Clinicopathological Conference

A Case of Hypertension, Anuria, and Uraemia

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

Clinical History

Dr. O. Wrong: The patient (Case No. 300365, P.M. No. 11312) was a married woman aged 39 at the time of her death from uraemia. There was no known history of hypertension or renal disease. In 1950 and 1952 she had had pregnancies which were apparently uneventful. In 1953 and 1955 further pregnancies were complicated by hypertension—noted at 37 and 12 weeks, respectively—but she went to term successfully. In 1957 her fifth pregnancy was also complicated by hypertension, and she prematurely delivered a living child at 36 weeks.

After the fifth pregnancy she was found to have persistent hypertension, which was investigated in New Zealand. Her fundi were said to show grade III retinopathy, while an intravenous pyelogram showed no abnormality. Her hypertension was thought to be essential in type, and treatment with hypotensive drugs was started. In 1963 she became pregnant again, and in March 1964 this sixth pregnancy was terminated at 29 weeks because of a blood pressure of 210/130, which persisted despite treatment with guanethidine and polythiazide. The blood-urea concentration was 48 mg./100 ml. and the haemoglobin level 10 g./100 ml. Subsequently she was well enough to resume domestic chores, look after her children, and play an occasional round of golf. She continued to take drugs for her hypertension. In February 1965 she had a short illness with back pain, fever, and slight urinary frequency. From that time on she had nocturia and frequent nausea and anorexia. In April she stopped taking her guanethidine because of this nausea.

Progress

By the end of April she was more nauseated and noticed that her urinary output was scanty. On 6 May she became breathless and was admitted to her local hospital with pulmonary oedema and a blood-urea level of 330 mg./100 ml. She was treated with digoxin, methyldopa, guanethidine, and ampicillin, being transferred to Hammersmith Hospital on the following day. Here she was found to be pale and confused, with a pyrexia of up to 39° C. There were multiple bruises on the skin. The jugular venous pressure was raised, but there was no ankle or sacral oedema. Her blood pressure was 170/105 mm. Hg, and the optic fundi showed scattered haemorrhages and exudates but no papilloedema. There was evidence of moderate cardiac enlargement and a left pleural effusion, and widespread rales were heard. The kidneys could not be felt, and she was unable to pass urine.

The blood urea was 350 mg./100 ml., serum sodium 130, potassium 5.8, and bicarbonate 24 mEq/l. The serum albumin was 3.5 g. and the globulin 1.9 g./100 ml., with a normal electrophoretic pattern (one month later the albumin was 2.3 and the globulin 5.5 g./100 ml., with an increased gamma-globulin fraction). A radiograph of the chest showed appearances consistent with a left pleural effusion and consolidation or oedema of both lower lobes; the right kidney appeared rather small in the abdominal x-ray film, but neither kidney could be clearly seen; a radiograph of the hands was normal. The haemoglobin level was 6.3 g./100 ml. (M.C.H.C. 28%) and the stained film showed fragmented and crenated red cells. The platelet count was 171,000/cu. mm. The antistreptolysin-O titre was 50 units/ml. An electrocardiogram showed left ventricular hypertrophy and non-specific T-wave changes; at a later date she was found to have auricular fibrillation.

Her uraemia was controlled with peritoneal dialysis and her hypertension treated with methyldopa. Details of the clinical course are shown in Fig. 1. She remained almost totally anuric for the rest of her life, the few drops of urine she did pass containing many red cells and 5 grammes of protein per litre but only scanty granular casts. Despite aspiration of her left pleural effusion and various antibiotics she repeatedly showed evidence of pulmonary consolidation with fever and purulent sputum.

On 15 May Klebsiella was grown from the peritoneal fluid, and she had slight abdominal pain and tenderness. Kanamycin was given, its dosage being controlled by blood levels. A renal biopsy on 25 May showed evidence of benign hypertension only, without either glomerulitis or the characteristic changes of malignant hypertension. Because of the failure to explain adequately her anuria a retrograde pyelogram was performed on 4 June, but showed no abnormality. Corticosteroid therapy was also started on that day (prednisone 60 mg./day) on the remote chance that she had a polyarteritis that was not revealed by the renal biopsy. Over the next few days peritoneal dialysis became increasingly difficult, with repeated growth of Escherichia coli in the fluid and occasional
FIG. 2.—Myocardium of left ventricle showing a focus of recent necrosis. (H. and E. ×40.)

FIG. 3.—Myocardium of left ventricle showing organization of an older necrotic region. (Picro-Mallory. ×40.)

FIG. 4.—Renal cortex with relatively normal glomeruli, a few atrophic tubules, and an afferent arteriole with its lumen almost obliterated by intimal thickening. (Elastic-van Gieson. ×190.)
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**Fig. 5.**—Afferent glomerular arteriole with its lumen almost completely occluded by the typical "onion skin" intimal proliferation of malignant hypertension. (Elastic-van Gieson. ×400.)

**Fig. 6.**—Normal afferent glomerular arteriole. (Elastic-van Gieson. ×210.)

**Fig. 7.**—Breast tissue showing secretory changes, probably due to chlorpromazine treatment. (H. and E. ×55.)
Pseudomonas pyocyanea, and had to be abandoned on 7 June. She died in uraemic coma on 20 June, six weeks after admission.

Clinical Diagnosis

(1) Oliguric renal failure, with uraemia resulting from either (a) malignant hypertension (? essential) or (b) polyarteritis nodosa.

Post Mortem Findings

Dr. E. D. WILLIAMS: The body was that of a thin middle-aged woman with a few purpuric spots on the arms and abdomen and slight oedema of the lower legs. There were peritoneal dialysis incisions below the umbilicus and in the left iliac fossa.

The heart weighed 400 g. (normal for patient 286 g.). The pericardium was normal. The left ventricle showed hypertrophy, being 21 mm. thick (normal 15 mm.), but the right ventricle was of normal thickness. All the valves were healthy and valve rings were of normal size. The coronary arteries showed only minimal atheroma without appreciable narrowing. In the basal half of the myocardium of the left ventricle there were numerous small foci (1–3 mm.) of grey tissue replacing the muscle. These were scattered indiscriminately around the circumference. Microscopically these were foci of muscle necrosis (Fig. 2) with fibrous replacement, which varied in age from early organization to full fibrosis (Fig. 3). In some of these foci the microscopic branches of the coronary arteries were occluded by fibrosis, usually together with partial or total destruction of the media. The aorta showed only mild atheroma in the form of fatty streaks and isolated plaques covering less than one-quarter of the surface. The renal arteries were normal, as were the other branches of the aorta.

The right kidney weighed 105 g., the left 95 g. (normal 115–155 g. each). Their surfaces were smooth, while the cortex was slightly thin and blotchy in colour. There was a small cortical adenoma in the right kidney. Histologically neither of the renal biopsy specimens (Fig. 4) showed more than a few glomeruli, and these were free from any sign of nephritis. There was some evidence of tubular atrophy. The interlobular arteries showed fibroelastosis, while the arterioles showed hyaline change and necrosis. The "onion-skin" intimal thickening of malignant hypertension was not seen. Histological examination of sections of the kidneys taken at necropsy confirmed the presence of tubular atrophy. The glomeruli were free from signs of nephritis and the arteries and arterioles showed the same changes as seen in the biopsy specimens, but in addition a number of arcuate and interlobular arteries did show typical "onion-skin" intimal fibrosis (Figs. 5 and 6). This finding, the lack of renal scarring and shrinkage, and the history of acute hypertensive treatment are consistent with a diagnosis of essential malignant hypertension. Microscopic examination of other arteries showed hyaline sclerosis with occasional points of necrosis in arterioles in the suprarenal, the pancreas, and the heart.

In the abdomen there were fibrinous adhesions between loops of intestine and the omentum, and layers of fibrin over the liver and in the pelvis. Microscopically these showed organizing fibrinous exudate, but few polymorphs and no organisms were seen. The appearances suggested a peritonitis that had been successfully treated. The parathyroids were within normal limits, and the bones were free from secondary osteitis fibrosa.

Other incidental findings included a few foci of acute pancreatic necrosis, and a few foci of pulmonary alveolar exudate that appeared to be treated bronchopneumonia. There were six mixed gallstones. The breast showed lobular hyperplasia and signs of secretion (Fig. 7), possibly due to the administration of chlorpromazine.

Pathologist's Diagnosis

(1) Treated essential malignant hypertension.
(2) Uraemia.
(3) Treated peritonitis with persisting fibrinous exudate.
(4) Focal myocardial necrosis, probably of vascular origin.
(5) Gallstones.
(6) Focal pancreatic necrosis.
(7) Hyperplasia of breast due to drugs.

Discussion

Dr. O. WRONG: One of the chief reasons why we thought she had the histology of malignant hypertension is that in the course of a year she had gone from a stage when her blood-urea level was 48 mg./100 ml. to total anuria with death in uraemia. It is quite likely that at some time during this period she went through a phase of papilloedema with a higher diastolic blood pressure than any we have recorded—particularly in the last month before admission, when she was already ill and stopped treatment. Obviously there must be patients with a condition intermediate between what one would accept as benign nephrosclerosis, on the one hand, and malignant nephrosclerosis, on the other—and she was in this no-man’s land, though perhaps more at the benign end of the spectrum histologically, and more at the malignant end clinically.

In the last two years we have had several patients with severe hypertension, progressive renal failure, and the histological features of malignant hypertension who have not had a papilloedema. We presume that the malignant hypertension is so rapid that they develop the lesions in the kidney causing uraemia without developing the papilloedema which is usually an accompaniment of the arteriolar lesions. Patients with histological malignant hypertension don’t always have papilloedema. I see that Dr. Kincaid-Smith is here today, and I would remind you that in her series of over 200 patients with histological malignant hypertension 3% did not have papilloedema.

Dr. P. KINCAID-SMITH: Yes, I agree.

Dr. WRONG: So we can make a diagnosis of malignant hypertension in a patient who doesn’t have papilloedema, particularly if he has got worse rather rapidly. At the moment we have a patient with this syndrome who has actually recovered some renal function after six weeks of dialysis and hypotensive drugs, and has been able to go out of hospital with a blood-urea level of about 200 mg./100 ml. With the patient we are discussing we were not able to persist with treatment for as long as this. I wish we could have gone on longer. Intermittent haemodialysis is probably the best way of treating someone with kidney disease who might have a chance of eventual recovery, but at the time we were not able to squeeze another patient on to our haemodialysis programme, and therefore had to use peritoneal dialysis.

I’m reassured that the infective complications of dialysis were not as bad as we thought they were, but we must do all we can to improve our technique of peritoneal dialysis, in which, at the moment, infection is a limiting factor, as it was here. In this hospital—at least in our unit—we have not so far managed to keep a totally anuric patient alive for more than four months by peritoneal dialysis, because of the technical difficulties caused by low-grade infection. I do find it surprising that this patient had anuria. The glomeruli looked pretty normal, so I presume the blood vessels had closed up completely.

Professor C. C. BOOTH: I find it equally puzzling, frankly, why this patient should have died in oliguric renal failure. I wonder, Dr. Kincaid-Smith, if you would like to comment?
Dr. KINCAID-SMITH: I don't really have much difficulty in understanding the case. I think she had "malignant" hypertension. I believe that she had the lesions in the blood vessels, which I would call treated malignant hypertension; she then blocked off these vessels when she stopped treatment, and became anuric. This used to be fairly common in the course of malignant hypertension—particularly in the days before treatment—and we've seen quite a number of them since treatment has been available. This usually occurs in a patient like this—one who stops treatment, or one who has never been treated. We have done renal biopsies in 80 patients who have been admitted to hospital with acute renal failure and in whom we've expected some sort of irreversible cause; 14 of these have had the vascular changes of malignant hypertension. There are two types of change which are associated with oliguria. The first is the "onion-layering" changes in interlobular arteries. If you follow a particular vessel along they may show definite narrowing in one area and little or none a bit further distally. The second type of change is that the arterioles are quite often occluded by little plugs of thrombosis. This is, I think, thrombotic thrombocytopenic purpura associated with malignant hypertension, and which I think may cause the anuria. I'm very intrigued by the vessels in the heart. I wonder if this had something to do with uraemia rather than hypertension, or whether it couldn't be polyarteritis treated by corticosteroids?

Professor Booth: Professor Doyle?

Professor AUSTIN DOYLE: There are one or two things that did occur to me. Dr. Kincaid-Smith has made the statement that if you follow these vessels along you may find obstruction—as far as I know this hasn't been looked for in much detail in this case. Certainly in this kidney there is evidence of ischaemic atrophy. Is it necessary to talk about essential hypertension or benign hypertension? It doesn't seem to me to be a very useful distinction to make. Clearly there are all degrees of involvement of arterioles, and clearly this is a patient who has some of the features pathologically of malignant hypertension and some of the features of benign hypertension, but blocked arteries have resulted in her death. I think it is rather uncommon to find these blockages occurring in treated patients, though, as Dr. Kincaid-Smith has said, if treatment is stopped this may happen rather quickly and startlingly.

Dr. C. T. DOLLERY: There are two points worth making. Firstly, the kidney is an organ which requires a high perfusion pressure, so a given degree of arteriolar obstruction will impair the function of the kidney more than other organs. Secondly, I agree with the kidney. Dr. Doyle has said about the distinction between malignant and benign hypertension. Our work on the retinopathy of Grade III hypertension shows focal damage to the wall of small arterioles, and many people take that as the stigma of malignant hypertension. There is some point perhaps in using the term "accelerated hypertension" to describe this kind of disease. The distinction between grade III and IV retinopathy is still worth while from the clinical point of view, because patients with papilloedema who are treated do a lot worse than those who have only cotton-wool spots.

Professor Booth: Why did she get hypertension, then? Were her kidney lesions the primary cause?

Dr. KINCAID-SMITH: Oh no, they were the result.

Dr. WONG: Why did she get hypertension, then?

Dr. KINCAID-SMITH: I suspect she had it in her genes.

Dr. WONG: You wouldn't argue that she had toxæmia of pregnancy and became hypertensive on the basis of repeated pregnancies?

Dr. KINCAID-SMITH: She wasn't hypertensive in her first two pregnancies?

Dr. WONG: Not as far as we know.

Professor Booth: Was there any evidence, Dr. Wong, that this lady had toxæmia in the pregnancy when she was hypertensive; did she have proteinuric?

Dr. WONG: Our evidence is very scanty—we never had any information from New Zealand.

Professor Booth: I think it has been suggested that toxæmia of pregnancy may damage the kidney and lead later to malignant hypertension.

Dr. KINCAID-SMITH: Certainly ours would support this—that toxæmic changes may leave permanent damage. I don't know how good the evidence is that it can cause hypertension, because we never really know which came first.

Dr. DOLLERY: Pollock in Chicago has some very convincing serial renal biopsies in a patient who had severe toxæmia. The lesions of the small arterioles have persisted—and even seem to be progressing—though the patient is not hypertensive. It makes one think that hypertension may develop in future.

Dr. C. OAKEY: Isn't this very unlike toxæmia if she didn't have toxæmia in the first pregnancies? The presence of hypertension in the subsequent ones sounds more like hypertension complicated by pregnancy.

Professor Booth: More like a pregnant patient who happens to have hypertension. We are back to Dr. Kincaid-Smith's genes.

Professor J. GOODWIN: Could we come back to the heart again? I would like to ask Professor Harrison whether the vascular changes could possibly resemble in any way the changes described by Saphir and his colleagues in old people who have been given various drugs such as noradrenaline. (I believe this patient had noradrenaline.) They attributed the changes in the myocardium to some sort of hypersensitivity angiitis leading to necrosis. I wonder if this is a possibility in this patient or whether there were any drugs given that might have done this?

Dr. WONG: I am afraid I have no information about this. The electrocardiograms showed left-ventricular hypertrophy and non-specific T-wave changes. I'm sorry I can't give you more information.

Professor Goodwin: Was there left-axis deviation, which might suggest fibrosis of the myocardium?

Dr. WONG: I don't know.

Professor Harrison: It is a bit difficult answering this. These changes, where you get a loss of muscle, a falling together of connective tissue, and finally fibrosis are found in patients with aortic regurgitation, or in patients who have had a prolonged period of low cardiac-output failure. The isolated change is common; what is so remarkable in this patient is the enormous number of them clustered together, and of a size that we could see with the naked eye. This is extremely unusual. The next point is the correlation between these and the vascular change accompanying them. Who can tell which is cart and which is horse? If you occlude the vessel surely you might get necrosis of the muscle. If you have dead muscle here are you not in danger of causing thrombosis of the local vessel? I don't know.

Professor Goodwin: Patients who have massive myocardial fibrosis or necrosis from cardiomyopathy tend to have normal vessels, so I'd have thought the vascular change came first.

Professor Harrison: That is why I suggested it, but it is impossible to prove it.

Professor Booth: Now these vascular changes are thought to produce changes in the red cells. Professor Dacie, would you like to comment on this?

Professor J. V. DACIE: Uraemic patients are often very seriously anaemic. Azotaemia and perhaps infection probably both result in anaemia by diminishing the life-span of the red cells and also by inhibiting erythropoiesis. On top of this we see in some patients—in particular, in those who are suffering from progressive and severe renal failure, often with anuria—a florid haemolytic picture. These patients have a raised reticulocyte count and show fragmented red cells in their blood films. It looks as if a superimposed haemolytic mechanism is active. At
necrosis is a characteristic finding is disease of small blood vessels of the sort we've seen in the patient we are now discussing. Why the red cells are destroyed is really anybody's guess, but one hypothesis is that they are destroyed in some way by contact with the damaged vessels. Whether this is a result of contact with necrotic tissue, or as the result of intimate contact with fibrin deposited in the vessels, we don't know.

Professor Booth: Does this imply that when you see created and damaged red cells in the peripheral blood there is fibrinoid necrosis, and that you're therefore dealing with severe hypertension, or accelerated hypertension, or malignant hypertension, or whatever you call it?

Professor Dacie: We believe this is so, but there are many other causes of this blood picture than malignant hypertension. One such cause is thrombotic thrombocytopenic purpura—or Moschcowitz's disease—where the blood-vessel changes are widespread and not confined to the kidneys. We see, too, a similar picture in cases of carcinomatosis where carcinoma cells are growing in the blood vessels or in the spleen or bone marrow.

Dr. Dolly: May I ask a question of our visitors? What do they think is the difference between benign and accelerated hypertension. If you compare two people with similar pressure levels, one of them may destroy his small arterioles and die with uremia, while the other goes on for years without suffering severe damage to small blood vessels.

NEW APPLIANCES

A Means of Speaking for Patients with Cuffed Tracheostomy Tubes

Dr. R. M. L. Whitlock, formerly registrar, Acute Respiratory Unit, Auckland Hospital, Auckland, New Zealand, writes: Cuffed tracheostomy tubes are used to protect the lower airways in conditions complicated by bulbar paralysis and to facilitate prolonged intermittent positive-pressure inspiration (I.P.P.R.) in the treatment of respiratory failure. Patients with these conditions are often unable to write because of paralysis or limb injuries and few people are skilled at lip reading. Because of the need for another means of communication a simple tracheostomy-tube attachment has been developed.

The attachment (Fig. 1) consists of an F.G. 8 or 10 disposable plastic suction catheter through which air or oxygen is passed to blow on to the vocal cords. The catheter passes through a hole bored in the lower edge of the flange of a Portex plastic tracheostomy tube (Portland Plastics, Great Britain) which has a detachable inflatable cuff at the distal end. It then runs below the tube until it curves round one side to direct the tip upwards towards the vocal cords. Its curved portion is held in position by the edge of the cuff. With the catheter in the correct position (Fig. 2) a gas flow of 5 litres per minute is sufficient for distinct speech in the average adult without discomfort. The supply can be from a small air compressor or an oxygen cylinder with a pressure-reducing valve. To avoid drying of the mucosa and discomfort to the patient it is preferable to warm and humidify the gas, especially if oxygen is used. A pressure-relief valve somewhere in the supply line is a desirable safety measure. The gas supply should not run continuously but only when the patient wishes to speak. If a small electrical air compressor is used the flow rate can be pre-set and the compressor switched on by a microswitch which can be operated by any movable part of the patient's body. Alternatively a nurse may switch on the gas supply.

This attachment is cheap and of simple construction, and does not interfere with tracheostomy management or I.P.P.R. It allows speech throughout the whole of the respiratory cycle, does not rely on I.P.P.R., and has no moving parts. (A specially constructed tracheostomy cannula that uses the patient's exhaled air through a sliding valve for speech has been described elsewhere, but it can be used only for patients on a Bird respirator.)

A delay of three days after tracheostomy is recommended before attempting to use the attachment. This interval allows time for the tracheostome to become sealed by granulation tissue, thus preventing escape of air around the tracheostomy tube or, worse, into the tissues of the neck and mediastinum.

Clinical trials on seven patients have been encouraging with six successes, though one of these found the flow of air too uncomfortable after a successful trial. The failure occurred in a patient with a tracheostome larger than usual which allowed the air to flow out round the tracheostomy tube more readily than through the vocal cords.

This speaking-aid not only makes communication easier but also relieves the patient from the frustration and fear of not being able to make his requirements known. There have been no complications from its use.

I thank Dr. M. Spence, medical officer in charge, Acute Respiratory Unit, Auckland Hospital, for permission to develop this device and for advice on its use.

REFERENCE

1 Asscher, A. W., Wilson, C., and Anson, S. G., Lancers, 1961, 1, 580.