THE VALUE OF PHYSIOLOGICAL TESTS OF RENAL FUNCTION.*

BY

E. B. VERNEY, M.A., M.B., F.R.C.P.,

PROFESSOR OF PHARMACOLOGY, UNIVERSITY COLLEGE, LONDON.

THROUGH the employment of the tests of renal function I presume that it is sought to determine the manner in which the kidney responds to a stimulus superimposed upon that which it is already receiving, and that the hope is entertained of interpreting this response in terms of renal reserve. I propose, therefore, to confine my remarks to some considerations based partly on experimental fact, partly on theory and analogy, as to the manner in which the kidney, endowed with varying degrees of renal reserve, responds on the one hand to an increase in the work which it is called upon to perform, and on the other hand to a diminution in its functional capacity. The assessment of the value of the many tests which have been introduced to prove the functional capacity of the kidney I shall leave to speakers whose experience in their use has been much wider than my own.

It is essential, therefore, that we should first attempt to form some picture of the reserves of the kidney. They may be divided into those of a structural and those of a functional nature. The former are represented by a large excess of renal tissue over and above that competent alone to carry on the excretory work demanded during resting metabolism. The latter are represented by an inherent and variable capacity exhibited by any given amount of renal substance for the performance, under an adequate increment of stimulus, of an increased amount of work. Let us pursue this question a little further. The architecture of the kidney, as Bowman clearly recognized and described, is repetitive in character, and the functional response of the whole kidney at any time is the integral of the responses of the individual units of which the kidney is composed. The number of such units in a human kidney is 4.5×10^6 , so that the normal man is provided with roughly ten million units, each potentially capable of supplying its quota of fully formed urine. That such an enormous number represents a considerable reserve of secretory tissue is indicated by the results of the experiments of Richards and his colleagues. Richards has shown by direct observation of the glomerular tufts of the frog's kidney that the number of active glomeruli—that is, those through which a flow of blood is visible—varies continuously, and that the number of active glomeruli in a given field can be increased by injection of diuretic substances and diminished by injection of vaso-constrictor substances. Each unit passes through alternate periods of rest and activity, and, as we should perhaps expect, these interruptions are not regular in occurrence and do not affect all the glomeruli within a single field at the same time. The number of units is so large that it is possible for the kidney as a whole to function efficiently under normal conditions when each unit comprising it works for a fraction only of its time. Such experiments give us a clearer insight into the meaning of the term "reserve of the kidney," since clearly, when increased work is called for, more units may be mobilized, and the units themselves may respond either by increasing their intervals of work at the expense of their intervals of repose or by increasing the intensity of their work during their active periods. This alternation of activity and rest which the units of the kidney undergo may be looked upon as the concrete representation of its first line of defence against the inroads of disease, and of a part of its total capacity for dealing with an increased load of work. A simple increase in the secretory stimulus, or stimuli if these are different in nature or if each has a different seat at which it becomes effective, may be expected, therefore, to cause an increase in the output of urine by requisitioning units previously inactive, and by diminishing the rest pauses of the active units. It is

not necessary to assume that such an increase would be necessarily accompanied by any change in the composition of the urine. As the work demanded of each unit increases still further its commencing failure will be reflected in a change in the composition of its secretion—a change which exhibits an approach towards the composition of the blood plasma. Such a change is seen in the polyuria of chronic nephritis, and is the expression of the involvement of the functional reserves of the units, as contrasted with that of the anatomical reserves of the kidney to which attention has just been directed. This functional change is probably initiated by a local increase in the pressure stimulus—namely, the glomerular capillary pressure—and it may be instructive to compare such a change with that occurring in the heart when its load of work is increased.

When the heart of the dog is isolated and disposed in such a manner that the blood entering the right side of the heart is ejected by the left ventricle against a measurable and variable resistance—the heart-lung preparation of the late Professor Starling—it is possible to vary at will the amount of work performed by it. As the heart tires under a constant load, or if it is given more work to do, it dilates, and we speak of this dilatation as an indication of partial failure. Its "tone" is diminished and its functional reserves are dwindling. An analogous state of affairs is found in the case of the kidney. Here, however, the work performed is osmotic in character, and the sign of failure on the part of the kidney is an approach in the composition of the urine towards that of the blood plasma. Obviously, if the composition of the urine were the same as that of the plasma, no energy would be expended in its formation. And since the osmotic pressure of the protein fraction of the plasma is so very small any work involved in its separation is negligible. We may state therefore with accuracy that a kidney which is engaged in producing a urine having the same composition as the protein-free filtrate of the blood plasma is doing no work; failure is complete. Any degree of approach, then, in the composition of the urine to that of the plasma is a sign of renal failure, and in this respect is analogous to dilatation in the case of the heart.

We may, indeed, press the analogy still further. We have already referred to the fact that the heart responds, by dilatation, in two main conditions—first, when its tone is diminishing under a constant output of work, and, secondly, when an increase in the work performed is demanded of it. Likewise, the kidney responds in two main conditions by secreting a urine the composition of which moves towards that of the plasma—first, when its tone is diminishing under a constant stimulus, and secondly, when an increase in the stimulus to secretion is effected. This stimulus, upon which the function of urine secretion by the kidney is absolutely dependent, is in all probability the glomerular capillary pressure, and it is perhaps not stretching analogy too far in drawing a functional comparison between the glomerular capillary pressure and the right auricular pressure. By definition, then, if two kidneys, each having the same amount of functioning tissue, each being supplied with blood of the same composition, and each receiving the same pressure stimulus, secrete urines at the same rate but of different compositions, the reserve capacity for performing work of that kidney the composition of the urine from which more nearly approaches that of the blood plasma is smaller than that of the other kidney. But clearly such a definition is of no practical value in clinical medicine unless some means are available of measuring these reserves. We may summarize our knowledge of the reserves of the kidney as follows:

Anatomical reserve	Number of renal units in kidney.
Functional reserve	(Magnitude of pressure stimulus to secretion.
	"Tone" of secretory unit.

A fall in the functional capacity of the kidney is to be regarded as being due to a diminution in one or more of these three factors. The fall may be explicable in terms of a diminution in the number of renal units, or in the magnitude of the pressure stimulus, or in terms of a diminution in the tone of the secretory units. It is of interest to observe that a relationship may be shown

*Read in opening a discussion in the Section of Physiology and Biochemistry at the Annual Meeting of the British Medical Association, Manchester, 1929.

experimentally to exist between the first two factors. Rose Bradford demonstrated that a diminution in the amount of kidney substance led to an increase in the urine production by the remaining tissue, and it can be shown in the case of the isolated kidney of the dog that functional removal of a part of the kidney leads to an increased flow of urine from the remainder, and that this increase in urine flow is accompanied by just those changes in composition which occur when the perfusion pressure to the kidney is raised. A diminution in the anatomical reserves of the kidney is thus partially or completely compensated by an encroachment upon the functional reserves, in that the pressure stimulus to secretion becomes more effective, and polyuria of varying intensity results. This is of interest, since the excretion of urea and of substances eliminated by a similar mechanism is dependent mainly upon the amount of kidney substance, that of chloride mainly upon the rate of urine flow.

We may, then, recognize theoretically three main types of renal failure corresponding to the primary involvement of one of the reserve factors indicated above. That type, resulting from a severe diminution in the number of renal units, would be expected to be the most serious, since the disturbance could be rectified only by profuse regenerative changes. Renal failure resulting from a fall in the magnitude of the pressure stimulus or in the tone of the secretory units might well be of temporary duration and susceptible to therapeutic intervention. Is it possible that the primary involvement of each of these theoretical factors in the decrement of renal reserve has its clinical and pathological counterpart in polyuria with cirrhosis of the kidney, in oedema with parenchymatous nephritis, and in nephritis associated with toxæmia?

The three factors mentioned are possibly indissolubly involved in any given case of renal impairment, but their recognition may indicate the principles upon which any test of renal function should be based and the limitations to which its interpretation should subscribe. Since our present knowledge of the physiology of urine secretion suggests that the most important factors upon which the successful mobilization of the reserve of the kidney would seem to depend are the number of renal units and the pressure stimulus to secretion, a systematic investigation of the effects of some substances which, in the normal kidney, increase this number and pressure, might reasonably be supposed to give some indication of the magnitude of these reserves. Caffeine is such a substance. It was shown by Richards and his colleagues that this drug increased the number of active glomeruli in the frog's kidney, and it can be shown in the case of the isolated kidney of the dog that the increased flow of urine is explicable in terms of an increased effectiveness of the pressure stimulus. These facts suggest that the systematic employment of this drug under controlled conditions in nephritis might throw some light on the capacity of the kidney to perform extra work. A large response would point to a correspondingly large functional reserve, a small response to a small current reserve, which might or might not increase with the lapse of time. It will be of great interest to hear the experiences of members of this Association in the use of this drug, and their views as to the significance of the results obtained.

With regard to the employment of substances eliminated by the kidney as a test of renal function, it would seem that the surest indication would be given by the results of the administration of urea or other bodies eliminated by a similar mechanism, such as phenol red. And in this connexion it would seem advisable to take the amount eliminated over a given period of time at any given concentration of the substance in the blood plasma compared with that eliminated under similar conditions by the normal kidney as an index of the current reserves of the kidney. But the practical application of the present state of our knowledge of renal function and renal adaptation to the evolution of methods of assessment of renal reserve is fraught with difficulty, and it should prove most instructive to hear from those who are interested in this problem which tests they employ and the interpretation they are inclined to place on the results obtained.

RADIUM TELETHERAPY: CLINICAL EXPERIENCE WITH A TEMPORARY "BOMB."*

BY

E. ROCK CARLING, F.R.C.S.,
SURGEON TO WESTMINSTER HOSPITAL;

AND

A. J. LESLIE-SPINKS, M.A., B.M., CH.B.

WHEN it became possible to employ a gram of radium as one unit, at a distance from the skin of 10 cm., the staff of the Westminster Hospital (to nine of whom we tender thanks for permission to use their notes and cases) had already constant personal familiarity with interstitial and surface methods. This practical experience had taught, or driven home, lessons others had learned. First and foremost was the paramount importance of screenage; but there were also the capabilities of small total doses; the difficulty of gauging sensitivity, or regulating doses, by histological appearances; the diversity between immediate response, especially of primary growths, and ultimate prognosis; the difference in the response of glandular metastases from tumours themselves not very dissimilar in their response at the primary site; the want of a reliable means of increasing, differentially, the sensitivity of cancer cells, or of influencing their metabolism; the conviction that cure of disseminated cancer must probably not be looked for from focal irradiation.

Whilst, on the one hand, it was learned that a patient with advanced fixed fungating cancers of both breasts and extensive glandular metastases, seemingly near her end, might resume what appeared to be radiant health; on the other hand, a patient with a rapidly advancing cancer of the vulva and vagina, in the moment of satisfactory success as to her "growth," might die—of what? The necropsy supplied no answer, and the rest is speculation. It was found, as others had found before us, that anaemia was an inconstant factor, often amenable to control by administration of liver; that irradiation of the liver was accompanied by severe disturbance in the gastro-intestinal tract, and disorder of its own functions. As to the skin, it was known that, with exceptions, it was possible to steer clear of lasting injury, and that warnings, generally speaking, are timely. So far as it already burdens the lymphatic vessels and glands in relation to a growth, sepsis is a grave menace to success. Neuritis in the presence of sepsis about a nerve trunk, or actual invasion of the sheath by growth, is to be feared even with well-screened radium; and particularly in the case of the mouth and jaw.

On commencing work with a provisional teletherapy apparatus, it was not entirely an advance into an unexplored field—partly because others had been there long before us, partly because interstitial methods inevitably involve irradiation of the tissues surrounding the mass in which needles were implanted, and at least no obvious harm has come, in our cases, from screened rays reaching the tissues of and round the uterus and rectum, the colon, the breast, the cervical glands, and other parts. In teletherapy, however, unless very narrow beams can be directed with great accuracy on a growth, important structures, such as the heart, the spleen, the liver, the ovaries, the bone marrow, the thyroid, the thymus, and so on, must at times be irradiated. Always there must be a considerable intensity, and a considerable dose, of irradiation upon subcutaneous and more important intervening tissues. In cases treated by teletherapy the element of infective oedema is generally absent, but in local extensions the lymphatics are often blocked, and it is to reach infiltrating extensions, as well as primary growths difficult of access, or visceral metastases, that the method lends itself.

As to the difficulty of obtaining a valid intensity at the depths required for visceral growths, a preliminary physical inquiry could start from the observation that when certain growths were needed, notwithstanding an irradiation

* Sequel to the article by Francis Rock Carling, B.Sc., published in the *British Medical Journal*, May 11th, 1929, p. 845.