insulin retard moderately so, and zinc protamine insulin being relatively delayed.

Shortly after the last test shown in Fig. 1 the man had a hypoglycaemic attack just before breakfast. The dose of zinc protamine insulin was dropped to 40 units. As it was feared that this reduction would permit much sugar to escape during the morning, 10 units of ordinary insulin were given along with the zinc protamine insulin. The patient was discharged on these doses and now appears to be satisfactorily controlled.

REFERENCES

- Campbell, Fletcher, and Kerr (1936). *Trans. Ass. Amer. Phys.*, **51**, 161.
 Hagedorn, Jensen, Krarup, and Wodstrup (1936). *J. Amer. med. Ass.*, **106**, 177.
 Himsworth, H. P. (1932). *Lancet*, **2**, 165.
 — (1934a). *Ibid.*, **2**, 888.
 — (1934b). *British Medical Journal*, **2**, 57.
 — (1936). *Treatment in General Practice*, **2**, 338. H. K. Lewis and Co., London.
 Joslin (1935). *The Treatment of Diabetes Mellitus*. Lea and Febiger, Philadelphia.
 Krarup (1935). *Clinical Investigations into Protamine Insulinate*. Gad, Copenhagen.
 Lawrence and Archer (1937). *British Medical Journal*, **1**, 487.
 Rabinowitch *et al.* (1936). *Canad. med. Ass. J.*, **35**, 239.
 — Ritchie, and McKee (1934). *Ann. int. Med.*, **7**, 1478.
 Scott and Fisher (1936a). *J. Pharm. Exp. Therap.*, **55**, 206.
 — (1936b). *J. biol. Chem.*, **114**, 88.
 White (1932). *Diabetes in Childhood and Adolescence*. Lea and Febiger, Philadelphia.

NON-SURGICAL RENAL EMERGENCIES

A POST-GRADUATE LECTURE

BY

JAMES M. STALKER, M.D.

Physician, Dundee Royal Infirmary

It would be an unprofitable exercise to attempt in one lecture an exhaustive survey of what I have called the non-surgical emergencies of the kidney. Suffice it, then, to recall that though there are rare conditions such as paroxysmal haemoglobinuria and less rare ones like the renal crisis of tabes dorsalis, which are independent of any abnormal condition of the kidneys themselves, the great mass of the subject is concerned with some serious anomaly of the function of these organs.

Starting with the kidney itself in a state of disorder, or with some developmental abnormality, or perhaps a constitutional weakness in the general vascular system which renders it incapable of standing up to the progress of "wear-and-tear," we may arrive at substantially the same end-result. That end-result may take on a multiplicity of forms which we group under the term "uraemia." It may be that uraemia is the most natural termination of life that we know, but at the same time in the face of every emergency, medical or surgical, that arises in practice we should ask ourselves the question: "Ought this to have come about or were we in a position to prevent it?" Acute illnesses such as a pneumonia or a fulminating appendicitis we will always meet without having had any forewarning of their approach, but there are other conditions of emergency which are recognizable in their pre-emergency stage—a stage that ought never to be far from our minds.

The boundary between the pre-emergency and the emergency involving the function of the kidneys is so ill marked that it is easy to lose sight of it altogether, but its clinical recognition, by which I mean the bedside recognition, is

so important that I stress it. For it is generally easier to modify the life of an individual so as to bring it within the compass even of a grossly impaired kidney function than to persuade a completely arrested kidney to take up its role again.

Illustrative Case No. 1

Take the case of a woman who has passed the allotted span of years. She has suffered in the last few years from a good deal of headache and pain about the back of the neck; her eyesight is not very good, she is breathless, and she has signs of aortic leakage without the large heart of the "aortic" patient in the prime of life: her aortic valve is the seat of that slow sclerosing endocarditis which we know to be associated with some degree of granular kidney. We are called to see her and find her breathless, but there is no obstruction to the breathing; the respirations are long and deep; there is a hyperpnoea rather than a dyspnoea. She has been unable to sleep for a few nights, the skin is hot and dry, there are many moist rales all over the chest, and she has passed no more than a few ounces of urine during the last twenty-four hours.

She is within sight of acute uraemia. How is she to be treated? Complete withdrawal of all food, abundant water to drink, a warm room and many blankets on the bed, and a large compress of antiphlogistine over the loins are the immediate indications and may achieve a very striking transformation; but the relief of such a condition is at best only temporary: her kidneys are permanently impaired and secondary changes elsewhere are already established.

Illustrative Case No. 2

Here is a very different picture, where a situation which appeared desperate was fortunately got over, with, in all likelihood, little or no damage to the kidneys.

A woman of 43 is troubled with oedema of the legs during the last weeks of her first pregnancy, but no changes are found in the urine. An hour after her successful delivery she has an eclamptic fit and the urine is found to contain much protein. In the next three days the amount of albumin steadily diminishes to little more than a trace, when it begins to rise again and she becomes very breathless. She is admitted to hospital on the tenth day post partum. She is very ill: the pulse 108, the respirations 44 per minute, and the temperature 98.4°; she coughs much and brings up a purulent spit. She is flushed, with a slight cyanosis, there is much oedema of the legs and back; there is a nasty burn on the dorsum of the left foot, a relic of the fit. The urine becomes almost solid on boiling, the blood pressure is 174/88. The breath sounds are loud and harsh with many rales, mostly dry. A large needle is inserted into a vein in front of the elbow and a few ounces of dark viscid blood are withdrawn, but clotting in the needle is so rapid that the vein is exposed by dissection and a cannula inserted. The cannula too is quickly blocked, and in all not more than eight ounces of blood have been drawn and a like quantity of saline infused.

Next morning the patient is in a parlous state. A few more ounces of blood, not so dark and thick as on the previous evening, are aspirated by syringe, more perhaps as a salve to the conscience than anything else. The woman, rather stout and plethoric, is literally struggling for breath, but seems to get a measure of relief from oxygen administered by intranasal catheter. She is coughing incessantly and bringing up much frothy sputum, and there is a dusky cyanosis in spite of the oxygen. Her distress is explained by an examination of the chest; there

is a widespread acute oedema of both lungs, and it is clear that fluid is accumulating in the air channels more rapidly than it is being got rid of. She looks likely to die. Most of us are dubious regarding the use of morphine in the presence of impaired kidney function, but Sir William Osler was a strong advocate of its employment in uraemia, and no one could say that Osler favoured short-sighted enthusiasm. I compromise, giving this patient 1/20 grain of apomorphine hydrochloride hypodermically. Ten minutes later she is reported to be in a more desperate state than ever, restless and delirious, but in the next hour or two she loses no more ground. In fact the quality of the pulse seems to improve a little and she is getting rid of her copious spit with a little less effort. Four hours after the first dose the apomorphine is repeated, and again in a few minutes she becomes notably confused. In the course of the afternoon she is given an enema of an ounce of magnesium sulphate, two ounces of glycerin, and three ounces of water, better known in the surgical wards as a flatus enema, but a preparation well adapted to rid the body of a large amount of water by the bowel. This is a really drastic measure, which I only commend to your notice in the case of a water-logged patient who is not too exhausted. At 7 p.m. a third dose of apomorphine is given, and I am at least hopeful that our patient is not in such danger of drowning as she was in the morning. At 10 p.m. it is clear that all other ends must be sacrificed to the necessity for sleep, and 1/4 grain of morphine with 1/100 grain of atropine is administered. In the course of the night she gets a few hours' uneasy sleep, and has further doses of apomorphine at 2 a.m. and 6 a.m. Twenty-four hours have seen a striking improvement: cyanosis is less, the pulse is 84, the respirations have dropped from 60 the previous afternoon to 36, coughing is less insistent, the lungs not so full. The enema is repeated in the afternoon, the apomorphine at 6 p.m., the morphine at 9 p.m., and the apomorphine again at 3.30 a.m. Thereafter a satisfactory convalescence sets in, the bowels being kept active with jalap powder and magnesium sulphate by the mouth. During the first few days of this illness there has been incontinence, so that the amount of urine passed is difficult to state.

You will have noted that the patient was very oedematous, and I attribute some of our success in the elimination of water to the presence of the burn on the dorsum of the foot, an area of roughly twelve to fifteen square inches, which literally poured out water for several days. The mental disturbance shown in this case deserves a note. There is no doubt as to an access of confusion after each dose of apomorphine, but an equally striking disorder was a complete amnesia as to the events of a whole week before her admission to hospital, this amnesia persisting up to her discharge six weeks later.

Illustrative Case No. 3

A woman of 59 had a breast removed for cancer seven years ago, and as yet there is no recurrence. She has been subject to infrequent attacks of asthma, relieved by expectorants. She is taken ill with an attack of diarrhoea, with some pain in the chest and a pleural rub. Her temperature rises to 102°, there are moist sounds in the right lung. She perspires very freely for the first few days of this illness, and then the skin becomes dry and she passes but little urine. During the seventh day she passes no urine, but the bowels still tend to be loose; there is slight fever and she is becoming drowsy. In the evening she shows some mental confusion, she complains of headache, the blood pressure is 150/80, the breathing is em-

barrassed, the optic disks show a heightened colour. Three hours later she is only semi-conscious and has become restless and rather noisy; she does not recognize a familiar face or voice. A few ounces of blood are, with difficulty, drawn from a vein in the arm. It is thick and dark. At 1 a.m. she is given 1/20 grain of apomorphine. At 4.45 a.m. she is so noisy that 1/4 grain of morphine is given. At 10 a.m. she is almost comatose, but there is considerable resistance as I insert a spinal needle. She has passed a stool containing much blood in shreds, the skin is dry, the breathing difficult, and her pallid face reflects that slaty-grey cyanosis which we so dislike to see. The apomorphine is repeated, and the next two hours see some hopeful perspiration, but an hour later she is once more dry, restless, and noisy. Oxygen is being delivered by the nasal catheter, and again she is quieted with 1/4 grain of morphine. In the evening, barely conscious, she is able to swallow 3 drachms of the syrup of chloral, and the loin pack of antiphlogistine is applied. At 11.15 p.m. apomorphine, at 2.50 a.m. morphine, and in the morning she is to all appearance *in extremis*—we actually note that curious delineation of the nasal cartilages which always seems to say that a fatal issue is not far distant. At 10.45 a.m. I return to the apomorphine, and instruct that it be given every four hours, or sooner if she should again become restless, and that nothing else be given.

Twenty-four hours later she is conscious but wildly confused. She recognizes her husband, she recognizes myself, and when I offer her ice-cream she roundly abuses me for having withheld that delicacy so long. She is now coughing and has a free expectoration, and during the day she takes abundant water. A bromide and chloral sedative in the afternoon, 3 grains of soneryl at night, and next morning her confusion is lessening. Sleep on the following night is appreciably aided by 1½ drachms of paraldehyde, and the mental condition is now clear, she is passing a satisfactory amount of urine, the systolic blood pressure has dropped to 134, and the acute uraemia may be said to have been weathered. Here, too, there was a retrograde amnesia of about five days antecedent to her admission to hospital.

Nitrogen Retention

I come now to an observation in these two cases on which I have so far laid no stress—the blood urea. We are accustomed to think of this estimation as a chapter in the modern development of blood analysis, but the first note on increased nitrogenous retention in chronic nephritis came from the collaborators of Richard Bright himself more than a century ago. It remained to their successors to show that urea could be fed to the body till its concentration in the body fluids was equal to that seen in uraemia without causing symptoms of that disorder. It follows, then, that a high blood urea is not diagnostic of uraemia, and that we are not better placed in the matter of diagnosis when we have our colleagues of the laboratory at our immediate call than when we are dependent on our own unaided faculties. Uraemia is a syndrome which is recognizable at the bedside, be it in the clinic, the castle, or the croft. It is really after the condition has been recognized that the degree of nitrogenous retention should be estimated, for it does go some way to tell us what kind of kidneys we are dealing with, what hope there is that we can induce them to take up their proper role again, what likelihood of our patient resuming, if not a normal life, at least a life of modified usefulness.

"Uraemia"—A Note of Caution

We do not know with certainty how the symptoms of uraemia are determined, and I would warn you against the view that this is but a name for the terminal features of a chronic nephritis. We speak of chronic uraemia and acute uraemia, and we recognize that a patient with the former is in danger of the latter; but whether it be the sudden maniacal seizure, the onset of convulsions, or the rapidly developing coma, these emergencies are so distinctive of the acute condition that it would seem proper to limit the term "uraemia" to this group, and to regard the chronic as the pre-uraemic phase—a phase which has much in common with the acute disorder, but in which some further factor responsible for the catastrophe must, on the face of it, be lacking. Scarcely a single feature has been demonstrated in a case of uraemia, but it has been shown to be present in a patient who was not suffering from uraemia. The cerebral symptoms have been widely attributed to the very constant oedema of the brain which is found at necropsy, but oedema of the brain is also found in patients who have not to our knowledge had uraemia. So it is with the findings during life: this patient with uraemia has 100 milligrammes or more of urea in 100 c.cm. of blood; this one with the same concentration of urea has no uraemia. The toxæmia of eclampsia, even when it introduces a picture which outwardly cannot be separated from uraemia, is not attended by any appreciable rise in the blood urea, 42 mg. having been found in the patient I have described to you. The second patient showed 95 mg. at midnight and 125 at 10 a.m., undoubtedly an evil prognosis. And yet, in a most readable chapter on diseases of the kidney, Boyd (1931) cites a case where a man injured in an accident had complete suppression of urine for a week and a blood urea rise to 200 mg. without the least suggestion of uraemia in his condition.

Emergencies cannot be provided to meet a pre-arranged occasion. I have sought, therefore, to show you to the best of my ability one or two word-pictures of illustrative cases met with in the last year or two, but it would be misleading to confine my remarks to instances on which we can look back with some satisfaction. Here is a canvas of different hue.

Illustrative Case No. 4

A boy of 6 is seen in the out-patient department in August, 1935, on account of constipation and loss of appetite; a few moist sounds are noted in the chest, a common enough finding, and many such are admitted to the children's sanatorium. One day in September he is noted to be a little puffy under the eyes and there is a trace of protein in the urine, but a week later this has gone and he remains clear. Towards the end of November he has a slight cough, and again there are rales in the chest and a trace of albumin in the water. During the last week of the month his mother notices that his gums appear to have been bleeding in the morning, and for three days his motions have been black and he has complained of a sore head. Then he vomits a large quantity of blood, and he is brought into hospital. On the next day he has a small epistaxis; there is cough, but no adventitious signs in the lungs. A little albumin is found in the urine; he is pale, and has a considerable secondary anaemia. Two days later he becomes very restless and talkative. There is no fever; he develops a squint and has double vision. Then he becomes hemiplegic, and falls to the weakened side when he sits up.

The cerebro-spinal fluid is not under pressure. Next morning convulsive movements of the limbs lead up to a deepening coma, and this little patient dies. An hour or two before the end the spinal theca is tapped again, and the pressure within is seen to be more than normal. Subsequent analysis of the fluid reveals a urea content of 274 mg. in 100 c.cm. Too late we noted that though his urine showed no tube casts he was passing more than healthy kidneys should need to pass. This boy had a narrowing of his urethra, probably developmental in origin; the bladder and ureters were widely dilated, the kidneys shrivelled and shrunken, completely played out. I draw from this case the reminder that no age is exempt from uraemia, and that oliguria is not a necessary precursor of its onset.

Attempts at Clarification

Nine-tenths or more of our present-day knowledge of nephritis we owe to the master who first described it: Bright's disease is still Bright's disease. Over a full century one or another, clinician or anatomist, has tried to clarify our conception of the disorder by this or that terminology, to pigeon-hole, as it were, the various clinical entities or anatomical pictures which we meet, only to find that the partitions between the pigeon-holes are as broken as the kidneys they contain. Uraemia can occur in every form of the disease, the concomitant of every type of inflamed or degenerated kidney that we know, and there is no denial that with a long history of nephritis, a long losing battle against the failing excretory powers of the body, the advent of this syndrome finds us helpless. Yet we do less than our duty if we throw in our hand too soon; we must play it out to the last trick every time. For there are cases of uraemia which can rightly be regarded as crises in the life of the human machine, and which may, with fortune's favour, be got over.

Now a word from Richard Bright (1836):

"The first circumstance which strikes the mind is the extent and frequency to which the derangement of one organ is connected with the derangement of several others; yet we are not at liberty to assume that the disease of the kidney has been the primary cause on which the disease of the rest depended. It may be that some other organ has first suffered, and that the kidneys, together with the rest, have become involved. I confess I am inclined to believe that the kidney is the chief promoter of the other derangements. The only organ except the kidney which I think, on taking a review of the history of this disease, might probably act as the primary cause, is the skin; and this is so closely connected in its derangements with the kidney that the relation of their lesions, as regards cause and effect, becomes equivocal. . . . In almost every case the first impression which brings on the anasarca is suppression of perspiration. . . ."

This reference by Bright to the skin as a possible factor in the causation of nephritis is of some interest, for it is in the management of the disease rather than in the causation that the skin has been the subject of most attention. In point of fact we reached the anomalous position, which we still retained up till twenty years ago, that though we ignored the skin in our views of the aetiology, except in cases following extensive burning, we gave it pride of place in the treatment. We are more consistent to-day; gone are the hot packs, ousted by the radiant-heat bath until an unhappy patient, perspiring freely, came into contact with a bad insulation and was electrocuted; but the hot pack has never regained its once honoured place—honoured perhaps by ourselves alone, for it had long been damned by the nursing profession. So for a moment I

should like to examine this drift of our thoughts and practice relative to the part played by the skin in the uraemic state.

Maintenance of the Water Balance

The body is provided with four channels of elimination: the kidneys, the bowel, the lungs, and the skin. Reflection will show that of these the skin at least has no true excretory function at all, the elimination of water by this channel being really subservient to the necessary provision of a means for cooling the body. The normal water balance of the body ranges about an income of $2\frac{1}{2}$ litres per diem. Of this $1\frac{1}{2}$ litres are excreted by the kidneys, $\frac{1}{2}$ litre, in the proportion of $\frac{4}{5}$ and $\frac{1}{5}$, by the lungs and the intestine, the remaining $\frac{1}{2}$ litre being earmarked, as it were, for the use of the skin. If, under identical conditions of work and temperature, extra water is taken in the excess is got rid of by the kidneys. The normal kidney is able to maintain a substantial increase in water elimination for a long time, but if, by feeding with water, that capacity is worked up to its maximum possible, renal failure will set in. At this moment we are all eliminating water by our skin at a rate corresponding to half a litre in twenty-four hours. Although this is called insensible perspiration it does not denote any activity on the part of our sweat glands; it is not a slow sweating, but a process of osmosis and evaporation. If, however, the temperature of this room were to be raised our rate of water elimination would gradually increase to a point when we would begin to show visible perspiration, the secretion of sweat having been shown to begin in health when the body temperature reaches a height of 0.2° to 0.5° C. above normal (Kuno, 1930). Normal sweat has a specific gravity of 1003; it is the most dilute of all the body fluids. In other words, the sweat glands are designed to respond to any need of the body for increased evaporation, and not to nitrogenous surfeit. Even in the absence of visible perspiration we recognize that some skins are dry and some moist without subjecting our observations to precise measurement. Our hands, not our eyes, tell us that the patient with Graves's disease has a moist skin, and that he with uraemia is dry, even though his subcutaneous tissues may be literally a bog.

The Skin in the Uraemic State

In the later stages of sclerosis of the kidney the amount of real kidney tissue available for the bodily needs is but a fraction of the normal. The resulting failure is in part qualitative and in part quantitative. In the first place the kidney is unable to concentrate urea; in order, therefore, to excrete urea it has to exercise its faculty for excreting water to its utmost ability. But this, as I have said, is a limited faculty even in a healthy kidney; how much more restricted, then, in contracted kidney? So the unequal battle goes on; large amounts of water may be eliminated for a time, with ever-increasing difficulty, until the kidney is on the point of complete arrest. At this stage the lungs may excrete a watery sputum, the large bowel initiate a diarrhoea, but the skin remains inert. It seems as though the water were more urgently held elsewhere, either in the maintenance of osmotic balance or in excretory channels whereby it may relieve the body of nitrogenous waste. This is a condition in which the body cannot afford to sweat, for it is essential that any water leaving the tissues should carry with it its quantum of waste. At its best the skin is still parsimonious in its output of solids, even though it be profligate in expenditure of water. We know that it is often difficult to induce sweat-

ing in uraemia, but that, having seen it established, we ascribe the patient's ultimate recovery to our success. My own impression is that when the patient is ready to sweat—that is, when, the abnormal claim of other tissues on the water stores of the body having in some way abated, water is again available for the skin—then, and only then, he will sweat. The dry skin of uraemia only eliminates water when it is no longer dry. If, then, your patient is showing evidence of elimination by the lungs or bowel do all you can to aid the action of these organs and leave the skin alone. Keep him reasonably warm, watch for the first appearance of moisture on the skin, and then, if you will, apply your packs and your poultices. If there is no sign of tentative excretion by any of the accessory channels your patient will die; he is probably the subject of a widespread poisoning, the nature of which we do not yet know. There are two types of acute uraemia: in one the kidney has failed for the time being, but the subsidiary paths of elimination are capable of tiding over the crisis while the kidney undergoes a measure of recovery; in the other the poison is so far-flung that nothing we can do is of the least avail.

Conclusion

I have covered a bare tithe of the ground of uraemia, a fraction of chronic Bright's disease. We are tempted to ask if this patient with convulsions or coma, this one with nocturnal asthma, and this man with an obstinate dyspepsia are subjects of one and the same disease. Yet we recall other conditions which, alike in their origin, are as far apart as the poles in their appearances. Two men are suffering from parenchymatous syphilis of the central nervous system. One, a paretic, comes to you wearing, maybe, the cloak of a Pan-European dictator, maybe the motley of a genial clown; the tabetic retains his intellectual poise to the last. Look back for a moment: at some time in our childhood we were interested in the bewildering succession of patterns we saw in a kaleidoscope. Yet each little coloured component preserved its own shape through all these variations, and the plaything of a forgotten afternoon may have its counterpart in some of these fascinating problems of to-day.

BIBLIOGRAPHY

- Boyd (1931). *Pathology of Internal Diseases*, p. 433.
Bright (1836). *Guy's Hosp. Rep.*, 1, 360, 394.
Kuno (1930). *Lancet*, 1, 912.
Osler: *Principles and Practice of Medicine*.

The trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation received ninety-two applications for grants during 1936, thirty of which were approved, including one continued annual grant. Eighteen of the new grants were awarded to scientists in countries other than the United States. Among those receiving grants were Dr. Melville Arnott of Edinburgh, for research into the connexion between renal damage and hypertension. The annual report of the Foundation states that during the present great need for funds grants will be given in the sciences closely related to medicine without reference to special fields, the maximum amount being as a rule 500 dollars. There are no special forms of application, but letters asking for aid must state the qualifications of the investigator, the nature of the proposed research, the size of the grant requested, and the specific way in which the money is to be expended. Applications, which should include letters of recommendation from the directors of laboratories and clinics in which the work is to be done, should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695, Huntington Avenue, Boston, Massachusetts, before May 1.