. That stimulus would no longer act if the calcium became normal.

Professor FRASER: On the other hand, I think Dr. Wrong has had a number of similar patients in the later stages of severe

* Dr. Dawkins died on 27 June 1965.

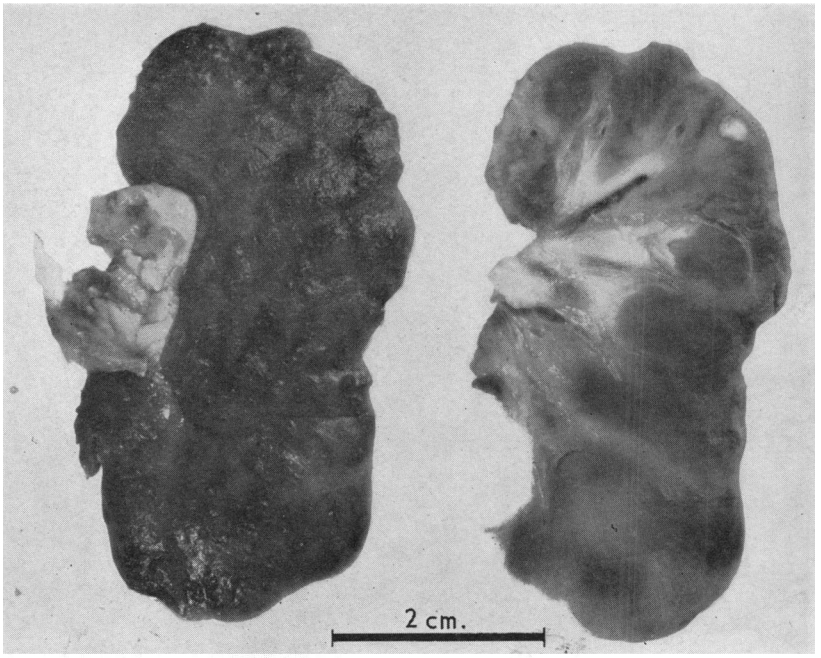

FIG. 2.—Cortical surface and slice of left kidney. Irregular nodules are present on the surface and on the slice gross destruction of most of the cortex with focal calcification can be seen.

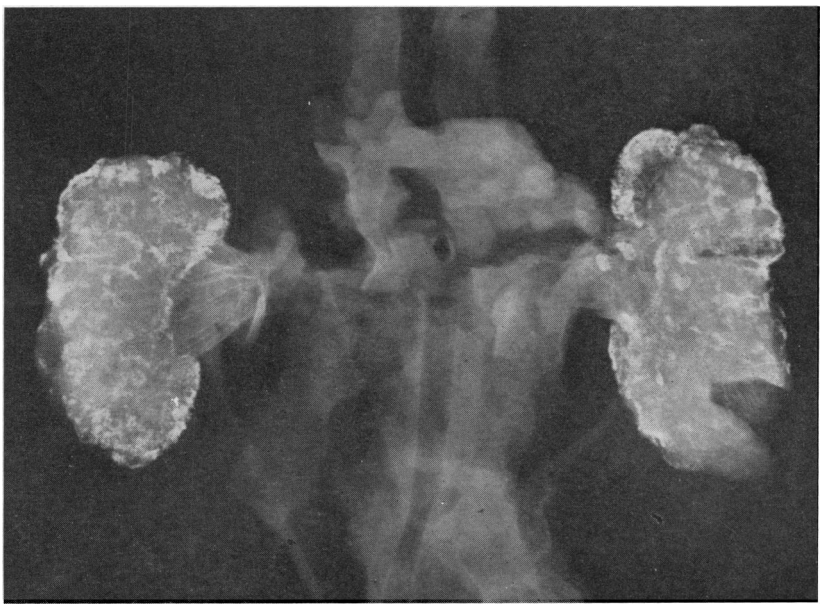

FIG. 3.—Post-mortem radiograph to show cortical calcification.

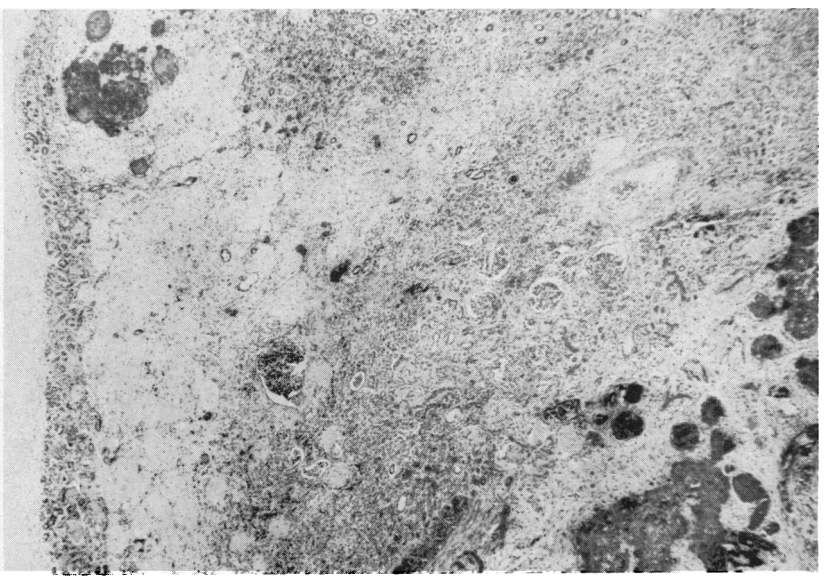

FIG. 4.—Fibrosis and focal calcification of renal cortex, with surviving subcapsular rim of tubules. (H. and E. ×40.)

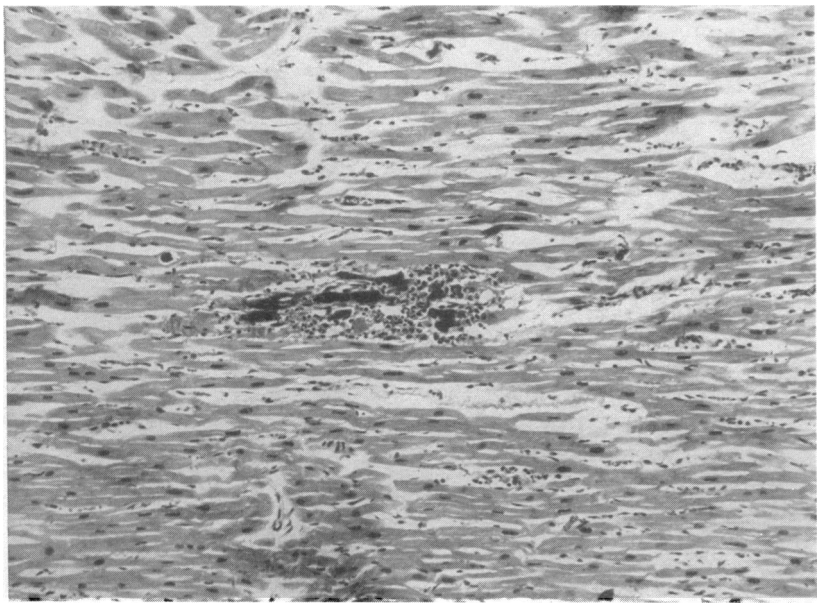

FIG. 5.—Focal necrosis with calcification of the myocardium. (H. and E. ×106.)

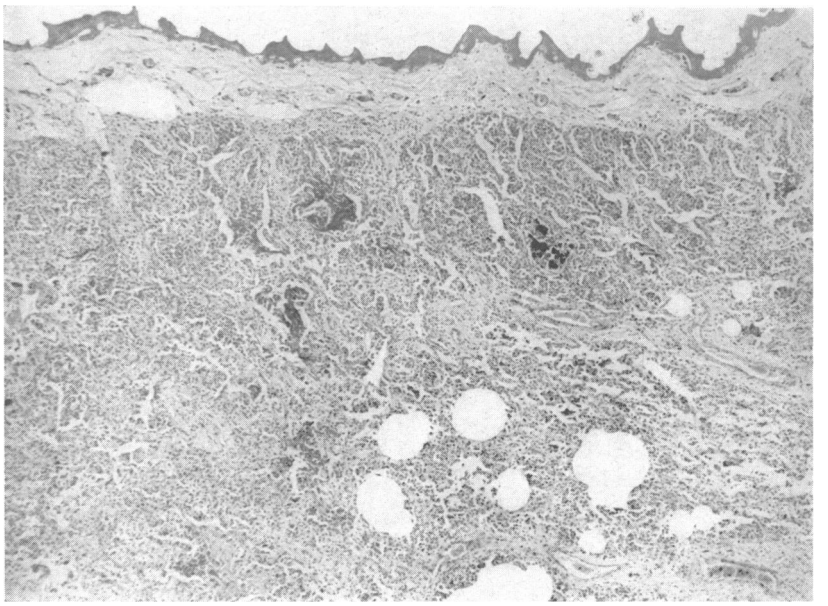

FIG. 6.—Lung to show fibrinoid pleurisy, numerous alveolar macrophages, and focal calcification of exudate. (H. and E. ×40.)

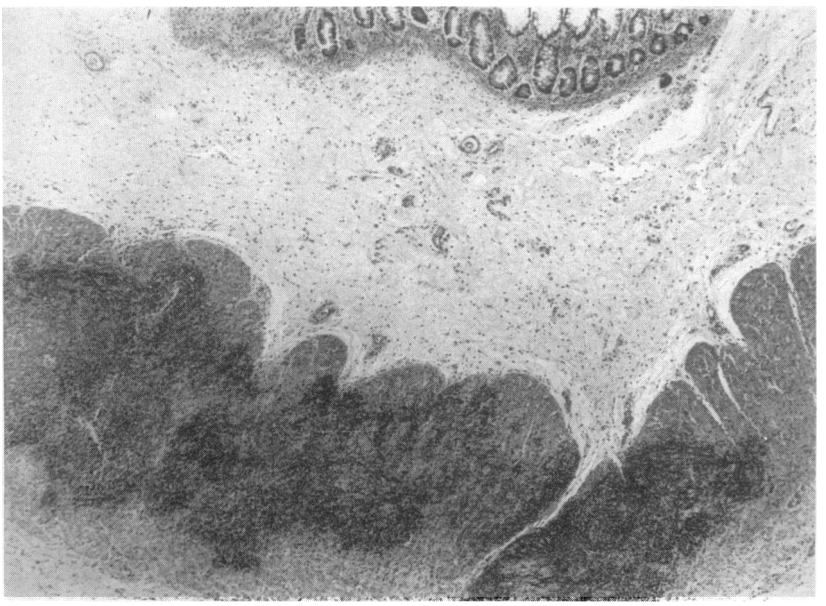

FIG. 7.—Focal necrosis with calcification of muscle coats of sigmoid colon. (H. and E. ×40.)

uraemia. You do undoubtedly see hypercalcaemia during recovery, which later disappears; presumably the hyperparathyroidism continues active for a while as the original stimulus subsides. I don't know whether that might apply to this patient.

Dr. WRONG: I agree; that can occur. However, the boy's illness ran a rapid course, killing him in less than a year. That is a very short time for a secondary hyperparathyroidism to become autonomous.

Dr. HOBBS: In view of his low albumin, showing that his ionized calcium was already too high, did you lower the concentration of calcium in the dialysis fluid?

Dr. MACINTYRE: No. The concentration in the dialysing fluid should be that of the normal plasma ionized calcium, whatever the level of plasma albumin. But surely if this child had a high plasma calcium which persisted for some time, doesn't it require us to say that he had a metabolic disturbance? Certainly not dystrophic calcification.

Association with Uraemia

Professor FRASER: We had a young patient about the same age as this child who was admitted with an episode of acute infection of the kidneys and a blood urea of 150. During the next month or two, while the blood urea was coming down to 60, there was a constant hypercalcaemia which puzzled us. We wondered if it was associated with the decrease in the uraemia.

Dr. WRONG: Secondary hyperparathyroidism can develop very rapidly, within a few months, but it is difficult to see why this should produce hypercalcaemia. The original stimulus to parathyroid activity is thought to be hypocalcaemia.

Professor FRASER: We have always taken the view that secondary hyperparathyroidism cannot usually produce a hypercalcaemic state. However, if there is a fluctuating degree of uraemia this may not be so.

Dr. MACINTYRE: The parathyroids respond rapidly to experimental changes in the plasma calcium level. It seems to me that, although secondary hyperparathyroidism might explain hypercalcaemia with a sudden improvement in renal function, it is a little hard to explain the continued production of hypercalcaemia over some time on this basis.

Professor FRASER: I suppose one could postulate that there was an intermittent degree of uraemia for a period while the blood urea was climbing up; then the peritoneal dialysis intervened. Might not this be the ideal way to produce hypercalcaemia due to uraemia and secondary hyperparathyroidism? For example, we see patients who have a retroperitoneal tumour which causes hypoglycaemia by stimulating the pancreatic islets. We followed one of these patients for 10 months afterwards and found she was still liable to hypoglycaemia; yet now, some two or three years later, she no longer gets it. Here residual hyperactivity of the islets has taken a long time to settle down. It may be the same with secondary hyperparathyroidism.

Dr. MACINTYRE: Were there any changes in the thyroid? Did you look to see whether the calcitonin-producing parafolliculae were prominent?

Dr. DAWKINS: No. The thyroid appeared to be quite normal.

Dr. B. E. HEARD: Dr. Newman asked if there was any connexion between the intestinal changes and the renal changes. I have seen two cases of ulceration of the ascending colon associated with renal cortical necrosis, and Sheehan and Moore[2] mention it in their monograph on renal cortical necrosis. The mucosa was intact at this late stage in the present case. Histologically our earlier cases showed similar arterial changes to the vessels in the kidney.

Professor FRASER: You think this may be even more widespread than just in the colon?

Dr. HEARD: Yes, I think this might be a sort of regional vascular effect.

Dr. WRONG: This case is extraordinarily like the first case reported by Professor Colin Campbell in the *Archives of Disease in Childhood* in 1949.[3] The patient showed gut lesions like these.

Professor FRASER: This may have something to do with the calcification problem.

Dr. WRONG: I don't know what the disease is, but the whole trouble started with diarrhoea; as it did in Professor Campbell's case, where the lesions in the gut were similar.

Cause of Renal Cortical Necrosis

Professor FRASER: We have not discussed the cause of the renal cortical necrosis in young children. Any suggestions? It is certainly easier to explain this in pregnancy.

Dr. WRONG: I would like to emphasize the difference between this and the renal cortical necrosis of pregnancy. I don't know why people get cortical necrosis following concealed accidental haemorrhage, but it doesn't have the features of an inflammatory disease; I suspect that it is entirely vascular, perhaps as a result of vascular spasm or something similar. But this boy's disease started with symptoms suggestive of a general systemic disease. He had diarrhoea and he may have had an arteritis rather than a spastic condition of his renal vasculature. Later he behaved rather like a glomerulonephritis in having large amounts of protein in his urine. I suspect that whatever the lesion in his renal vasculature might have been it was inflammatory. Perhaps something like polyarteritis nodosa affecting the kidney.

Possibility of Poisoning

Dr. J. A. DAVIS: I don't think we should neglect the possibility that this child was poisoned. The few cases of this condition that I have met with were all due to poisoning which was traced. Poisoning is quite common in boys of this age. He was living on a farm, so he could very readily have picked up something which nobody knew he had drunk; and this perhaps might also account for the presence of the lesions in the colon and in the kidney. I remember two children in one family who drank poison out of the same bottle. They had just this story of vague ill-health and diarrhoea for a week before the renal condition became manifest.

Dr. HOBBS: In that respect the renal cortex is metabolically quite similar to the liver. One wonders was there any evidence of liver regeneration in this patient?

Dr. DAWKINS: No.

Dr. HEARD: May I just comment on the lung histology? Dr. Dawkins very kindly showed me sections. I have never seen this sort of calcification in the alveolar exudate in uraemic oedema. Dr. Herdan and I have looked at quite a lot of cases now—all in adults—and we have seen frequently, as in the present case, fresh fibrin and red cells at all stages of organization, as Professor Doniach[4] described; but we have never seen clumped calcification like this before.

Professor FRASER: There still remain a few mysteries about the cause of his calcification in various sites, and the cause of his renal cortical necrosis. The suggested poisoning might be the easiest one to fit them together.

Dr. NEWMAN: What particular poisons did Dr. Davis have in mind?

Dr. DAVIS: There is a rather large list: it might be something like *Amanita phalloides* or possibly carbon tetrachloride,

(*Continued at foot of next page*)

Current Practice

ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Anticoagulants in Pregnancy

Q.—*Should anticoagulants ever be given in pregnancy?*

A.—It is important to differentiate between heparin and oral anticoagulants when considering anticoagulant treatment in pregnancy. Oral anticoagulants of the coumarin-indanedione groups pass through the placental barrier and represent a considerable hazard to the foetus. The higher mortality of newborn calves was observed during the early days of the investigation of "sweet clover disease" of cattle, and there have been a number of reports of foetal deaths recorded in patients receiving oral anticoagulants. In addition to crossing the placenta, coumarin-type drugs are also secreted in breast milk. They must therefore be avoided so far as possible during pregnancy.

Heparin, on the other hand, is devoid of these risks. The majority of cases of superficial thrombophlebitis or calf-vein thrombosis will resolve rapidly on a short course of heparin in adequate dosage. Intravenous injection of 15,000 units must be repeated 6-hourly, but intramuscular administration of 15 to 20,000 units 8-hourly produces a more gradual but more sustained anticoagulant defect. Provided a concentrated form (i.e., 25,000 units per ml.) is used there is not much pain at the injection site and little trouble from haematomas. Control by clotting-time tests is not usually required provided an adequate dose is given for not more than 48 hours. In this time the majority of minor episodes will resolve.

Cases of deep-vein thrombosis or pulmonary embolism during pregnancy will require a longer period of treatment and should be controlled after the first 48 hours by clotting-time determinations performed at the minimum blood levels (i.e., immediately prior to the next injection). If the result is then within the normal range increased dosage is advised, but if more than twice the normal mean the dose should be reduced. Heparin therapy may be continued for several weeks on this basis but should be neutralized by the calculated equivalent of protamine or polybrene at the onset of labour.[1]

If oral anticoagulants must be administered during pregnancy (e.g., because of grave risk to life of the mother from repeated embolism in a patient already on long-term therapy) conservatism of dosage is advised. The prothrombin activity should not be allowed to fall below the upper half of the therapeutic range. By this means the foetal mortality is reduced.[2]

REFERENCES

[1] Poller, L., *The Theory and Practice of Anticoagulant Treatment*, 1962. Wright, Bristol.

[2] Quenneville, G., Barton, B., McDevitt, E., and Wright, I. S., *Amer. J. Obstet. Gynec.*, 1959, **77**, 1135.

Antispasmodics and Bowel Motility

Q.—*Are there any antispasmodics which do not inhibit bowel motility?*

A.—Drugs which are used as antispasmodics all either possess atropine-like activity, which means that they are anticholinergic, or they act like papaverine, which has a direct relaxing effect upon smooth muscle cells. That being so it is unlikely that any of these substances will not interfere with bowel motility, which is due to smooth muscle activity and is controlled to a considerable extent by cholinergic nerve fibres of the autonomic nervous system.

It is known, however, that in man the response of the gastro-intestinal tract to atropine and atropine-like drugs is extremely variable and depends upon a number of factors—such as the state of the gut at the time of administration, the particular drug which is employed, its route of administration and dosage, and the technique of measuring the response.

Some antispasmodic drugs are said to have a greater effect upon one part of the gastro-intestinal tract than another—e.g., mepenzolate bromide (Cantil) is claimed to be more potent on the colon than on the small intestine.[1] Such claims, however, are based mainly upon experimental observations in animals, and it is by no means certain that they apply when the drug is used in therapeutic dosage in man.

In general it can be said that, by definition, an antispasmodic is a drug which relieves spasm of smooth muscle and that the effects of such a drug, unless it can be applied locally, cannot be localized to one particular organ and therefore some inhibition of bowel motility is bound to occur.

REFERENCE

[1] Lewis, J. J., *Introduction to Pharmacology*, 2nd ed., 1960. E. & S. Livingstone, Edinburgh.

Notes and Comments

Lambliasis.—Dr. D. W. F. CHARLTON (Grey's Hospital, Pietermaritzburg, South Africa) writes: With reference to the answer to this question ("Any Questions?" 13 February, p. 438) I would like to suggest that in areas where it is common giardia should be borne in mind rather more prominently than the statement "In the majority of infected patients there are no symptoms produced by *Giardia lamblia*" suggests.

The first case of giardiasis I ever saw occurred in a pilot later in the last war. This young man had done a bomber tour in the Middle East and was doing a course preparatory to another operational tour. He developed attacks of most severe vomiting for which no cause was evident, and it was thought that this vomiting was a psychological manifestation produced by the stress of impending further operational duty. However, investigation at the R.A.F. hospital at Halton revealed the presence of giardia, and treatment cleared up the symptoms.

At the other extreme, giardiasis can be the cause of no more than an "irritable child," so

(*Continued on next page*)

(*Continued from previous page*)

but this would probably have caused liver necrosis as well. It could have been swallowed just because it happened to be in a bottle that the child found attractive.

Dr. NEWMAN: What about the extreme arterial lesions? Could they possibly have been due to renal poisons?

Dr. DAWKINS: I simply can't answer that.

Dr. NEWMAN: I should have thought not. I should have thought that was one of the differentiating points between vascular necrosis and necrosis due to poisoning.

Dr. HOBBS: I would agree with Dr. Newman. With most of the known renal poisons liver damage is also the rule, and there is no evidence of this.

Professor FRASER: Well, perhaps we must leave that unsolved for the moment.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to Mr. W. Brackenbury for the photomicrographs.

REFERENCES

[1] Allen, A. C., *The Kidney. Medical and Surgical Diseases*, 2nd ed., 1962. Churchill, London.

[2] Sheehan, H. L., and Moore, H. C., *Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage*, 1952. Blackwell, Oxford.

[3] Campbell, C., *Arch. Dis. Childh.*, 1949, **24**, 269.

[4] Doniach, I., *Amer. J. Roentgenol.*, 1947, **58**, 620.