BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 30 1954

THE VALUE OF PHYSIOLOGY IN MEDICINE*

BY

GEORGE GRAHAM, M.D., F.R.C.P.

Consulting Physician to St. Bartholomew's Hospital

First of all I wish to thank you for the honour you have done me in inviting me to deliver the two hundred and thirty-fourth Harveian Oration; secondly, to commemorate the memory of William Harvey, and all other benefactors of the College. Although I had learnt a little about Harvey in my physiology days, I did not really appreciate the magnitude of his achievement until the tercentenary of the publication of his great work, *De Motu Cordis*, which was celebrated in this College in 1928. I was especially impressed by the cinematograph film prepared by Sir Thomas Lewis and Sir Henry Dale, which demonstrated most clearly the arguments and experiments which he used to prove that the blood circulated through the heart. The film is now shown to all physiology students, but it is unfortunate that many of the men and women who qualified before 1928 have not had an opportunity of seeing it, and of appreciating to the full the value of Harvey's work. I should have liked to show the film this afternoon, but it would have taken too long. I hope, however, that all the members of the staffs of teaching hospitals, and not only the physicians, will take the opportunity of seeing it when it is demonstrated to their students, and so realize the difficulties which Harvey overcame. He has been called the first of the physiologists, and it is for this reason that I have chosen as a title "The Value of Physiology in Medicine."

Although the science of physiology progressed slowly throughout the centuries, there was often a tendency to decry its value. This is well shown by the experience of Sir Henry Dale, when a little more than 50 years ago he clerked for that very able clinician, Dr. Samuel Gee. He was told, "When you enter my wards your first duty is to forget all your physiology. Physiology is an experimental science—and a very good thing, no doubt, in its proper place. Medicine is not a science but an empirical art, and it is as such that you may learn something of it here" (Dale, 1950). I do not know how much Dale learnt of the "empirical art," but he has carried out himself, and has directed, much research work which has been of very great value in the whole field of medicine. He has therefore greatly helped to advance the day which Gee indeed foresaw, that "some day medicine, too, might become an experimental science." When I came down from Cambridge 49 years ago nothing so foolish was said to me, but no one seemed to pay any attention to physiology. Thus when I was a surgical dresser I was astonished to hear Sir

Anthony Bowlby, an able surgeon, call for very hot saline in the course of an operation, and I was told that this was done to stop haemorrhage. This seemed most extraordinary, as the heat would, I thought, cause dilatation of the blood vessels and capillaries, and increase the bleeding, but the house-surgeon assured me that it did stop haemorrhage. I was too frightened to ask Bowlby for the explanation, which I think he might have known.

Advances in Physiology

The advances in physiology have been made not only by those who work in the physiological laboratories but also by the whole army of clinicians, chemists, biochemists, biologists, physicists, anatomists, pharmacologists, and pathologists who have contributed their experiences. The final building up of the subject must, I think, be done by the physiologists and biochemists, who test out the evidence provided by their colleagues and finally assess the value of the work.

Some clinicians have, in the past, spoken contemptuously of the value of physiology in medicine and expressed a disbelief in results obtained from a "pithed" frog. The frog has been most useful to mankind; it is cheap to buy and the brain is easily destroyed, so that the student can do his experiments without causing any pain. Many important studies have been made on its heart, and it was of value in the study of nervous reflexes, but has now been displaced by Sherrington's decerebrate cats. But it is of importance to repeat the work on different animals, for they often differ considerably. Thus the great advance which has taken place in our knowledge of scurvy was made possible by the guinea-pig. This is the only animal besides man which is unable to synthesize ascorbic acid, and develops scurvy, which can be studied, under controlled conditions, at all stages of the disease. In man, scurvy is nowadays rarely seen and it is difficult to carry out controlled experiments. But the work of Crandon *et al.* (1940) is of importance because, while Crandon was doing his full work as a surgeon, he abstained from eating anything known to contain ascorbic acid. After 116 days he had slight symptoms of scurvy, and a surgical wound on the 182nd day did not heal. Again, the first investigations on anaphylactic shock were made on guinea-pigs, which develop bronchial constriction, whereas a dog develops congestion of the liver from spasm of the hepatic veins, and in the rabbit the arterioles are constricted.

The dog has been invaluable in the study of diabetes mellitus. It was used by von Mering and Minkowski

*The Harveian Oration delivered at the Royal College of Physicians of London on October 16, 1953.

(1890) when they removed the whole of the pancreas to study fat absorption and found that the puppy developed diabetes mellitus, and much useful information has been gained by experiments on the depancreatized dog. Young (1937) also used the dog in order to produce diabetes by injections of extracts of the anterior pituitary gland, and so destroy the islands of Langerhans. The rat, on the other hand, does not develop diabetes, no matter how much extract of the anterior pituitary is injected, and the islands of Langerhans seem larger than usual (Marks and Young, 1939).

Anaesthesia

Anaesthesia, so valuable in the treatment of patients, sometimes makes the clinical observations most misleading. Thus it is known, as a result of x-ray films and opaque meals, that the stomach of man in the erect posture has a J shape. But even after this had been fully established, more than 40 years ago, some surgeons refused to accept the proposition, saying that they had never seen it at operations, or in the post-mortem room. This was understandable in the operating theatre, because under the anaesthetic all the muscles are relaxed, and, if they are not, the anaesthetist is blamed. In the post-mortem room this is nearly always the case, but every now and then the stomach is found firmly contracted and of the J shape. After I knew about the shape of the stomach I was lucky enough to see it myself four times in the five years or so that I performed post-mortem examinations, the cases varying from that of a child to that of a woman who had died with her stomach full of blood from a leaking aneurysm. The stomach in this case was enormous and extended into the pelvis, and the muscles were still firmly contracted. Two specimens are now in the anatomical museum at St. Bartholomew's Hospital, but I regret to say that at first they were mounted with the long axis in the transverse instead of in the vertical position. Many others must have seen similar specimens throughout the ages, but the evidence was neglected until x-ray films proved the point.

In experiments on animals a doubt always exists about whether the anaesthetic has affected the results. Pituitrin was thought to be a diuretic since it caused a diuresis in the anaesthetized animal, but if an anaesthetic was not given the flow of urine decreased, and this action is of great value in the treatment of diabetes insipidus. Again, the English workers were unable to show that stimulation of the vagus caused a secretion of the juice because of the anaesthetic. Heidenhain and others in Germany also failed because they did not use any anaesthetic, and the pain prevented the secretion. Pavlov succeeded in 1895 because he isolated the vagus nerve in the neck and made an exterior pouch of the stomach under an anaesthetic. When the dog had completely recovered he stimulated the peripheral end of the nerve painlessly and observed the flow of gastric juice. Histamine, again, will kill a cat with "shock" if an ether anaesthetic is given, while the unanaesthetized cat is quite unaffected.

Animals as Test Subjects

The difference between animals, again, is of very great value and certain species will take certain diseases. Thus, the distemper of dogs also affects ferrets, and this enabled Laidlaw and his co-workers to prepare the vaccine which protects dogs from the disease. The ferret is the only

animal which develops influenza when injected intranasally, though the mouse can be infected through intrapulmonary injections. Among the diseases which cannot be communicated to any animal are the common cold and rheumatic fever and infective hepatitis, and it is to be hoped that some animal will soon be found which will take these diseases, so that they may be studied more easily. Another instance is the variety of animals used for determining whether a woman is pregnant. Thus an immature female mouse (Aschheim-Zondek test), an immature female rabbit (Friedman test), a female frog (*Xenopus*), and an adult male toad (*Bufo arenarum*) are used, and the results in these four different species are said to be equally reliable. The early tests on the potency of insulin were made on the rabbit, the veins on the ear being most useful for collecting blood, but the mouse and the guinea-pig are also used for this purpose. Harvey studied the hearts of mammals, birds, snakes, fishes, and even shrimps, and insects like wasps. It is not easy to time the contraction of the auricle and ventricle by the eye in small animals, but he found it easy to confirm his impressions by watching contractions of the long heart of the adder and of the dying heart of the tortoise. These illustrations suffice to show that results which appear of value in one species must be tested on other animals, and the final experiments must be made on man himself if possible. In the physiology laboratories a good many observations are now confirmed on the students themselves, though those which involve danger cannot, of course, be performed.

Clinicians often differ very much over which hypothesis is the right one, and physiology in its wide sense is often able eventually to settle which school of thought is right. An instance of this is the treatment of rickets. One school stated that cod-liver oil was of great benefit, whereas another school asserted with equal conviction that treatment with olive oil gave results which were just as good. Mellanby's work on puppies showed that vitamin D cured rickets, and that olive oil contained none whereas cod-liver oil did, and that, if given in sufficient amounts and not diluted with malt and iron to one-quarter of its value, would cure rickets, and thus settled this controversy. The physiology which I visualize is a living and growing subject, and the principles which govern it are, I believe, of great value in the theory and treatment of medicine.

Coagulation Time

I said earlier on that as a young student I had not understood why very hot saline was used to stop oozing haemorrhage. I did not learn the explanation until nearly 20 years later when I was estimating the coagulation time of a patient with haemophilia by Dale and Laidlaw's (1911) shot method. They chose to work at a temperature of 37° C. because the coagulation time was least affected by slight alterations of temperature, and Macfarlane (1948) confirmed this.

The great shortening of the coagulation time at temperatures between 40 and 45° C. (Fig. 1) explains why the bleeding stops, although there is an increased blood supply as a result of the heat. I have asked several surgeons, and they tell me that it works

FIG. 1.—Effect of temperature upon coagulation time of normal blood.

but that they did not know the explanation. This had been given by Lister (1863) in an interesting paper on the coagulation of the blood, when he said, "It has long been known that blood coagulates more rapidly at a high temperature than at a low temperature, and that a little

above freezing-point remains entirely fluid." I suppose the use of very hot saline dates from very early days, but it is peculiar that the simple physiological explanation should have been forgotten by many people. The temperature of saline used in the operating theatre is 49° C. and that of the very hot saline is about 55° C., but it is unlikely that the tissues from which the bleeding is coming reach this temperature, since at this point the coagulation time has begun to

tion of 1 in 10,000 instead of calcium chloride, a heart which had just stopped beating in isotonic saline started again, but this time the diastole was lengthened and the heart eventually stopped in diastole. Ringer made numerous trials, and found that both potassium and calcium were necessary, and that the best results were obtained when they were present in the same concentration as in frog's plasma (Table I). If too much potassium was added so that the heart tended to stop in diastole, the addition of extra calcium prevented the poisonous action, so that poisonous doses of both

FIG. 2.—Effect of temperature upon coagulation time of haemophilic blood.

increase again. Haemophilic blood obeys the same law, and Macfarlane has observed the coagulation time at different temperatures (Fig. 2). I doubt, however, whether the shortening of the coagulation time to 12 minutes in this patient at a temperature of 55° C. would be enough to counteract the increased flow of blood.

Changes in Electrolytes after Operation

There are so many diseases in which physiology is of the greatest importance that it was difficult to choose what to talk about. I finally decided to discuss the changes which take place in the water and electrolytes of the body after severe operations. A proper understanding of these has greatly improved the treatment of patients. The co-operation of the surgeon and the physician with the physiologist, biochemist, pathologist, and others in the study of disease is necessary both to advance knowledge and to apply it to the treatment of the patient. Unless this co-operation exists, practice lags far behind theory. The first advances in our knowledge were made by Sydney Ringer, Professor of Medicine to University College Hospital, 71 years ago, and were at first neglected by the clinicians. In the past ten years great advances have been made in our knowledge of electrolytes in medicine, which call for the closest co-operation of all concerned with the treatment of patients. These are well described by Gamble (1947), Darrow and Pratt (1950), and many others.

Ringer (1880-2) found that a frog's heart would beat for some hours in a solution of 0.65% NaCl—which is isotonic for the frog—as made up by his laboratory's assistant. But when the assistant fell ill, and Ringer made up his own solution with distilled water, the heart very soon ceased to beat. When the assistant recovered, and made up the solution, the heart once more continued to beat. Ringer then found that the assistant, being lazy, had not bothered to use distilled water but had used tap-water instead. This contains calcium and potassium, and Ringer (1883-4) proceeded to determine the ideal conditions for enabling the heart to beat. If calcium chloride was added to 0.65% saline, in the proportion of 1 in 19,500, a heart which had just stopped beating started again. The diastole, however, grew shorter and shorter and the heart eventually stopped in systole. If potassium chloride was added to 0.65% saline in a propor-

TABLE I

	Ringer's Solution for Frogs	Ringer-Locke Solution for Man
NaCl	0.65 g.	0.9 g.
KCl	0.014 "	0.042 "
CaCl ₂ .. .	0.012 "	0.024 "
NaHCO ₃ ..	0.02 "	0.05 "
NaH ₂ PO ₄ ..	0.001 "	—
Glucose ..	0.2 "	0.1 "
H ₂ O	to 100 ml.	to 100 ml.

potassium and calcium might be present without affecting the heart at all (Ringer, 1884-5). I do not think many intravenous injections were made in those days, as surgical operations were nothing like so numerous or severe as they have now become.

When I came to hospital in 1905, saline, if thought necessary, was usually given subcutaneously. Many students, fresh from their physiology, must have asked, as I did, why Ringer's solution was not used, only to be told by a house-surgeon that the potassium and calcium were not necessary. I think that this was correct then, as it was rare indeed for more than 1 pint (570 ml.) of isotonic saline to be given intravenously, and it was assumed, if it was thought about at all, that the reserves of calcium in the bones and potassium in the cells would supply the necessary amounts. During the past 48 years, however, operations have increased enormously in number and magnitude. Many operations on the stomach, oesophagus, and intestines prevent any feeding by mouth for several days, and also involve evacuating the stomach or intestines by suction to prevent dilatation of these organs. Under these circumstances the amount of fluid given intravenously has been as much as 3,000-3,500 ml. a day for many days. This was sometimes isotonic saline, so that 27 g. or more of sodium chloride might be given in the day; sometimes two-thirds or one-third isotonic, so that 18 or 9 g. of sodium chloride might be given together with glucose in 5 or 10% concentration, the patient receiving as much as 150-300 g. of glucose daily.

The syndrome which results from long-continued intravenous injections of sodium chloride was first described by Whipple (1923) under the name pancreatic asthenia. He had observed asthenia, amnesia, nausea, vomiting, tendency to bleed, ptalism, abnormal stools, epigastric pain and tenderness, rapid emaciation. These symptoms came on 2-10 days after operations on the pancreas and gall-bladder and disappeared when the patient could start eating. Hartmann (1934) stressed the importance of giving not only sodium chloride but also some potassium, calcium, magnesium, and phosphates, and used the Ringer-Locke solution. Many others, myself included (Graham, 1938), hoped that this solution would give better results, but it is now recognized that potassium is contraindicated for 24 hours or more after an operation, and that after this time the amount of potassium is too small to be of any value. Further, the proportion of sodium to potassium, 16:1, is so high that the action of the potassium is completely swamped by that of the sodium.

Excretion while Fasting

Since many patients are unable to take any food by mouth after serious operations, the observations which have been made on men who have fasted for 20-40 days are of importance, and I will first describe them and then discuss how the operation alters the normal reactions of the body. The

most comprehensive of these researches was carried out by Benedict in 1915, on a man aged 40 and weighing 60.1 kg., and lasted 31 days. I shall refer only to the excretion of water and nitrogen and the electrolytes in the first 14 days, though there are many other points of interest in the monograph which repay study (Table II). The amount of water given

TABLE II

Days	Intake	Output					
	Water (ml.)	Urine (ml.)	Nitrogen (g.)	Chlorine (g.)	Sodium (g.)	Potassium (g.)	Calcium (g.)
1	750	660	7.1	3.77	2.07	1.63	0.217
2-4	750	582	10.5	0.80	0.926	1.368	0.243
5-6	750	638	10.29	0.41	0.276	1.445	0.274
7-8	750	555	10.03	0.44	0.154	0.883	0.253
9-10	750	636	10.40	0.30	0.128	0.944	0.237
11-12	900	540	10.19	0.33	0.10	0.975	0.219
13-14	900	604	10.49	0.29	—	—	0.226
15-16	900	823	9.02	0.15	0.109	0.814	0.250
30-31	900	566	6.94	0.13	0.053	0.606	0.138

to drink was 750 ml. daily for the first ten days, and the volume of the urine was about 600 ml. daily. Although the man did not complain of thirst the intake was raised to 900 ml., and four days later the output rose to over 800 ml.; the average output in the last 10 days was 688 ml. The excretion of nitrogen before the fast was 11.54 g. and after an initial drop to 7.1 g. the average output for the second to fourth days was 10.5 g.; it then remained fairly steady above 10 g. up to the fourteenth day, when a sudden drop occurred to below 10.0 g. The small excretion on the first two days is ascribed to the sparing effect of the glycogen in the body. After the third day the nitrogen excretion must come solely from the breakdown of the muscle and other cells.

The excretion of chlorine, sodium, and potassium is higher on the first day than on the next three days, and this is thought to be due to the amount in the previous diet. The figures for the second to fourth days show that more potassium is excreted than sodium and that after the sixth day the sodium and chlorine decrease rapidly, while the potassium remains high. The muscles and other tissues of the body which are used up in a fast contain very little sodium, and this explains the great decrease in the output, though it is known that the kidney tubules are able to reabsorb some sodium and so reduce the amount lost from the body. The potassium excreted in the urine comes almost entirely from the breakdown of the muscle and other cells, and the N:K ratio is thought to be about 10:1. In Benedict's case the N:K ratio was 10:0.77 on the second to fourth days; altered to 10:1.1 on the seventh to ninth days, and then slowly changed to 10:1.21 on the 31st day. For a ratio of 10:1 on the second to fourth days the potassium excretion should be 1.05 g. instead of 1.368 g., so that rather more potassium was being excreted than the ratio allows; while on the 31st day 0.606 g. was excreted instead of 0.734 g. This decrease in the potassium excretion might be due to the broken-up muscle containing less potassium at the end of the fast or to the tubules of the kidney reabsorbing more of the potassium and so conserving it in the body; the latter hypothesis seems the more likely.

Metabolic Changes Following Shock

When an operation is performed the shock which may occur alters the metabolism of the patient very profoundly.

(1) Water Output

The fluid intake, 900 ml., with an output of urine of 700-800 ml., is much too small for patients after operation. Thus, Maddock and Coller (1937) have estimated that the water lost by the skin and lungs after operation varies from 1,000 to 1,500 ml. a day, and this amount will be increased by, say, 500 ml. if fever is present. The healthy kidney can excrete all the electrolytes in 500 ml., but the damaged kidney needs 1,500 ml. to achieve the proper excretion. Avery Jones and Naunton Morgan (1938) have also stressed

the importance of giving plenty of fluid, 3,000-3,500 ml., to patients after operation, and of increasing this amount to make up for the loss of fluid vomited or removed from the stomach after severe abdominal operations. They also stress the danger of giving too much salt in uncomplicated cases. Le Quesne and Lewis (1953) gave patients a fluid diet containing 4,000 ml. before operation, and the urine output decreased from 3,195 to 1,115 ml. (average of 15 cases) on the day of the operation. Hence the fluid intake after operation should be 1,500-2,000 ml. for the afebrile patient with healthy kidneys, and 3,000-3,500 ml. for the febrile patient with poor kidneys. If sulphonamides are required, an output of more than 1,000 ml. is necessary to prevent any ill effects in the urinary tract.

(2) Protein

If a patient after operation takes very little food there is bound to be much destruction of protein, such as occurred in Benedict's starving man. This may amount to 7-10 g. a day, and will coincide with the excretion of 1 g. or so of potassium a day. If, however, the patient is able to take the same diet on the operation and subsequent days as he did before operation, the extra nitrogen loss is so small that it does not seem that the operation causes any destruction of body protein (Werner *et al.*, 1949).

(3) The Electrolytes Sodium and Potassium

The effect of the operation on the sodium and potassium is to cause a considerable increase in the potassium excretion but a decrease in the sodium excretion. The increase in the potassium excretion is to be expected from the increased protein breakdown due to lack of food, but it is much greater than could be expected from this cause, and the paradoxical condition may arise in which the serum potassium may be very high at a time when the potassium in the muscle has been greatly depleted. This discrepancy is due to the kidney being unable to excrete the extra potassium. The giving of sodium as isotonic saline in amounts of from 9 to 27 g. of sodium chloride, which has been the current practice for so many years, has obscured the fact that, coincident with the increase in the potassium excretion, there is a decrease in the sodium excretion. This change has been studied by Tabor and Rosenthal (1945). They applied a tourniquet to one leg of a mouse for two hours, and estimated the change in the injured and uninjured muscles. One-third of the potassium left the muscles and was replaced by sodium. The excretion of potassium in the urine was greatly increased, but in spite of this the serum potassium was also increased. The excretion of sodium, on the other hand, was decreased and sodium chloride given intravenously might be retained. Fox and Baer (1947) repeated these observations on a rat and analysed the tissues four hours later (Table III).

TABLE III

	Sodium in Muscle		Potassium in Muscle		Sodium and Potassium mEq/kg. Water	Na/K Ratio
	mEq/kg. Water	mg./100 g.	mEq/kg. Water	mg./100 g.		
Normal	81 ± 3	186 ± 5.75	126 ± 3	492 ± 7.8	207 ± 3	0.644:1
Shock leg	142 ± 2	327 ± 4.6	48 ± 3	187 ± 19.5	190 ± 4	2.96:1
Opposite leg ..	77 ± 4	177 ± 9.2	133 ± 3	520 ± 11.7	210 ± 4	0.578:1

This experiment shows a great reduction in the potassium and its replacement by sodium, and a change of the sodium/potassium ratio from 0.644:1 to 2.96:1. They also estimated the sodium space by means of the radio sodium and radio bromide method, and found that the sodium was much increased. Darrow (1945) showed that half the potassium might leave the muscles and that the intracellular sodium was equal to one-half the extracellular sodium. This was the case in animals, and he thought that similar, if less marked, changes occurred in man. Both the above pairs of workers observed that the mice were very ill after removal

of the tourniquet, and Tabor and Rosenthal produced symptoms of potassium poisoning by injecting small amounts of potassium. They were able to prevent death in shock by giving isotonic saline by mouth or through a stomach tube in 24 hours in a volume equal to 10 or 15% of the body weight. In severe cases it was necessary to give it intravenously. If only a volume equal to 5% of the body weight was given the percentage recovery was less (10% of the body weight in a man of 65 kg. would be 6,500 ml.). A 5% solution of glucose gave little better results than in the controls, but a 10% solution of glucose was not used. These amounts per kg. are much more than those used in man, and the shock produced must have been very great. The increase in the amount of sodium in the muscles and the decrease of potassium seemed very surprising, as it had been believed that the sodium could not enter the cells. But Darrow (1945, 1946) showed that sodium could cross the cell membrane and enter the cells and that potassium left them. This effect can be produced by giving sodium chloride intravenously, and as much as half the potassium may leave the cell.

It had previously been shown by Fenn and Cobb (1936) that when the muscle of the rat was stimulated for three hours, at a frequency of over 400 a minute, the potassium in the muscle decreased greatly, while the sodium increased. When the muscle was allowed to recover for two hours the potassium increased slowly while the sodium decreased rapidly. These observations on animals have been confirmed in patients after operation. Idris Evans (1950) showed that the amounts of sodium and potassium present in muscle were altered after operation (Table IV).

TABLE IV

	Muscle Removed at Operation		Serum Potassium	
	mEq/kg. Wet Muscle	mg./100 g. Wet Muscle	mEq/litre	mg./100 ml.
Case 1 { Sodium Potassium	39.2 72.4	90 282	3.63	14.2
" 2 { Sodium Potassium	46.5 41.3	107 161		
			1.7	6.65

Both the sodium space and the bromide space after operation have been investigated by Eliel *et al.* (1950), by injections of radio sodium and radio bromide. They found a great increase in the sodium space—showing that sodium had entered the muscles—and a decrease in the bromide space. Another consequence of the migration of the sodium is that there may be insufficient sodium to combine with bicarbonate, and a persistent hypochloraemia may result. The sodium/potassium relation in muscle is also upset by injections of deoxycortone. Darrow and Miller (1942) injected 2–4 mg. a day into rats for 30 days, and showed that the potassium in muscle decreased from 48.9 to 38.4 mEq per litre (191 to 150 mg. per 100 ml.) per 100 g. of fat-free solids, and that areas of necrosis occurred in the cardiac muscle, which resembled those produced by low-potassium diets.

When a dog is injected with 25 mg. of deoxycortone daily for four weeks it develops a polyuria at once, and, after some time, weakness and finally a paralysis of the muscles (Ferrebee *et al.*, 1941). The potassium in the serum decreased from 4 to 2.9 mEq per litre (15.6 to 11.4 mg. per 100 ml.) after four weeks; the sodium and chlorine increased slightly. The potassium in the muscle decreased from 82.5 to 54 mEq per litre (325 to 211 mg. per 100 ml.) per 100 g. of fat-free muscle in one experiment, while the sodium increased from 33.9 to 55.6 mEq per litre (78 to 128 mg. per 100 ml.) and the chlorine from 24.7 to 26.6 mEq per litre (87.6 to 94.5 mg. per 100 ml.). Eliel *et al.* (1950) have suggested that the surgical trauma increases the production of A.C.T.H. from the pituitary fluid, and this stimulates the adrenal cortex and is thus responsible for the excretion of the potassium and retention of the sodium. MacPhee (1953) also thinks that these "electrolytic charges

are the result of increased adrenocortical activity" and "are the natural response of the body to trauma." These observations suggest that the use of deoxycortone after operation is contraindicated, since the changes in the potassium and sodium of muscles are similar to those which occur two to four days after operation.

Effects of Potassium-deficient Diets

The changes which occur in the potassium after operation, and the symptoms which may arise, are so remarkable that the effect of diets containing little potassium has been studied on rats, dogs, and man. Follis *et al.* (1942) observed the effects in rats. After the 15th day opaque white areas could be seen macroscopically beneath the epicardium. Microscopically, definite changes could be seen as early as the eighth day. These were a loss of structure of individual muscle fibres and a failure of the hyaline fibres to stain with eosin. By the 15th day the opaque areas were shown to be necrotic and the heart muscle contained 35% less potassium than the controls. The skeletal muscle did not show any change, but the first convoluted tubules of the kidneys were dilated and the cells were vacuolated. Dogs kept on low-potassium diets developed periodic paralysis and respiratory failure, which was made worse if excess of sodium was given. On microscopical examination the myocardium was unaffected, but a waxy degeneration of the skeletal muscle was present.

The effect of a diet containing little potassium has been studied by two pairs of workers in England. A diet was given from which the potassium had been absorbed by means of an exchange resin "zeo-karb 225 sodium" (Black and Milne, 1952a, 1952b), or the resin was eaten with a fixed diet (Fourman and Ainley-Walker, 1952). Black and Milne's experiments lasted six to seven days, and a loss of 268 and 289 mEq (10.48 and 11.3 g.) of potassium was observed. A metabolic alkalosis was produced and the serum potassium decreased from 4 to 3.1 mEq per litre (15.6 to 12.3 mg. per 100 ml.) and 3.2 mEq per litre (12.5 mg. per 100 ml.), but the potassium in the red cells was unaltered. The symptoms observed were a little general apathy. The only change in the E.C.G. was the appearance of a U wave. Fourman and Ainley-Walker's three experiments lasted longer, 12 and 11 days, and the negative balance for potassium varied from 338 to 839 mEq per litre (13.2 to 32.8 g. per 100 ml.) and in their cases a slight acidosis instead of a metabolic alkalosis occurred. The subjects felt and looked ill, became absent-minded and then confused, and one developed oedema of the face and legs. The change in the E.C.G. was the appearance of a prominent U wave. Black and Milne pointed out that the amount of potassium lost was about equal to that lost after an operation, and doubted whether the symptoms occurring after operation were due to the lack of potassium. If these experiments are repeated it would be of great interest to determine the sodium and bromide space and also the amount of potassium and sodium in the muscle tissue. The injection of 18 g. of sodium chloride a day intravenously might also intensify the symptoms, since some of the sodium might enter the cells and increase the loss of potassium. The giving of glucose and insulin might produce great weakness or even paresis of the limbs like a periodic paralysis. This sometimes occurs after serious operations.

The changes which occur as a result of intravenous injection of sodium chloride before and after operation have been studied by Marks (1950). He carried out a complete water, nitrogen, chlorine, sodium, and potassium balance for three days on a patient with pyloric obstruction before operation. The actual amounts of fluid and electrolytes given intravenously varied from day to day, and the figures are given for the three-day period in Table V. The amounts excreted in the urine or removed from the stomach by suction were measured, and enable a proper balance to be struck.

Table V shows that there was an apparent positive balance of 1,020 ml. of fluid in the three days. But no allowance is made for the loss of fluid from the skin and lungs, and it is probable that a negative balance of more than 2,000 ml.

TABLE V

Fluid	Intake for 3 Days	Output for 3 Days			
		Urine	Gastric Contents Obtained by Suction	Balance	
Fluid	10,850 ml.	4,390 ml.	5,440 ml.	+1,020 ml.	
Sodium	mEq 907 g. 20.86	mEq 134 g. 3.08	mEq 191 g. 4.39	mEq +582 g. +13.39	
Calculated as sodium chloride	53.0	7.83	11.2	34.0	
Potassium	7.4 0.29	156 6.1	37 1.45	-185.6 -7.25	
Calculated as potassium chloride	0.55	11.6	2.76	-13.8	
Nitrogen	7.2	36.5	4.4	-33.7	

occurred in the three days in spite of the large intake of fluid. This was due to the large amounts of fluid removed from the stomach, which amounted to 5,440 ml. in the three days. It is now recognized that the fluid vomited or removed from the stomach or intestine by suction should be measured and an equivalent volume added to the intravenous injection so as to ensure that the body does not suffer from lack of water. Since some potassium as well as sodium is lost from the stomach, the intestines, and biliary tract, the appropriate solutions for each tract should be used (Darrow, 1945). The chlorine and sodium figures show that a retention of 13.39 g. of sodium or 34 g. of sodium chloride occurred in three days, while there was a loss of 7.25 g. of potassium or 13.8 g. of potassium chloride. The nitrogen intake was very small and a loss of 33.7 g. occurred in the three days, which would account for a loss of 3.37 g. of potassium, leaving 3.88 g. of potassium unaccounted for.

The changes in the blood, which occurred in the three days (Table VI), show that the treatment with saline was satisfactory in that there was a decrease from 42 to 24.1 mg. in the blood urea nitrogen, although it is still a little too high. The alkali reserve, which had been very high, was now within normal limits. The chloride, which had been on the low side, was within normal limits; the sodium content, which had been slightly on the low side, was within normal limits. The potassium, which had been normal at 4.3 mEq per litre (16.8 mg. per 100 ml.), was now very low at 2.75 mEq per litre (10.75 mg. per 100 ml.). The patient developed gastric retention after the gastrectomy and was quite ill for three weeks. Small doses of potassium chloride were given by mouth, but two and a half weeks elapsed before the serum potassium and the electrocardiograph returned to normal. Table VI shows the changes in the blood serum during the course of the treatment.

TABLE VI

Days	Blood Urea Nitrogen mg./100 ml.	HCO ₃ mEq/l.	Vols. CO ₂ per 100 ml.	Chloride		Sodium		Potassium	
				mEq/l.	mg./100 ml.	mEq/l.	mg./100 ml.	mEq/l.	mg./100 ml.
1	42.2	50.2	112	85	303	137.0	315	4.3	16.8
2	36.8	45.2 } 38.3 }	102 } 85.7 }	89	316	{ 139.0 141.5 }	320 } 325 }	{ 3.4 3.1 }	{ 13.6 12.2 }
3	32.2	37.4 } 32.0 }	83.7 } 71.6 }	96	340	{ 137.0 139.0 }	315 }	{ 3.2 2.8 }	{ 12.5 10.95 }
4	24.1	27.0	60.5	102	362	140	322	2.75	10.75

Another patient was studied four days after operation. Sodium was omitted and the potassium was increased to 2.34 g. in four days. The potassium excreted in the urine and that removed from the stomach in four days was 4.395 g. The negative balance of potassium was 2.005 g., which is much less than in the other patient, to whom 20.82 g. of sodium was given in four days.

Randall *et al.* (1949) have also made careful observations which show that the loss of potassium that occurs after operations considerably exceeds the amount of potassium that could possibly come from the breakdown of

protein, and which emphasize the decrease in the serum potassium which occurs after three to four days. This can be prevented by giving potassium by mouth or intravenously, starting 24 hours after the operation.

Symptoms Ascribed to Hypopotassaemia

These have been analysed by Eliel *et al.* (1950) in 32 patients, and are similar to, though more severe than, those described by Whipple (1923). They consisted of lethargy, apathy, and depression, 17; nervousness, irritability, and apprehension, 7; confusion, disorientation, and delusions, 4; irregular pulse, 3; muscular twitching and tetany, 3; muscular weakness, 13; abdominal distension and cramps, 19; anorexia, nausea, and vomiting, 15; paralytic ileus, 7; shallow respiration, 7; oedema, 9 cases. When the serum potassium is less than 4.2 mEq per litre (16.4 mg. per 100 ml.) the E.C.G. shows definite changes. The T wave becomes smaller and smaller the lower the serum potassium, and may be almost absent. When potassium chloride is given intravenously the T wave reappears. Fig. 3 shows the changes in the electrocardiogram due to hypopotassaemia, and the restoration to normal after potassium has been given.

FIG. 3.—Electrocardiogram showing the changes which occur when the serum potassium is low, and after treatment with potassium.

Effect of too Much Potassium in the Serum after Operation

Ever since Ringer (1883-4) showed that the heart stopped in diastole if too much potassium was present, there has been great fear of causing potassium poisoning if any potassium was given intravenously, even the small amount in Ringer-Locke solution. This fear has been intensified by the work of Winkler *et al.* (1939). They showed that when an isotonic solution of potassium chloride was injected into a 21-kg. dog at a rate of 112 mg. a minute the dog died in 50 minutes after 5.96 g. of potassium chloride had been injected. In this time the potassium in the serum increased from 4.1 to 14.7 mEq per litre (16 to 57.5 mg. per 100 ml.). Death occurred with the heart in diastolic arrest, and the E.C.G. showed characteristic changes—an increase in the amplitude and a shortening of duration of the T wave. This occurred in a concentration of 5 to 7.8 mEq per litre (19.5 to 30.6 mg. per 100 ml.) and the T increased in size until it equalled that of the QRS complex. Later the ST segment dropped below the isoelectric line, and the QRS complex became wider and finally completely disorganized. The critical concentration seemed to be 14-16 mEq per litre (55-62.5 mg. per 100 ml.), or nearly four times the normal figure. Fig. 4 shows the changes in the electrocardiogram due to hyperpotassaemia.

Three points in that paper seem to have escaped general notice: (1) If this amount was given slowly to healthy dogs no ill effects occurred. (2) The effect of adding glucose to the solution was not tried. The glucose would have enabled the muscles and liver to lay down more potassium with the glycogen and thus reduce the amount of potassium in the serum more rapidly. (3) The equivalent amount of potas-

FIG. 4.—Electrocardiogram taken when the serum potassium was 10.3 mEq per litre (40 mg. per 100 ml.).

sium chloride for a man of 65 kg. is 19.3 g., which is rather more than has been suggested even for patients suffering severely from hypopotassaemia.

It is very remarkable that these experiments on healthy dogs should have deterred many workers from using potassium in the past and should still frighten some. Since the giving of potassium is regarded by many as a dangerous procedure it is important to consider how much potassium is present in the blood and extracellular and intracellular fluids. If 1 g. of potassium (1.9 g. of potassium chloride) is quickly given intravenously to a man weighing 65 kg. whose serum potassium was 4.5 mEq per litre (17.6 mg. per 100 ml.) the maximum increase would be 12.3 mEq per litre (48.4 mg. per 100 ml.), which would be nearly a poisonous dose. But if the solution was given slowly, say in eight hours, the potassium would enter the extracellular fluid and then the intracellular fluid, and some would be excreted in the urine. The maximum rise would be 2 mEq per litre (7.8 mg. per 100 ml.) if the extracellular fluid alone was entered, and 0.56 mEq per litre (2.2 mg. per 100 ml.) if it was spread equally over the intracellular fluid. It follows that if the potassium is taken up equally by the extracellular and intracellular fluids of a 65-kg. man, a deficit of 1 mg. per 100 ml. in the serum potassium will mean a deficit of 0.0079 g. of potassium per kg. (0.0133 g. of KCl)—that is, 0.455 g. = 0.87 g. KCl per 65 kg.

It is generally agreed by those who have found potassium valuable in post-operative treatment that it should not be given until more than 24 hours have elapsed since the operation, when the kidneys have recovered their power of excreting water and the chance of a retention of potassium in the blood has passed.

Symptoms due to Hyperpotassaemia

These have been described in patients with renal failure (Finch *et al.*, 1946). The patient rapidly develops a true paralysis of two or four limbs, with shallow, laboured breathing. The reflexes are absent, but sensation of pain is present though numbness of hands may occur. The condition is said to resemble a Landry's ascending paralysis. The heart sounds are characteristically "dulled, prolonged, as if the heart were beating in slow motion"; bradycardia is present, with frequent irregular pauses. Bull *et al.* (1953) have also reported the rather sudden onset of paralysis in three patients with uraemia. At first sight the symptoms of hyperpotassaemia resemble those due to hypopotassaemia. But in the latter they develop slowly several days or more after the patient has been operated on. Again, the condition of the limbs is described as a weakness rather than a paralysis such as occurs in hyperpotassaemia. These differences should be enough to make a differential diagnosis easy after an operation. Thus, hyperpotassaemia may occur after a severe operation if the kidney fails to excrete the potassium liberated from the muscles.

Eliel *et al.* (1950) found one patient with a serum potassium of 12.2 mEq per litre (48.5 mg. per 100 ml.) on the day after operation, and Tabor and Rosenthal (1945) noted that mice were very sensitive to injections of small amounts of potassium some hours after the tourniquet had been removed from the leg. Any risk of this occurring should be

past by 24–36 hours after operation, provided sufficient water, sodium chloride, and glucose are given. In the next two to six days hypopotassaemia may develop, and any weakness of the limbs occurring at this time must be due to the lack of potassium, which can be confirmed by the flat T wave in the E.C.G., and a serum potassium which may be very low. This condition must be treated with potassium, and the weakness of the limbs will soon disappear. If, now, paralysis of the muscles develops suddenly in a patient who is receiving or has just finished a potassium injection, the condition can safely be diagnosed as due to hyperpotassaemia. The fact that paralysis or weakness of the limbs occurs both with excess and with lack of potassium seems extraordinary, but there is a parallel in diabetes mellitus, in which coma develops, owing to ketosis, when insulin is lacking, but also when insulin is in excess, owing to the lack of sugar in the blood. In this case, also, the history of the onset is of value, since when insulin is lacking the coma develops slowly, whereas when insulin is in excess the coma develops very rapidly. Thus in both hyperpotassaemia and hyperinsulinism the treatment consists in giving glucose as soon as the diagnosis is made.

Treatment for a Dangerous Hyperpotassaemia

An immediate injection of 20–30 units of insulin should be given, followed by 50 g. of glucose by mouth, or, in an emergency, by injection of 1,000 ml. of 10% glucose (Bywaters, 1944; Bull, 1951–2). This will cause an immediate deposit of glycogen and potassium in the liver and muscle (Fenn, 1939) and will cause a reduction in the serum potassium. Bull (1951–2) has reported a case of anuria in which the potassium was 10 mEq per litre (39.1 mg. per 100 ml.), and two hours after the giving of 50 g. of glucose intravenously and 50 units of insulin, the potassium had decreased to just over 7 mEq per litre (27.4 mg. per 100 ml.) and the character of the T wave of the E.C.G. was much less abnormal. But the action of the glucose can only be temporary, for as soon as the glycogen is needed for energy requirements the potassium will be liberated and will again enter the serum. It is probable that by this time, 6–12 hours, some of the potassium will already have been excreted in the urine, unless renal failure is present. If necessary the glucose and perhaps the insulin can be repeated in eight hours, but the possibility of hypoglycaemia occurring must be remembered, and the blood sugar estimated before more insulin is given. Darrow and Pratt (1950) found that a calcium injection was as useful but had a temporary effect only. To be of real value the dose of calcium necessary to neutralize the poisonous action of potassium would also have to be a poisonous one (Ringer, 1884–5), and after the potassium excess had passed the calcium might cause equally serious symptoms. If it is known that the serum calcium is definitely lowered, 1–2 g. of calcium gluconate should be given intravenously, and 1–2 g. of calcium carbonate given by mouth every four hours if vomiting is not present, together with 10,000 units of calciferol or 3.75 mg. of tachysterol by mouth to ensure the absorption of the calcium from the gut.

Pre-operative Treatment

It is important to consider how the patient should be prepared for operation so as to steer between the Scylla and Charybdis of too much and too little potassium. The diet taken by patients with a good appetite contains about 3 g. of potassium, but patients who are being strictly dieted for a gastric ulcer with, say, 20 oz. (570 ml.) of milk, 25.6 mEq (1 g.) K; 3 eggs, 5.27 mEq (210 mg.) K; 2 oz. (57 g.) of biscuits, 2.56 mEq (100 mg.) K; 3 oz. (85 ml.) of orange juice, 3.84 mEq (150 mg.) K, will take 37.4 mEq (1.46 g.) K daily. If an oesophageal or pyloric obstruction is present the amount of potassium imbibed may be very much less, and a diarrhoea or a biliary fistula (Darrow, 1948) will cause great loss of potassium. In this type of case 1 g. of potassium should be given three times a day in order to ensure that the body has a proper store of potassium. The serum potassium should be estimated and an E.C.G. taken. The following amounts of potassium salts each contain

approximately 1 g. of potassium and can be taken in 30 ml. (1 oz.) of orange juice and water.

Potassium chloride, 1.91 g. = 1 g. K = 25.6 mEq K

Dipotassium hydrogen phosphate, 1.36 g. }

Potassium dihydrogen phosphate, 1.36 g. } = 1 g. K. = 25.6 mEq K

Potassium citrate, 1 g. }

Potassium acetate, 1 g. } = 1.15 g. K = 29.4 mEq K

Potassium bicarbonate, 1 g.

If a patient is vomiting, or is unable to swallow, the potassium should be given intravenously. Before this is done the serum potassium and the size of the T wave should be determined. If these show a definite lack of potassium, 1 g. of K (1.9 g. KCl) in 1,000 ml. of 5% glucose in distilled water should be given intravenously in eight hours twice a day until the serum potassium and the T wave are within normal limits. An operation should not be performed, except in an emergency, until the serum potassium and the other electrolytes are within or nearly within normal limits. This procedure might reduce the necessity for gastric and duodenal suction after the operation.

Post-operative Treatment

From what has been said already it is plain that the problem is very complex, and the correct treatment varies according to the degree to which the sodium and potassium balance has been upset (1) by the "shock" of the operation; (2) by the treatment necessary to combat the effects of the "shock"; and (3) by the rapidity with which the serum potassium returns to normal, making it possible to give adequate amounts of potassium and so enable it to re-enter the muscle cells and displace the sodium. In most patients the "shock" of the operation is not serious. Soon after recovery from the anaesthetic the patient may be able to take fluid by mouth, and an effort should be made to give some 3,000 to 3,500 ml. a day. The next day some food may be given, and, since this will contain potassium, the chances of a serious lack of potassium developing is negligible. If fluid cannot be taken by mouth (or this is not considered desirable) it should be given per rectum—2,000–3,000 ml. If fluid only is needed, tap-water is probably the best, as it does not seem to irritate the rectal and sigmoid mucous membrane and is well absorbed. Avery Jones and Naunton Morgan (1938) have found that one-fifth isotonic saline is well tolerated, and 3,000 ml. will contain 5.4 g. of sodium chloride, which is adequate for patients in whom the "shock" is slight and in whom food containing both sodium and potassium will soon be eaten. The shock of the operation and the 5.4 g. of sodium chloride will have probably displaced little potassium from the intracellular space, and as soon as food containing potassium is taken by mouth the convalescence should be smooth. When the "shock" is more severe it may be necessary to give the fluid intravenously, since more sodium chloride will be needed than can be absorbed from the sigmoid and colon. The volume of intravenous fluid should be 3,000–3,500 ml., but the amount of sodium chloride given must depend on the assessment of the degree of "shock" which has occurred. If 9 g. of sodium chloride is needed, the 3,000 ml. can all be given as one-third isotonic saline, with 5 or 10% glucose; if 18 g. is needed, 2 litres of isotonic saline and glucose and 1 litre of 10% glucose; while if 27 g. is needed, it can all be given as isotonic saline with 5 or 10% glucose. Any fluid recovered from the stomach and intestines must be added to the volume given as I have already pointed out. The composition of this additional fluid depends on whether the fluid lost comes from the stomach or intestines, since the amount of potassium lost directly in this way varies (Darrow, 1945). Cooke and Crowley (1952) have suggested the use of two solutions for this purpose.

For loss of gastric fluid:

	mEq		g.
Ammonium	.. 70	} or {	
Sodium	.. 63		Ammonium chloride .. 3.74
Potassium	.. 17		Sodium chloride .. 3.68
Chlorine	.. 150		Potassium chloride .. 1.27

Water to 1,000 ml.
Sodium to potassium, 3.7:1

For loss of intestinal fluid:

	mEq		g.
Sodium	.. 138	} or {	Sodium chloride .. 5.15
Potassium	.. 12		Sodium lactate .. 5.6
Lactate	.. 50		Potassium chloride .. 0.895
Chlorine	.. 100		

Water to 1,000 ml.
Sodium to potassium, 11.5:1

Some 24 hours after the operation, when the "shock" is over and the urine output good, an assessment of the case is necessary to determine how much sodium chloride is necessary and when the potassium can be started to replace that which has been lost from the intracellular space. In these severe conditions it is usually impossible to give the potassium by mouth, and there is no evidence at present that it is absorbed per rectum. It is necessary to give it as an isotonic solution with 5% glucose either subcutaneously or intravenously. If the hypopotassaemia is not very marked a mixture of sodium and potassium chloride can be given, and that used by Randall *et al.* (1949) seems suitable. After 24–36 hours, if the patient is not seriously ill they give:

110 mEq sodium, 2.53 g.	} or {	Sodium chloride, 6.44 g.
30 mEq potassium, 1.172 g.		Potassium chloride, 2.44 g.
140 mEq chloride, 4.87 g.		Glucose, 50 g.

Water to 1,000 ml.

This gives a proportion of sodium to potassium of 2.16:1, compared with 16:1 in Ringer-Locke solution. Either 2,000 or 3,000 ml. is given in the day. If the patient is more seriously ill and the serum potassium is already low and the E.C.G. suggests a hypopotassaemia Randall *et al.* give:

30 mEq potassium, 1.173 g.	} or {	potassium chloride, 2.24 g.
30 mEq chloride, 1.066 g.		

In 1,000 ml. of 5% glucose.

Two or three litres is given, depending on serum potassium and the E.C.G.

Conclusion

I spoke earlier of steering between Scylla and Charybdis, and I would like to elaborate the point. During the period after the operation, when the serum potassium may be high, it is necessary to steer away from the Scylla of hyperpotassaemia and towards Charybdis, using plenty of water, salt, and glucose, but as soon as the danger of being wrecked on Scylla is passed, and Charybdis with its low serum potassium and ileal stasis is being neared, the helm must be put over for Scylla, using water, potassium, and glucose, and either greatly reducing or omitting the sodium altogether. In this way the ship will slip easily between these two hazards and reach port safely—that is, the patient will make a rapid recovery. To ensure the proper co-ordination of treatment of these difficult cases it is necessary to have a team consisting of a surgeon and a physician, who should both have a real appreciation of the physiological principles involved. They should be able to call on the electrocardiograph department and on the biochemist for the essential determinations which govern the treatment. The registrar, house-surgeon, and nursing staff should appreciate the difficulties which may arise and report them promptly. The giving of potassium injections should not be left to the night nurse, and if it is necessary to do so at night a senior person should be responsible.

I have here been concerned with the changes which take place in the sodium and potassium in the body. The work on Addison's disease has shown that the sodium in the body is controlled by the hormones of the adrenal cortex. If they are deficient, the sodium in the blood decreases. At present there is no direct evidence on how the potassium is controlled, though it is clear that the sodium and potassium are closely linked. The giving of deoxycortone causes an excretion of potassium in the urine (Ferree *et al.*, 1941; Darrow and Miller, 1942) and the giving of potassium to a patient with Addison's disease causes an excretion of sodium. The conditions under which hypopotassaemia occurs are "surgical shock," diarrhoea due to any cause, loss of bile (Darrow, 1945), and periodic paralysis, and all these can be

successfully treated with potassium salts. A syndrome associated with cardiac symptoms, muscular weakness, and hypotension has been described by Kjerulf-Jensen *et al.* (1951). The hypopotassemia in these conditions suggests that a hormone directly concerned must be present, though where it is formed is unknown. If this indeed exists, it would seem that it is upset in surgical shock and that if and when it is known it would be of great use in preventing this condition. I realize that I am putting forward a wholly unproved hypothesis, but the analogies to the control of other electrolytes like iodine by the thyroid, calcium by the parathyroid, and sodium by the adrenal cortex are very close. I believe that each electrolyte in the body is controlled by a hormone and not by pure physical laws, and that it is only a question of time before the hormone is discovered.

I wish to thank my friends with whom I have discussed my problems: Dr. R. G. Macfarlane for the slides, Professor V. H. Mottram, Professor A. Wormall, Dr. E. F. Scowen, and especially Dr. F. Avery Jones for much assistance.

Since the Oration was delivered my attention has been drawn by Professor E. C. Dodds to the papers by Simpson *et al.* (1952) and Grundy *et al.* (1952). These show that a hormone has been isolated from the adrenal which has a specific effect on the potassium as distinct from the sodium.

REFERENCES

- Benedict, F. G. (1915). *A Study of Prolonged Fasting*. Carnegie Publications, Washington.
- Black, D. A. K. (1953). *Lancet*, 1, 305, 353.
- and Milne, M. D. (1952a). *Ibid.*, 1, 244.
- (1952b). *Clin. Sci.*, 11, 397.
- Bull, G. M. (1951-2). *Proc. roy. Soc. Med.*, 45, 849.
- Carter, A. B., and Lowe, K. G. (1953). *Lancet*, 2, 60.
- Bywaters, E. G. L. (1944). *J. Amer. med. Ass.*, 124, 1103.
- Cooke, R. E., and Crowley, L. G. (1952). *New Engl. J. Med.*, 246, 637.
- Crandon, J. H., Lund, C. C., and Dill, D. B. (1940). *Ibid.*, 223, 353.
- Dale, H. H. (1950). *British Medical Journal*, 2, 1185.
- and Laidlaw, P. P. (1911). *J. Path. Bact.*, 16, 351.
- Darrow, D. C. (1945). *New Engl. J. Med.*, 233, 91.
- (1946). *J. Pediatr.*, 28, 515.
- (1948). *Bull. N.Y. Acad. Med.*, 24, 147.
- and Miller, H. C. (1942). *J. clin. Invest.*, 21, 601.
- and Pratt, E. L. (1950). *J. Amer. med. Ass.*, 143, 373, 435.
- Eliel, L. P., Pearson, O. H., and Rawson, R. W. (1950). *New Engl. J. Med.*, 243, 471, 518.
- Evans, E. Idris (1950). *Ann. Surg.*, 131, 945.
- Fenn, W. O. (1939). *J. biol. Chem.*, 128, 297.
- and Cobb, D. M. (1936). *Amer. J. Physiol.*, 115, 345.
- Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W., and Loeb, R. F. (1941). *Ibid.*, 135, 230.
- Finch, C. A., Sawyer, C. G., and Flynn, J. M. (1946). *Amer. J. Med.*, 1, 337.
- Follis, R. H., Orent-Keiles, E., and McCollum, E. V. (1942). *Amer. J. Path.*, 18, 29.
- Fourman, P., and Ainley-Walker, K. M. S. (1952). *Lancet*, 2, 368.
- Fox, C. L., and Baer, H. (1947). *Amer. J. Physiol.*, 151, 155.
- Gamble, J. L. (1947). *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid*, 6th ed. Harvard Univ Press, Cambridge, Mass.
- Graham, G. (1938). *Trans. med. Soc. Lond.*, 61, 15.
- Grundy, H. M., Simpson, S. A., Tait, J. F., and Woodford, M. (1952). *Acta endocr., Kbh.*, 11, 199.
- Hartmann, A. F. (1934). *J. Amer. med. Ass.*, 103, 1349.
- Jones, F. Avery, and Morgan, C. Naunton (1938). *St. Bart's Hosp. Rep.*, 71, 83.
- Kjerulf-Jensen, K., Krarup, N. B., and Warming-Larsen, A. (1951). *Lancet*, 1, 372.
- Le Quesne, L. P., and Lewis, A. A. G. (1953). *Ibid.*, 1, 153.
- Lister, J. (1863). *Proc. roy. Soc.*, 12, 580.
- Macfarlane, R. G. (1948). *J. clin. Path.*, 1, 126.
- MacPhee, I. W. (1953). *British Medical Journal*, 2, 528.
- Maddock, W. G., and Coller, F. A. (1937). *J. Amer. med. Ass.*, 108, 1.
- Marks, H. P., and Young, F. G. (1939). *J. Endocr.*, 1, 470.
- Marks, L. J. (1950). *Ann. Surg.*, 132, 20.
- von Mering, J., and Minkowski, O. (1890). *Arch. exp. Path. Pharmacol.*, 26, 371.
- Randall, H. T., Habif, D. V., Lockwood, J. S., and Werner, S. C. (1949). *Surgery*, 26, 341.
- Ringer, S. (1880-2). *J. Physiol.*, 3, 380.
- (1883-4). *Ibid.*, 4, 29.
- (1884-5). *Ibid.*, 5, 247.
- Simpson, S. A., Tait, J. F., and Bush, I. E. (1952). *Lancet*, 2, 226.
- Tabor, H., and Rosenthal, S. M. (1945). *Arch. Surg., Chicago*, 51, 244.
- Werner, S. C., Habif, D. V., Randall, H. T., and Lockwood, J. S. (1949). *Ann. Surg.*, 130, 688.
- Whipple, A. O. (1923). *Ibid.*, 78, 176.
- Winkler, A. W., Hoff, H. E., and Smith, P. K. (1939). *Amer. J. Physiol.*, 124, 478.
- Young, F. G. (1937). *Lancet*, 2, 372.

A COMPARISON OF CORTISONE AND CODEINE MEDICATION AS AN ADJUVANT TO MANIPULATION IN RHEUMATOID ARTHRITIS

A REPORT TO THE JOINT COMMITTEE ON CORTISONE AND A.C.T.H. IN CHRONIC RHEUMATIC DISEASES OF THE MEDICAL RESEARCH COUNCIL AND THE NUFFIELD FOUNDATION

A common problem in dealing with rheumatoid arthritis patients is that of flexion deformities of the knee-joints. These commonly arise during periods of rest in bed when the position of the knees has not been controlled by rest splints. In a proportion of cases these contractures cannot be corrected by conservative methods, and manipulation under a general anaesthetic is required. It was thought that the period of increased pain and disability due to the trauma of this operation might be curtailed, or even avoided altogether, by performing the operation under cover of cortisone. At the same time it would be possible to observe the effect of such treatment on the general as well as on the local reaction following manipulation, to note any general exacerbation of the disease that may sometimes, it is said, follow this procedure, and to assess the long-term usefulness of such therapy as it affects the manipulated limb and its function. Accordingly a small-scale controlled trial was set up by a Subcommittee of the Medical Research Council/Nuffield Foundation Joint Committee on Cortisone and A.C.T.H. in Chronic Rheumatic Diseases* in which four centres participated: Bath (Dr. G. D. Kersley and Mr. J. Bastow), Sheffield (Dr. H. F. West and Mr. G. Gordon), Stanmore (Dr. Harwood Stevenson and Mr. H. J. Seddon), and Taplow (Dr. E. G. L. Bywaters and Mr. G. P. Arden). The analysis of the results of the trial was made by Dr. J. T. Boyd, of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine.

Type of Patient

The patients selected were between the ages of 5 and 64 years; they had been diagnosed as having arthritis beyond any clinical doubt, and had four joints or more involved. Each had a knee contracture which had been present for at least six months and was in need of manipulative correction. Patients with severe disease activity or with completely ankylosed knees were excluded.

Allocation to Treatment

After admission to the trial patients were allotted to treatment with cortisone acetate or tab. codein. co. according to instructions given in serially numbered and sealed envelopes prepared in advance in random order. Approximately half the patients were allotted to each type of therapy.

Dosage

Following five days of preliminary observation and assessment, a total of 2.15 g. of cortisone was given to 18 patients over a period of 16 days at the level of 200 mg. for the first day; 300 mg. on the second and third days; 200 mg. on the fourth and fifth days; 150 mg. on the sixth, seventh, and eighth days; 100 mg. on the ninth and tenth days; and 50 mg. on the eleventh to the sixteenth day. The drug was given by mouth in three divided doses daily.

*The members of the subcommittee were: Dr. E. G. L. Bywaters (chairman), Mr. W. D. Coltart, Dr. J. J. R. Duthie, Professor A. Bradford Hill, Dr. G. D. Kersley, Dr. F. H. Stevenson, and Dr. H. F. West.