Clinicopathological Conference

A Case of Cushing's Syndrome with Misleading Urinary Steroids

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

Clinical History

Dr. C. L. COPE: The patient (Case No. 297379; P.M. No. 11154) we are considering today was a housewife aged 45 at the time of her death.

She was well until 1950, when she developed diabetes mellitus with thirst, polyuria, and loss of weight starting three months after the birth of her only child. She was started on insulin therapy at this time. In 1956 she was found to be hypertensive and in 1958 she was admitted to hospital because of tiredness. Her blood pressure was then 180/110 mm. Hg and at subsequent outpatient attendances the diastolic pressure varied between 120 and 150. By 1960 she was feeling more tired. She now had dyspnoea on exertion and intermittent swelling of her ankles. She had attacks of orthopnoea and she herself noted rounding and redness of her face, with growth of hair on both face and chin. She had also noticed that her abdomen had got larger but that her extremities were thinner. Her menses were regular. She reported easy bruising of her skin. Her diabetes was stabilized on a 1,800 calorie diet with 48 units soluble insulin and 24 units P.Z.I. each morning.

In 1961 she was admitted to a teaching hospital, where typical Cushingoid skin, facies, hirsuties, buffalo hump, and easy bruising were all noted. At that time she also had oedema of ankles and sacrum. Her blood pressure was 150/120 mm. Hg and there were bilateral basal crepitations in the chest. There was marked muscle weakness and muscle wasting. The clinical conclusion was "this should be Cushing's syndrome."

Accordingly, tests to confirm the clinical diagnosis were done. But the levels of urinary oxogenic steroids were 8.3 and 16 mg. and those of 17-oxogenic steroids were only 12.3 and 15 mg., analyses being done in two separate laboratories. A presacral air insufflation was not sufficiently clear for a useful opinion of adrenal size to be given, and the response to four days of corticotrophin was reported as being in the normal range, the level of 17-oxogenic steroids rising to 70 mg. on the fourth day.

She was discharged free of oedema on a regimen which included insulin, digitalis, guanethidine, reserpine, chlorothiazide, and potassium chloride. The diagnosis made was diabetes mellitus with essential hypertension.

By 1962–3 she had become irritable and restless and her memory was poor. Her menses were scanty and her exercise tolerance had become smaller still. By March 1964 her amenorrhoea was complete.

In October 1964 she was admitted to hospital elsewhere because of three to four months of attacks of nocturnal dyspnoea. She now had what was described as a typical Cushingoid appearance, though without striae. There was congestive cardiac failure and she had attacks of acute pulmonary oedema in which the blood pressure rose to 240/140 mm. Hg. The fundi showed pin-point haemorrhages but no exudates or papilloedema. There was glycosuria but no albuminuria or ketonuria. The haemoglobin was 14.4 g./100 ml., with a W.B.C. 14,200, of which polymorphs were 89% and eosinophils 1%. The blood urea was 49 mg./100 ml. The urinary 17-oxosteroids were reported as 32 mg. but 17-oxogenic steroids as only 4.7 mg. She was treated with digoxin, mersalvl, cyclopenthiazide, and methyldopa, but made relatively little improvement.

Final Admission

She was transferred to Hammersmith Hospital on 10 December 1964. By now she had ceased to have attacks of pulmonary oedema, but her pulse was 140 and regular. The blood pressure was 150/114 mm. Hg and the jugular venous pressure was +1 cm.

There was now a heavy albuminuria and the blood urea was 60 mg./100 ml. The plasma sodium was 13, potassium 3.3, bicarbonate 34, and the chloride 88 mEq/l. The blood sugar varied between 200 and 320 mg./100 ml. The urinary calcium loss was 220 mg. daily.

X-ray studies showed an enlarged heart with several healed rib fractures in thin bones. The spine showed no evidence of vertebral collapse. The skull was thought to show osteoporosis; the sella turcica was not enlarged but did show asymmetry of its floor.

There was calcinosis in the pulp of several fingers and the thumbs. There was also extensive destruction of the articular surface of the distal interphalangeal joint of the right index finger.

Steroid studies left no doubt of the existence of a severe degree of Cushing's syndrome. The 17-oxosteroids were normal, as is commonly found (11.7 and 12.7 mg.), but the 17-oxogenic steroids were raised at 23 and 34 mg. The levels of plasma 11-hydroxycorticoids (cortisol) were 30.5 μg. at 9 a.m. and 28.5 μg. at midnight, a very high figure. The urine level of 11-hydroxycorticoids was 1,600 μg. daily and the urine true cortisol was 580 μg. a day, both values being about three times the upper limit of normal. The plasma levels of 11-O.H.C.S. after five days of suppression with 8 mg. of dexamethasone daily were not reduced, the morning value being 37 μg. and the midnight 24 μg. Suppression was therefore not observed. But the adrenals were shown to be corticotrophin dependent by a rise of 17-oxogenic steroid excretion to 93 and 118 mg. after metyrapone in a dose of 4.5 g. daily.

Management

Her glycosuria was fairly well controlled by soluble insulin and P.Z.I., but because of her borderline left ventricular failure she was not considered fit for major surgery or even for air

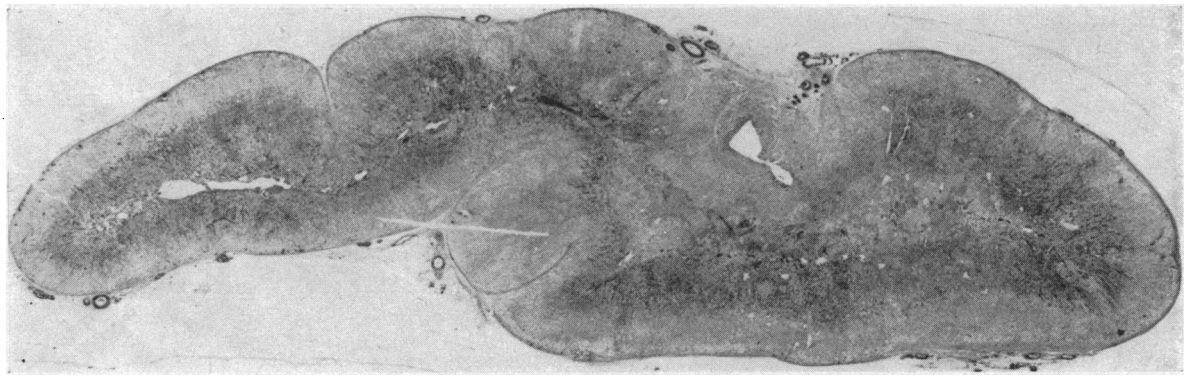

FIG. 1.—Hyperplastic adrenal cortex. (H. and E. ×5.4.)

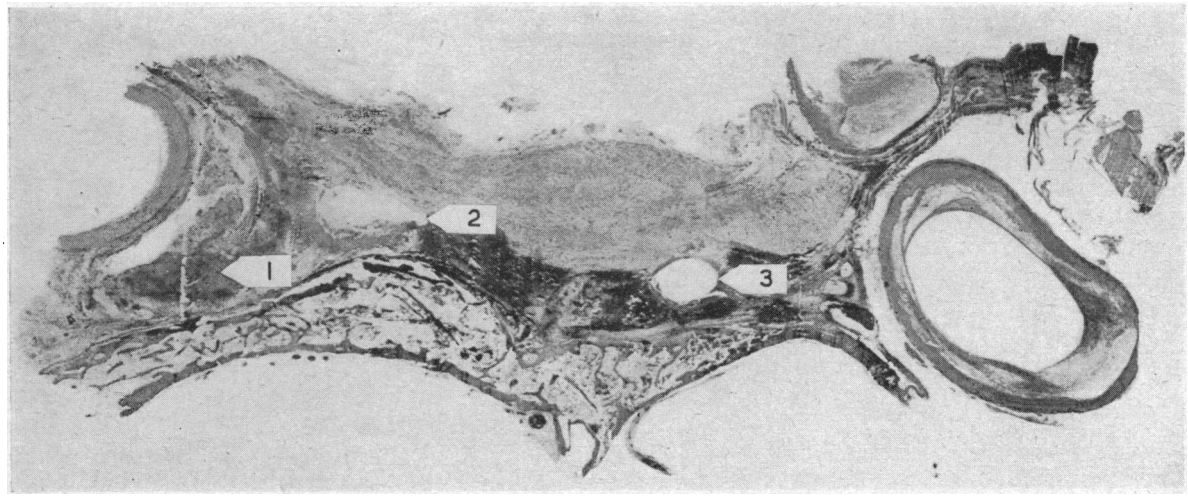

FIG. 2.—Coronal section of pituitary fossa. (Picro-Mallory. ×7.) The carotid arteries are present at either side, the dark central mass is haemorrhagic and necrotic tissue. The holes (2 and 3) are the site of the yttrium seeds. The tumour (1) partly surrounds the right internal carotid artery.

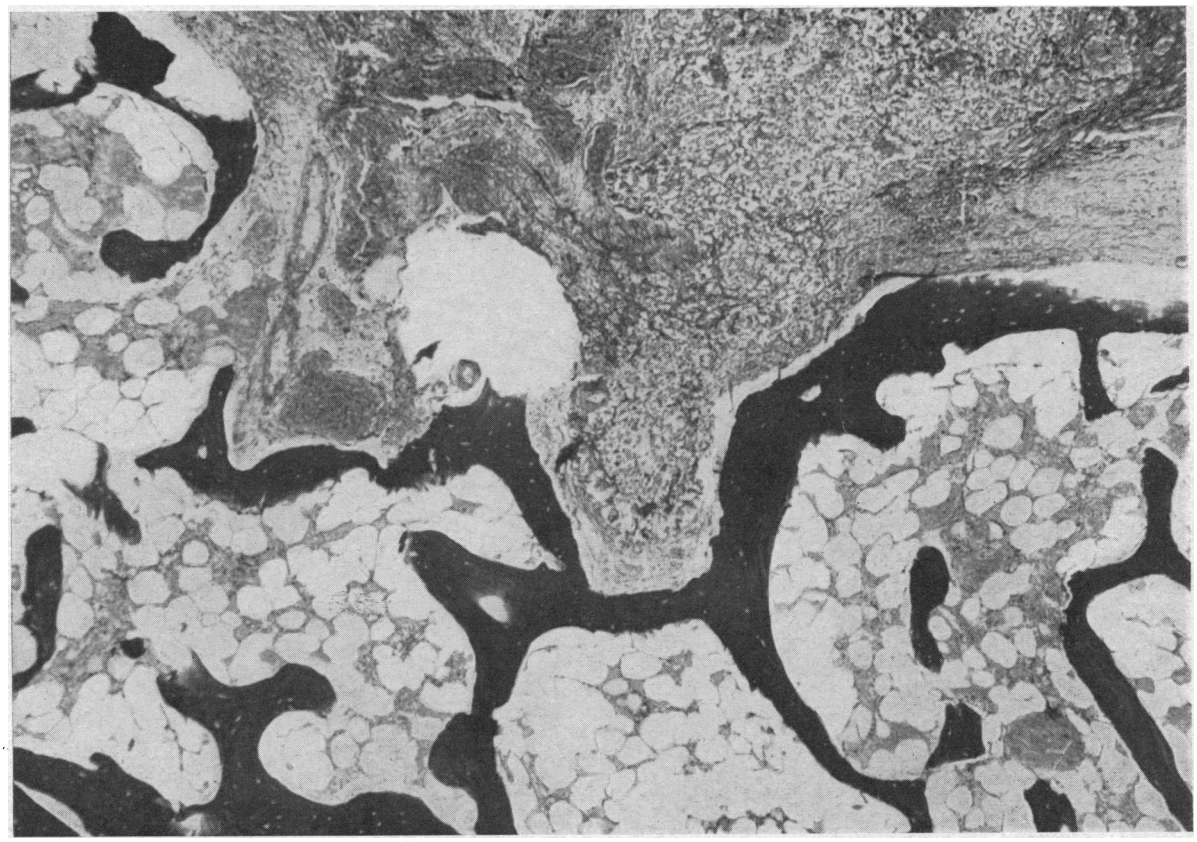

FIG. 3.—Coronal section of pituitary fossa. (Picro-Mallory. ×60.) The bony floor of the fossa is being eroded by an invasive pituitary tumour.

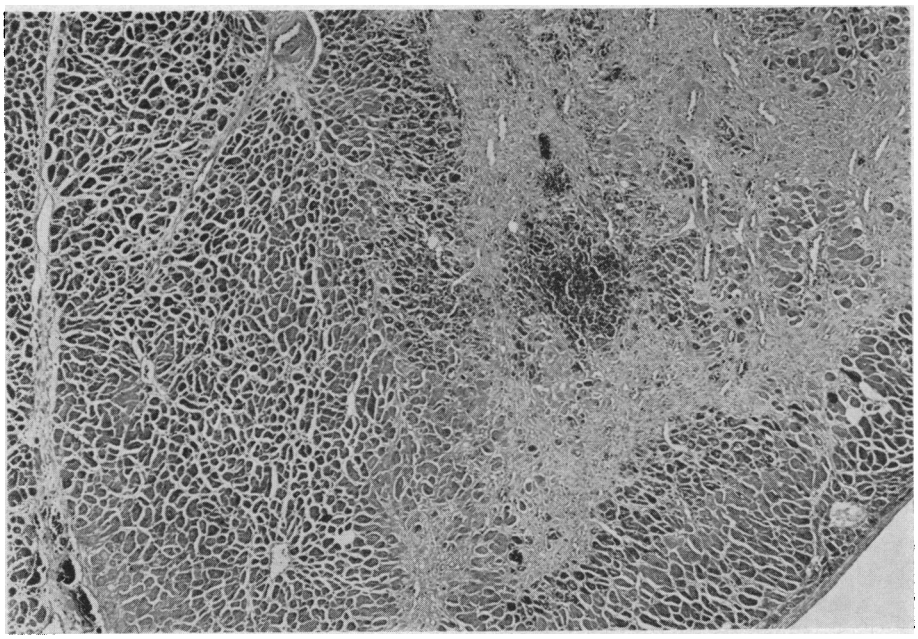

FIG. 4.—Focus of fibrosis in one papillary muscle. (H. and E. ×45.)

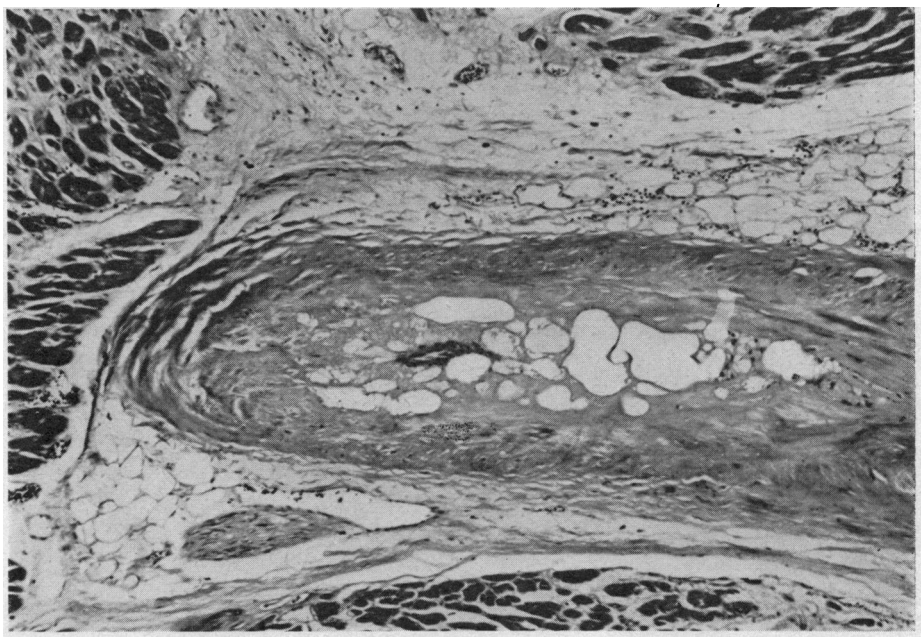

FIG. 5.—Small artery, from myocardium adjacent to Fig. 4, showing a lumen almost completely obliterated by atherosclerosis. (H. and E. ×70.)

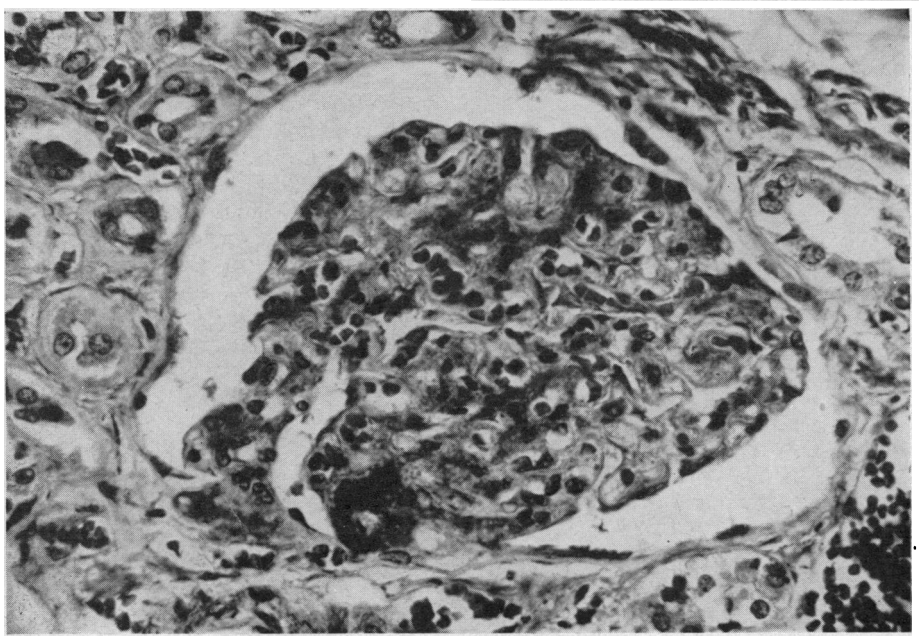

FIG. 6.—Renal glomerulus showing hyaline change in the afferent arteriole at the base of the tuft and some diffuse stromal thickening. (Martius Scarlet Blue. ×450.)

insufflation. On 22 January a pituitary implant of yttrium-90 was inserted by Dr. M. Hartog.

On 25 January the plasma level of potassium was 2.5 mEq/l., although she was receiving 3 g. of potassium chloride four-hourly. The sodium was 141, bicarbonate 39, and chloride 74 mEq/l. The blood urea was 42 mg./100 ml. On 27 January she felt fairly well, her blood pressure was 150/90, but she had attacks of palpitation. The plasma potassium had fallen to 2.1 mEq/l., and intravenous potassium chloride in 5% dextrose was given at 20 mEq per hour until the plasma potassium was raised to normal.

The urinary 17-oxogenic steroids were still raised, figures of 38, 46, and 31 mg. being found.

On 28 January she suddenly collapsed at 7 a.m., an E.C.G. showing ventricular tachycardia. Therapy with procainamide, mephentermine, and cortisol resulted in restoration of sinus rhythm, but a tendency to ventricular ectopic beats persisted. She was soon restored to full consciousness and was well enough to start breakfast. At 9.30 a.m. she had a further sudden collapse, this time due to asystole. The electrical defibrillator was of no avail and she died.

Clinical Diagnoses

(1) Left ventricular failure.
(2) Hypertensive heart disease.
(3) Cushing's syndrome, due to hyperplasia.
(4) Diabetes mellitus.
(5) Suspect Kimmelstiel–Wilson kidney.
(6) Yttrium implant.

Post-mortem Findings

Dr. E. D. WILLIAMS: On examination this woman was rather short and showed the features of Cushing's syndrome described in the clinical presentation.

Both *adrenals* were enlarged (10 and 11 g.) with diffusely hyperplastic cortices (Fig. 1), in which microscopical study showed compact cells extending out to the zona glomerulosa. The *pituitary* was removed with the surrounding bone (Fig. 2), and sectioned after the centrally placed yttrium rods had been removed. The tissue around the rods was necrotic and haemorrhagic. On the left side the peripheral part of the anterior pituitary survived, though it was somewhat haemorrhagic. In this area numerous hyaline basophils (Crooke cells) could be identified. On the right side there was a tumour (Fig. 3), about 6 mm. in diameter, in the lateral part of the lobe, extending laterally into the cavernous sinus, with a tongue of tumour spreading above and below the carotid artery. Microscopically the tumour was a chromophobe adenoma, with a few cells containing basophil granules. Scattered cells in the tumour showed hyaline pale blue cytoplasm with the Crooke–Russell technique. The floor of the pituitary fossa showed only a single small area of invasion by the tumour. The dorsum sellae was intact, and there was no meningitis.

The *parathyroids* were slightly enlarged but showed the normal ratio of glandular cells to fat. The *thyroid* was normal. The *pancreatic islets* were enlarged but did not show any hyaline degeneration. The pancreas otherwise was very autolysed but did show very prominent centroacinar cells. Numerous hyaline arterioles were present.

The *heart* was moderately enlarged (480 g.), with marked left ventricular hypertrophy (2 cm. thickness). The valves were essentially normal. On microscopy there were small scattered areas of fibrosis throughout the myocardium, and a single small old infarct about 3 mm. in diameter in the left posterior papillary muscle (Fig. 4). This showed central scarring, while some adjacent muscle bundles showed nuclear and cytoplasmic changes suggestive of recent extension of the old infarct. A small artery (Fig. 5) adjacent to this was virtually occluded by atheroma. The main coronary arteries showed non-occlusive atheromatous plaques. The aorta showed moderate atherosclerosis with calcification and ulceration in the lower abdominal aorta.

The *lungs* were oedematous but otherwise normal. On section a single asbestos body was an unexpected chance finding. In the alimentary tract the stomach showed recent mucosal haemorrhage; the large and small intestines were normal. The *liver* (1,775 g.) showed a large yellow clearly demarcated subcapsular area, a localized area of fatty change.

Both *kidneys* were of normal size and macroscopic appearance. Microscopically the glomeruli showed a mild diffuse stromal thickening (Fig. 6) but no nodular lesions of Kimmelstiel–Wilson type. The afferent glomerular arterioles showed a prominent hyaline change and a few proximal convoluted tubules showed coarse vacuolation attributable to hypokalaemia.

Several healed *rib* fractures were present. Sections of the vertebrae showed moderate osteoporosis. In the sections of one interphalangeal joint there was almost complete loss of the joint cartilage, with eburnation of the underlying bone. Considerable new bone formation was present.

In the *eye* sectioned there was hyalinization of some choroid vessels, and one retinal capillary showing aneurysmal dilatation.

Pathological Diagnosis

(1) Chromophobe adenoma of pituitary.
(2) Bilateral adrenal cortical hyperplasia.
(3) Left ventricular hypertrophy with patchy fibrosis and a small infarct of one papillary muscle.
(4) Mild diffuse diabetic glomerulosclerosis.

Discussion

Dr. COPE: I admit that I left out originally the diagnosis of diabetes mellitus. Whether we should call that part of the Cushing's syndrome or not I do not think we can answer here. We did not know enough about this patient before she came to us in her terminal illness. If successful treatment of the Cushing's syndrome had greatly relieved the diabetes we could have included it in the Cushing's syndrome. I think we might have made a case for her having separate diabetes mellitus, but I think it is largely speculative. She had a heavy albuminuria, and I would have expected that she would have shown some Kimmelstiel–Wilson changes. But the fact that she did not leaves the albuminuria unexplained unless we attribute it to the severe hypertension. To me the main interest of this patient by far is the events that happened in 1961, when an expert clinician and an endocrinologist came to the clinical conclusion that this should be Cushing's syndrome. But too much reliance was placed on laboratory diagnostic tests, which, even at that time, were known to be very fallible. The clinical impression was completely overruled and a final diagnosis of diabetes with independent essential hypertension was made. There is a very good object lesson here, I think. No one should interpret a diagnostic laboratory test to the point of taking action on it unless he knows how valid it is. Surely one of the functions of a clinician these days, an admittedly difficult one, is to seek evidence for the reliability or otherwise of the vast numbers of laboratory tests that are poured out every day. Urinary 17-oxogenic steroid assays are known to be fallible, and a whole series of them seem to have been misleading on this one single patient. In

such circumstances the physician should relinquish his clinical impression with reluctance.

However, there are other points about the case; there are indeed many. We were handicapped in many ways by the fact that she was so ill, and that we therefore did the minimum with her in the way of investigation. She was strongly suspected to have an adrenal hyperplasia, pituitary-dependent. The sella turcica was practically normal in *x*-ray, but there was asymmetry of the floor of the sella which was compatible with the development of tumour formation.

Dr. J. LAWS: No, I wouldn't agree there. The report said that there was asymmetry of the floor of the fossa and suggested tomography. This confirmed that the fossa was not enlarged.

Dr. COPE: Maybe that was the order of events. You were quite right to suggest that tomography of the floor may be helpful. Unfortunately we have not got those pictures, but one of the things to discuss is the extent to which *x*-ray tomography can give an indication of the degree of invasion. As I was looking at the films it struck me that she was a candidate for a meningitis in the near future. I have seen that happen before in a patient diagnosed as a diabetic. A pituitary tumour was found eroding into the sphenoidal sinus, producing a meningitis which complicated the whole clinical picture.

Another aspect of interest is the potassium troubles which she had towards the end. They were admittedly terminal, but we were very conscious of them. We were unable to keep her plasma level of potassium up and we didn't know why. It is possible that she had been severely potassium depleted before she came to us. The final circumstances of her cardiac breakdown are also worth discussion: ventricular tachycardia on the one hand—the type unfortunately unspecified—and the final asystole from which she never recovered.

Importance of Clinical Diagnosis

Professor Sir JOHN MCMICHAEL: I think, as Dr. Cope has emphasized, this case is full of lessons. The important part of the diagnosis of Cushing's syndrome is really clinical. The laboratory tests, now of course more refined, could be misleading. I would like to get the record straight: it was reported in the other hospital in 1964 that she had no albuminuria. Did she develop it in the later stages?

Dr. COPE: She had it all the time she was with us from 10 December until her death on 28 January.

Professor MCMICHAEL: I see. On those grounds—albuminuria in a diabetic—together with the evidence of aneurysms of the retina and hypertension, one must make the diagnosis of Kimmelstiel–Wilson syndrome; but, as has been shown by Dr. Williams, there were no characteristic glomerular lesions, though there was some thickening of the basement membrane.

Dr. WILLIAMS: There was a diffuse stromal lesion in the glomerulus, not truly a basement membrane thickening.

Professor MCMICHAEL: So the glomeruli did show something which I presume could have antedated heavier deposition?

Dr. WILLIAMS: Yes, indeed this could have been responsible for the albuminuria. At the time it was detected, however, she was also a hypertensive in heart failure.

Unusual Infarction

Professor MCMICHAEL: The other thing that is of great interest to me is that she had evidence of a small infarcted area in the capillary muscles of her heart without gross obstruction of the main coronary arteries on the surface of the heart. Now this is rather exceptional. Generally speaking, the basis of coronary disease is occlusion—and occlusive changes in the visible vessels on the surface. Very seldom do occlusive changes develop in the penetrating branches of the coronary artery. An infarcted area is usually related to obstruction of the surface vessels. This is the first time I can recollect seeing an infarct due to occlusion of the penetrating branches of the coronary arteries running in towards the papillary muscles. That will no doubt call for comment from Professor Harrison.

Professor C. V. HARRISON: I'm casting my mind back to the various cases I have seen with very small vessels involved. They have all been in cases of polyarteritis nodosa. They have been still visible on the surface of the heart, so that they were not the ones that dip down into the muscle.

Dr. J. P. MOUNSEY: Can I make another point? We are told that the necropsy showed infarction of a papillary muscle. Functional mitral incompetence sometimes accompanies this anatomical lesion. Was there in life at any time a systolic murmur?

Dr. COPE: Not one of any significance. There may have been a slight one, but there was none recorded, and I have never heard one myself.

Professor MCMICHAEL: There has to be considerable loss of function to the papillary muscle for that to occur. It may be ruptured or it may be unable to contract, so that the cusps may be blown out to give a systolic leak.

Dr. MOUNSEY: I wanted to know whether what we have been shown was purely of morbid anatomical interest or also of physiological and functional interest.

Dr. WILLIAMS: I should comment that it was only a small infarct, perhaps a third of the area of the papillary muscle in section. I wondered whether in the papillary muscle the blood supply was more tenuous, depending on a single artery rather than several anastomotic branches. This, therefore, may be a special case. I would like to stress that it was a small infarct; there were numerous smaller areas of fibrosis, which one could not dignify with the name of infarct, scattered over all the sections of the left ventricle.

Dr. COPE: If there was only such a very small infarct, why did she have hypertensive heart failure?

Professor MCMICHAEL: Hypertension as such can cause overload failure.

Dr. COPE: I don't think that's an adequate explanation.

Professor HARRISON: May I throw a spanner in? We are fooling ourselves by equating the word fibrosis or necrosis and the word infarct. Now, may I refer you to the work of Mitchell and Schwartz,[1] of Oxford, who analysed these small lesions in the myocardium. They found that the big ones were constantly associated with disease of arteries. They found no association between small amounts of fibrosis and arterial disease. Dr. Williams said he is referring to a small point of fibrosis in a papillary muscle. To call this an infarct is, I think, misusing the English language.

Dr. WILLIAMS: It depends where you draw your size difference. I agree that most of the lesions were tiny and irrelevant. This was of the order of, say, two or three mm. across.

Professor HARRISON: Oh, this is in the non-significant group.

Professor MCMICHAEL: You showed us an occluded vessel, so that I think that this very small infarct is an exception to the Mitchell rule.

Dr. J. P. SHILLINGFORD: I wonder if I may throw a few spanners, too? I believe that one finds in heart failure secondary to long-standing hypertension small areas of fibrosis throughout the myocardium.

Professor HARRISON: Yes.

Dr. SHILLINGFORD: Therefore it seems that in hypertensive heart failure there is some replacement of muscle fibres by fibrous tissue. Secondly, the heart lesions could possibly have been secondary to an embolus in a small artery.

Dr. WILLIAMS: There were two occluded arteries in separate sections; they may have been the same one. There were quite

a few small plaques of atheroma without significant occlusion in the major vessel. No other small artery, in the sections I have looked at, showed this change. I don't know where on earth this hypothetical embolus is coming from.

Dr. J. G. AZZOPARDI: I think it's fair to point out that ulcerating atheroma of the coronary arteries with peripheral embolization has rarely been described. It has more often been described in the abdominal aorta, where you get it embolizing to the spleen and the kidneys. There was very little atheroma in this case.

Dr. WILLIAMS: Just a few small plaques.

Urinary Steroid Tests

Dr. L. R. I. BAKER: Could I ask Dr. Cope what his experience is of urinary steroid tests in patients who may have defective renal function.

Dr. COPE: One cannot generalize about steroid tests. Most of the ordinary tests, if they are reliable, will remain reliable in the presence of quite a big drop in renal function; down to about 40% of the normal, perhaps. But with some of these tests—and the urinary cortisol is one of the sensitive ones—renal function can fall even further below normal. Even a blood urea raised above 100 mg. can still be compatible with a well-raised cortisol in the urine.

Dr. G. F. JOPLIN: May we take up one or two of the questions which Dr. Cope raised for discussion. I think the first point that he raised was the relationship between the diabetes and the Cushing's disease in this patient. Now we have it recorded here that the diabetes came on in 1950 and she was not hypertensive until 1956. This would be a very unusual order of events in the natural history of the evolution of Cushing's disease. For a start, only a small proportion of Cushing's cases develop diabetes even in the terminal phase of the disease. One would guess, therefore, that the odds are very much that the diabetes was unrelated to the Cushing's disease. There is another point here, which often puts off physicians from making the diagnosis of Cushing's disease, in that in 1960 the menses were recorded as regular. Now this is sometimes advanced as evidence against the diagnosis of Cushing's disease; but in our own series of about 50 patients with Cushing's disease about half of the women continued to menstruate after they'd clearly developed Cushing's disease. So continuation of menstruation by no means precludes the diagnosis.

On the question of the normal basal urinary steroids in the presence of Cushing's disease: in our own series we had three or four patients who had quite obvious Cushing's disease on clinical grounds, yet repeatedly normal urinary oxogenic steroids as recorded in our own laboratory; what showed these patients as being quite abnormal was the resistance to dexamethasone suppression. I would guess that if the dexamethasone suppression tests had been employed it's quite possible that a biochemical diagnosis might have been made.

A most important aspect of this case from the endocrine point of view is the pituitary tumour. Now review of the necropsy *x*-rays certainly would lead us to raise no questions of pituitary tumour here. This was a very, very normal pituitary fossa radiologically, and yet there was an unequivocal early tumour, which may have been invasive. This is of considerable importance in that it has been alleged that the reasonably high incidence of pituitary tumour following adrenalectomy for Cushing's disease is a consequence of the adrenalectomy. Our own series goes right against that view, in that a fifth of all the Cushing's cases had radiological evidence of pituitary tumours even before any treatment was done. Today's case is a very important bridge case, in that it shows quite clearly that tumour formation can occur in the absence of radiological abnormality. Could I finally ask Dr. Cope a question about the terminal illness? How many milliequivalents per day of potassium was this patient being given after implantation, and was she still getting this potent diuretic combination?

Dr. COPE: No, she was not having diuretics. She was getting potassium quite definitely, 3 g. potassium chloride four-hourly, that's six times a day, 18 g., and it was stepped up intravenously later. I can't help wondering whether the rapid swings in the potassium level didn't have an adverse affect on the myocardium, and I suspect, in fact, that metabolic myocardial trouble was vastly more important than any vascular. But that's an imponderable at the moment.

Dr. SHILLINGFORD: I should have thought that with the size of the area of ischaemia this is correct. Sudden death or sudden asystole, ventricular fibrillation, or ventricular tachycardia seldom occurs in hypertension without other cause. It is frequent in disturbances of potassium and other electrolytes, and with a potassium of 2.1 mEq one would perhaps expect some sort of arrhythmia in this condition, either ventricular tachycardia or ventricular fibrillation; I suspect at the end she developed ventricular fibrillation, then asystole.

Dr. JOPLIN: Was she receiving digitalis then?

Dr. COPE: No, she wasn't.

Dr. O. WRONG: The histological changes of potassium depletion in the kidney are not very common. I know they're regarded as characteristic, but in the majority of cases I've seen with hypokalaemia, who have had biopsies or who have come to necropsy, these changes have not been present. I think these changes indicate that there must have been a very considerable potassium deficit.

Dr. COPE: I think we may well stop at this point.

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

REFERENCE

[1] Mitchell, J. R. A., and Schwartz, C. J., *Arterial Disease*, 1965. Oxford.