THE TREATMENT OF RENAL DISEASES*

BY

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Sir Walter Scott faced his last illness with the same fortitude and resolution as he had earlier shown in the financial straits to which he had been reduced by the brothers Ballantyne. In his journal we read: "Within these three days I have passed (you may alter the vowel A to the vowel I) a formidable quantity of blood. When a man makes blood instead of water, he is tempted to think of the possibility of his soon making earth." He makes no definite comment on the medical treatment which he received, but he probably did not expect much from it, for in connexion with the illness of a grandson he says, "I calculate upon his recovery with the greater certainty that I am well assured there is no medical man within reach."

I doubt if the lay attitude to kidney trouble has altered very much in the intervening years. An affection of the kidneys is still regarded as a death sentence which is not likely to be commuted by any doctor. In the lay mind, the kidneys seem to join the heart and brain in the inner circle of really vital organs, while the lethal potentialities of diseases of the lungs, liver, stomach, and blood-vessels are less seriously regarded. I would like here to examine how far lay people (and many doctors) are justified in associating renal disease with extreme gravity and with medical impotence.

I have chosen what I think is a natural and familiar title for my subject: but in actually dealing with it I would like to broaden the idea of "treatment" into that of management, and to discuss not the specific "renal diseases" but rather the symptom-complexes, or syndromes, which may be based on renal disease of widely differing aetiology. Sir Harold Himsworth (1949) drew attention to the "liberation of medical thought by the substitution of syndromes for 'disease entities' as the units of illness." His theme was diabetes mellitus; but a similar change in thinking has been equally productive in the study of renal disease. To quote further—for I know no better definition of the significance of the syndrome—"The syndrome, on the other hand, has its philosophical basis not in specific disease factors but in a chain of physiological processes, interference with which at any point produces the same impairment of bodily function. The same syndrome may thus arise from many different causes. This newer view inspires a far more catholic concept of aetiology and renders pointless many existing controversies."

This summarizes one aspect of the impact of applied physiology on clinical medicine. Since treatment is my theme, I may draw attention to another, even more practical, aspect of thinking in terms of syndromes. It often happens that we are either uncertain of the precise aetiology of a renal syndrome or else without power at present to correct its cause; but we can still do a great deal to mitigate the effects of the renal disorder on the patient's well-being. For example, a patient with

massive renal oedema may be suffering from nephritis, from renal-vein thrombosis, from diabetic nephropathy, from lupus nephritis, to mention only a few of the possibilities whose clinical differentiation may be very difficult; but lack of certainty in aetiological diagnosis need not prevent us from treating the oedema, often with good effect. To say that we can treat our patients even when we do not know what is wrong with them is of course a dangerous half-truth; the treatment of a syndrome based on applied physiology, however efficient it may be, remains essentially palliative treatment, and in no way absolves us from prosecuting the search for a complete diagnosis. But the relief of symptoms is one of the classical aims of clinical medicine, and the concept of the syndrome has contributed materially to its fulfilment.

Space does not allow me to be either comprehensive or detailed. What I hope to do is to outline the principles of management of four syndromes of renal disorder which are commonly met with. I am supported in this endeavour by the substantial measure of agreement among nephrologists, including those in other countries, as shown, for instance, in a recent German textbook of renal disease (Sarre, 1959). By remaining, as I hope, within the area of nephrologic agreement, I shall forswear the gloss of newness and the spice of controversy: but perhaps I may be able to help some doctor to help his patient with a renal disorder. My four topics will be acute renal failure, massive renal oedema, chronic renal failure, and acute urinary infection.

Acute Renal Failure

This term is preferable to its synonyms "anuria" and "suppression of urine," because complete failure to pass urine is most exceptional, and should indeed suggest an obstruction in the urinary tract rather than a renal disorder. Acute renal failure has its functional basis in a gross impairment of the renal circulation or, much less commonly, in the effect of various toxic agents. Its structural basis is a necrosis of tubular epithelium, with possibly some damage to the glomeruli as well. Clinically, there is a phase of extreme oliguria, commonly associated with haematuria, followed by a gradual increase in urine output with recovery. The inevitable consequence of acute renal failure is a progressive uraemia, which may be suspected clinically, but whose progress can be followed by blood-urea estimation. My reason for including this condition is not its frequency in general practice but its interest and general medical importance. In hospital practice, acute renal failure is being seen more often, as patients who would formerly have died from the shock of burns or trauma, or from an overwhelming infection, are now surviving as a result of resuscitation, accident surgery, and antibiotics. Medical causes of the syndrome include severe acute nephritis, the collagen diseases, papillary necrosis, leptospirosis, and haemorrhage or

*Lecture given to the Section of General Practice of the Manchester Medical Society on October 26, 1959.

flux from the gastro-intestinal tract; acute renal failure may complicate abortion or accidental haemorrhage; and there is a trickle of iatrogenic renal failure from mismatched transfusion and drug reactions.

Recovery is possible in the majority of patients with acute renal failure who have a potentially reversible renal lesion. The crux of management is the maintenance of the patient in reasonable condition for the period of one to two weeks during which effective renal function is lacking. This is done by minimizing protein breakdown, and by preventing the intake of water and electrolytes which the patient cannot excrete. Protein breakdown is minimized by eliminating dietary protein; by giving 100 g. of carbohydrate, which will provide enough calories to bring the calorogenic breakdown of body-protein to a minimum; and by controlling infection and trauma, both of which lead to increased breakdown of protein. In patients with an involuting uterus, anabolic steroids have been shown to diminish the rate of protein breakdown. The intake of water and electrolytes must also be controlled. In a few patients, loss of fluid from the body has been the cause of acute renal failure; in these the loss must be made good.

In most patients there is no deficit of fluid, and any attempt to force fluids is highly dangerous; I would feel guilty of labouring the obvious, did I not still see patients who have been bloated with fluids, supposedly diuretic, to which their damaged kidneys cannot respond. The water intake is limited to 500 ml., and no salts are given; fruit juice should not be given, as it has a high potassium content. Since the "diet" contains only carbohydrate, vitamins of the B complex should be given; fats by mouth are nauseating, and we now usually leave patients to find their own fat from the body stores. Some patients will take 100 g. of glucose (or lactose) in 500 ml. of water in small doses by mouth; others prefer a gastric tube. When vomiting is serious—and this is less common when no fat is given—the mixture can be given by plastic catheter passed through the saphenous vein into the inferior vena cava. This purely conservative regime, introduced in its essentials just after the war by Borst and Bull, has been the most important single step in reducing the mortality from acute renal failure; and it remains adequate in "medical" patients.

The situation is very different in "surgical" patients. When tissue breakdown is accelerated by trauma, or infection, or the metabolic response to surgery, there are two main dangers. The rate of accumulation of nitrogenous waste products is increased severalfold; the increase in blood urea is a general measure of this, and urea itself has been found in animals to reduce survival rate (Grollman and Grollman, 1959) and to increase the irritability of the cerebral cortex (Stevenson *et al.*, 1959). More definitely, the release of potassium from traumatized or infected tissue can lead to a rise in the concentration of potassium in the plasma which may cause cardiac arrest. The hazard from potassium can be lessened by removing potassium from the body with exchange-resins; or by promoting a shift of potassium from the plasma into the cells of healthy tissue by measures such as giving insulin and glucose, or alkalis. The treatment which I have found most effective, apart from dialysis, in lowering the plasma potassium rapidly—and that is what is needed—is the intravenous infusion over a three-hour period of 200 ml. of molar sodium

lactate. It is in this group of "surgical" patients, with accelerated breakdown of tissue, that dialysis with the artificial kidney can be life-saving. The value of and indications for dialysis have been reviewed by Parsons and McCracken (1959).

Massive Renal Oedema

This syndrome arises when urinary loss of protein, and especially of albumin, is so great and prolonged as to lead to severe hypoproteinaemia. This situation has been summed up in the phrase "protein-losing kidney" (Platt, 1959); and, as I have already indicated, its causes are multiple. The syndrome is often known as the nephrotic syndrome, but I prefer the more purely descriptive term which I have used, perhaps influenced by the trenchant comment of Jean Oliver (1950), that "nephrosis" means a condition in which the kidney is full of kidney. It is tempting to add the qualification "hypoproteinaemic," as indicative of the chief mechanism of this type of oedema; but economy and even elegance should have a voice in our terminology, in preference to the fear of missing something out which has coined so many burdensome titles.

While this type of renal disease is still serious, some progress has been made towards mitigating the discomforts and dangers which surrounded the patient twenty years ago. Very occasionally, a real cure can be effected in special cases—for example, by eliminating tuberculous infection which has led to renal amyloidosis, or by stopping teething-powders in children with mercurial nephropathy. Death from intercurrent infection can now be prevented by antibiotics; and there is some evidence that prophylactic treatment with oral penicillin may retard or prevent progress of the lesion. General measures for the long-term control of oedema have been reinforced by the development of effective oral diuretics. These are worth a trial in massive renal oedema, for some patients respond well; but they are not to be persevered with in patients with refractory oedema. As Rosenheim and Spencer (1956) have shown, when the oedema is controlled by a low-salt high-protein diet, supplemented by exchange-resins, about half the patients go into full clinical remission, with normal plasma-albumin levels and no significant proteinuria.

The control of oedema, and almost certainly the long-term prognosis of the syndrome, has been improved by the development of adrenal steroids of the glucocorticoid group which are almost free from any direct effect on the renal excretion of electrolytes. When cortisone was used, it was common to see a transient increase in oedema, followed later by a diuresis, often after the end of a 7- or 14-day course. This transient diuresis is not the important effect of steroids, which are used with the object of cutting short the proteinuria. With prednisone or prednisolone the frequency and speed of remission are greater than with simple control of oedema. The real test of success is disappearance of the proteinuria: steroids should be given until this happens, and continued for at least a month thereafter, to be resumed again if proteinuria should recur. The dosage should be low and intermittent—for example, 20 mg. of prednisone on four days each week. The dosage should not be increased in an attempt to control oedema, which should respond rather to diet and resins; I have seen striae and other signs of corticoid-poisoning from this

course of action. Nor should the dosage be continuous, as even prednisone produces some increase in potassium excretion, and breaks in the course allow the resulting potassium loss to be made good from the diet or from potassium supplements.

Some patients show severe hypertension or azotaemia soon after the apparent onset of their illness, and in these the prognosis has to be poor. Of the remaining majority, some will remit spontaneously if oedema and infection are controlled; but a greater number of remissions can be achieved with steroid treatment. The decision about steroid treatment may be difficult in the individual patient: renal biopsy may be helpful, for there is already some indication that a good response to steroids is much less likely in patients with established glomerular damage. At present, however, steroids should probably be given except in the two extreme situations of proteinuria without significant oedema and, on the other hand, advanced renal failure or hypertension.

Chronic Renal Failure

There are several reasons for preferring this term to the common "uraemia" or the slightly precious "azotaemia." Both these words have a chemical implication which is misplaced in the description of a clinical syndrome—especially if we reflect on the state, sometimes misnamed "acute uraemia," in which the blood urea is not greatly increased and the symptoms are probably due to hypertensive encephalopathy. Again, the chemical terms focus attention on failure of the excretory function of the kidney, to the exclusion of the regulatory function of the kidney; yet disturbance of the renal regulation of the amount and composition of body fluid lies at the root of many symptoms, and these are more amenable to direct treatment than the nitrogen retention, which can only be palliated by protein restriction. Interesting and important as it is, I cannot deal adequately with the complex chemical alterations in renal failure, many of which have been reviewed by Platt (1952); and it could indeed be claimed that chronic renal failure is not one, but a whole collection of syndromes. I shall concentrate my own remarks on two topics—chronic failure which is potentially reversible, and those measures of palliation which can be simply achieved.

Reversible Chronic Renal Failure

I have set out in a Table some of the causes of chronic renal failure which are reversible in their early stages, but whose neglect can lead to progressive renal damage. While the investigation and relief of obstruction of the urinary passages is the work of the urological surgeon, he cannot do it if he does not see the patient: it is the responsibility of the physician to remember that renal failure can have a "surgical" cause; to ask about prostatic symptoms and other disorders of urination; to feel for enlargement of the

Some Causes of Reversible Chronic Renal Failure (Modified from Merrill, 1955)

Obstructive uropathy	..	..	..	..	Calculus Prostatic hypertrophy Urethral stricture and valve Periureteric fibrosis
Infection	..	..	..	..	Superimposed acute pyelonephritis
Metabolic	..	..	..	..	Hypercalcaemia: Milk-alkali syndrome Vitamin-D overdosage Sarcoidosis Hyperparathyroidism Potassium depletion Sodium depletion

prostate, bladder, or kidney; and to refer selected patients for intravenous pyelography or full urological study. Chronic renal failure is not in itself associated with fever, except in its terminal stages; and the complaint of chills or dysuria, or the observation of pyrexia, at once raises the possibility of pyelonephritis or, more remotely, of renal tuberculosis or the nephropathy of bacterial endocarditis. Unfortunately, the suspicion of a renal infection may be hard to confirm, even with repeated urine cultures; and even when an infection has been demonstrated, it may still be hard to eradicate: but this need not stop us from trying to clear up infection with a short course of broad-spectrum antibiotics, judging our success by the alleviation of symptoms, if we have no better guide. Recurrent infection after treatment should stimulate the search for a local abnormality of the urinary tract; even though in most patients none will be found, the exceptions serve to approve the practice.

Simple Palliative Measures

Comparatively few patients with chronic renal failure owe it primarily to deranged metabolism; but the possibility of treatment justifies some attention to this problem, and of course secondary disturbances of metabolism are very common in renal failure, whatever its primary cause. Most patients with renal failure have a low serum-calcium level, but in a few patients hypercalcaemia is present, and may be the cause of the trouble. Hypercalcaemia can occasionally be suspected when the intake of calcium and alkali, or of vitamin D, is known to be high; or when anorexia, vomiting, and mental disturbance are striking, though the blood-urea level is only moderately raised; or when there is great thirst and polyuria, or a metallic taste in the mouth, again at low levels of blood urea. Such a suspicion has to be checked by estimation of the serum calcium. If hypercalcaemia is established, full metabolic investigation is needed, so that dietary causes can be eliminated, the hypercalcaemia of sarcoidosis reduced by steroids, or a parathyroid tumour removed. Potassium and sodium depletion are less common than excess of calcium as primary causes of renal failure; also, a depletion sufficient to cause renal failure will be obvious on other grounds, which is not always so with hypercalcaemia. However, secondary depletion of sodium, and to a less extent of potassium, is common in renal failure, and warrants attention in management.

In dealing with patients with chronic renal failure, we must not be frightened by figures, and especially not by a blood-urea result obtained soon after the patient has been admitted in some form of crisis. A patient with a blood urea of 100 mg./100 ml. may be symptom-free, but he is very vulnerable. In a day or two he may become critically ill from the tissue breakdown in an acute infection, from the loss of fluid from a gastrointestinal upset, or even from drinking too little (or too much) when his kidneys have lost their plasticity of regulation. When we see him in this state, as it seems of terminal illness, it is easy to give up, and regard any treatment as meddlesome interference. I believe this attitude is wrong, not because I have any interest in prolonging a life of misery, but because so many of these patients can be made symptom-free again. We can never tell without trial how much the illness of a patient with renal failure is due to permanent renal damage and how much to reversible extrarenal factors. The

principles of management are similar to those which I have described for acute renal failure, with one very important exception.

While a chief danger of acute renal failure is excess fluid, most patients in a crisis of chronic renal failure are short of fluid, because of deficient intake and often vomiting and diarrhoea. They tend to have a low serum sodium and are markedly acidotic, so it seems justified to give hypertonic sodium lactate intravenously. I have used 200 ml. of molar sodium lactate by drip, and if this brings down the blood urea and improves the patient's condition it can be repeated daily until the vomiting abates to allow treatment by mouth. This treatment with alkali may aggravate tetany, in which event calcium gluconate should be added to the infusion. In some patients chlorpromazine has seemed to diminish vomiting as well as apprehension: only about 10% of a dose of chlorpromazine is excreted normally in the urine, so the presence of renal failure does not compel any material modification of dosage.

While intercurrent episodes of infection or dehydration call for active management, the patient with chronic renal failure may at other times have few or no symptoms, and should not be subjected to niggling restrictions. These patients, especially if they are normotensive, can live for some years, and they should be allowed to do what they like. At any given level of renal insufficiency, the blood-urea level increases with the protein content of the diet. Excess of protein should be avoided, but a severely restricted protein intake is called for only in episodes of superimposed extrarenal uraemia. Salt restrictions should be avoided, except when hypertensive cardiac failure is imminent; and a few patients may even need large supplements of salt, in the "salt-losing" form of renal failure. Some patients may need potassium supplements, but this again is very exceptional, and the need must be established by a study of metabolic balance. In limiting myself to palliative measures which can be simply achieved, I am unfortunately compelled to omit any account of the remarkable symptomatic and objective improvement which can be achieved in the osteodystrophy of chronic renal failure (Stanbury, 1957).

Acute Urinary Infection

If the generality of patients are inclined, if anything, to overestimate the seriousness of nephritis in any of its forms, they make the opposite mistake with acute urinary infection. The usual lay term for acute urinary infection perhaps discloses this attitude—"a chill on the bladder," something accepted as a nuisance comparable to a cold in the head. But as a cause of chronic renal failure or of severe hypertension of renal origin, chronic pyelonephritis—the possible sequel of neglected acute urinary infection—is at least as important as glomerulonephritis.

I need scarcely describe the familiar symptoms of a typical attack of acute pyelonephritis. However, since clinical recognition is the necessary (but not sufficient) prelude to effective treatment, it may be worth mentioning two points which seem not to be universally recognized. One is that overt haematuria in a febrile illness may indicate acute urinary infection rather than acute nephritis or even bacterial endocarditis. The other is that dysuria and frequency may be so minimized that an acute urinary infection may present as a pyrexia of uncertain origin, or in infancy

as a failure to thrive (James, 1959). Acute urinary infection is a common disorder, and the family doctor should have open access to the facilities needed for eliciting the essential sign—the demonstration of pus cells and organisms in the urine. I think we have an opportunity here for improving our practice of preventive medicine. It is more important to send the urine forthwith to the clinical laboratory than to arrange for the patient to attend an out-patient clinic, by which time the urinary sediment may have cleared and the chance of specific treatment been lost. I am not suggesting an orgy of domiciliary catheterization—there is too much evidence that infection can be introduced into the bladder in this way. In the male, a mid-stream specimen is satisfactory; in the female, a clean specimen after perineal swabbing can be used as a first screen, followed if necessary by a catheter specimen.

The key to treatment, as to diagnosis, lies in adequate bacteriological characterization of the infecting organism—and this of course includes assessment of its sensitivity to sulphonamides, antibiotics, or nitrofurantoin. Sensitivities can conveniently be tested by the disk technique (Fairbrother, 1959). The appropriate specific treatment can then be given. Whatever agent is chosen, the dosage must be adequate to give an effective concentration in the blood and tissues, as well as in the urine; for example, sulphadimidine should be given in a dose of 1.5 g. six-hourly, and not in the lower doses sometimes used. After a week of treatment a further specimen of urine should be examined, and a later specimen after specific treatment has been stopped for a few days. When relapse occurs with a sulphonamide-sensitive organism there may be a place for the long-acting drugs such as sulphaphenazole. Recurrent bouts of urinary infection justify a search by intravenous pyelography or by full urological investigation for local conditions of the urinary tract which would lead to stasis. The necessary procedures may include urethroscopy (Winsbury-White, 1959). Exemption from this search is, however, conferred by pregnancy.

I have said nothing of the palliative treatment of dysuria. Making the urine alkaline may indeed alleviate symptoms, but it does nothing to eradicate the infection. In a patient with impaired renal function the giving of alkalis is positively dangerous, since it may lead to a systemic alkalosis, or to potassium-poisoning when citrate of potassium is chosen. If the symptoms of urinary infection are definite it is better to give a soluble sulphonamide, once a urinary specimen has been taken for bacteriological examination. When the results of sensitivity tests are known the treatment may be changed to a broad-spectrum antibiotic or to nitrofurantoin, if indicated. In the absence of bacteriological facilities lack of response to sulphonamide may justify a similar change of treatment.

I have assumed that the energetic investigation and treatment of acute urinary infection would lessen the frequency of chronic pyelonephritis. Though this seems a reasonable assumption, I have to admit that I know of no adequate figures of the incidence of chronic pyelonephritis following an acute urinary infection, whether adequately treated or not—let alone any comparison designed to bring out the effect of treatment. May I end by pointing out that this would be a most useful investigation, and one which for several reasons could best be carried out in general practice. Acute

urinary infection is reasonably common in the community, but few patients in the acute attack enter the practice of a hospital. Strict criteria of diagnosis can be established, using the facilities available in any clinical laboratory. Given these facilities, treatment can be standardized, and its short-term success or failure can be established. Finally, the long-term result will become apparent only after many years, during which the patient will have no symptoms that would make repeated visits to a hospital for follow-up seem reasonable; but his family doctor could check his blood-pressure and examine his urine without any particular disturbance.

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THE INNERVATION OF SKELETAL MUSCLE*

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[WITH SPECIAL PLATE]

Although our knowledge of the pattern of innervation of skeletal muscle and its functional significance is still incomplete, there is much that throws light on the problem of control of postural and so-called volitional movement. In this brief review attention will be confined to the nerve-supply of mammalian striated muscles and to the connexions that these neurones make in the central nervous system.

The Motor Unit

The smallest functional unit in a muscle is the motor unit, which consists of a single anterior horn cell, all its processes and all the muscle fibres supplied by it.^{1,2} It follows that the strength of contraction depends, in part, upon the size of these motor units as well as on the number brought into activity.³ Recent estimates of the average number of muscle fibres in human motor units range from 5–9 for extrinsic ocular muscles⁴ to 1,600–1,900 for one of the calf muscles.⁵ The endings of the motor nerves lose their myelin sheaths as they pierce the sarcolemma and break up into fine branches which rest in the shallow troughs that form the sub-neural apparatus.⁶ These troughs are lined by structures which are rich in cholinesterase,⁷ the enzyme that destroys acetylcholine, which is the chemical transmitter of the nerve impulse across the neuromuscular junction (Special Plate, Figs 1 and 2). The motor end-plates may be confined to a localized band or be scattered throughout the substance of a muscle. In some muscles

—for example, the extrinsic ocular and facial muscles—more than one motor ending can be seen on a single fibre; and these end-plates are sometimes supplied by nerve fibres which approach from different directions.^{8,9} Since motor nerve fibres not only branch in the main nerve trunks³ and muscles,¹⁰ but also may form intramuscular plexuses (Special Plate, Figs. 3 and 4), histological preparations of healthy muscles do not give reliable evidence about the parent neurones of the divergent fibres. For larger muscles in which the physical difficulty of examining long fibres throughout their length is increased, there is only scant reference to histological evidence of multiple endings on a single fibre, but electrophysiological experiments have shown that large motor nerve fibres may innervate individual muscle fibres at two or more places.^{11–13,17} These multiple endings may be derived from the branches of a single neurone or from several neurones. The muscle fibres of a unit may be in a compact bundle or they may be separated widely from each other and give rise to a diffuse motor unit.^{8,10,14–17}

Whatever the spatial arrangement of the motor units within the muscle belly, however, there is anatomical and physiological evidence that the motor nerve cells supplying individual muscles are grouped together in the brain-stem and spinal cord, where they form nuclei.^{18–26} Sharrard²³ reconstructed the lumbar and sacral segments to scale from serial sections of three normal spinal cords and of seven from patients who died at intervals ranging from three months to eight years after the onset of anterior poliomyelitis. The reconstructions took no account of the dendrites and axons, but gave the relationships between the bodies of the anterior horn cells. By correlating the histological and clinical observations it was possible to demonstrate the arrangement of the nuclei supplying individual muscles. These nuclei varied in size; some occupied several segments of the cord, while others were confined to a single segment, and functionally related nuclei were anatomically related to each other. Thus the nuclei supplying the tibialis anterior and posterior muscles were contiguous. Both these muscles invert the foot; the former dorsiflexes the ankle-joint and the latter plantar-flexes it.

The lower motor neurones which activate the motor units form the “final common pathway”²⁷ between the central nervous system and the muscles, and once they degenerate there is no longer any effector pathway between the central nervous system and the muscle fibres. Anterior horn cells have many dendrites which lie inside and outside the grey matter of the cord^{28,29} and these processes account for the greater part of the total surface area of the cells,³⁰ thus increasing the area for contact with the “end feet,” or *boutons terminaux*, of other neurones. It is through these *boutons* that neurones from other levels of the nervous system exert their influence on the lower motor neurone. It has been estimated that about 80% of the surface of an anterior horn cell is related to the *boutons*,³¹ at least 2,000 of which may rest on the surface of a single large cell in the cat.^{29,31,32} This does not necessarily mean that there are synaptic connexions with 2,000 other neurones, for the nerve terminals branch, and many of the *boutons* might be derived from one parent cell. The *boutons* vary in size, but even with electron microscopy it has not proved possible to distinguish

*A paper read to the Section of Anatomy and Physiology at the Annual Meeting of the British Medical Association, Birmingham, 1958.