HORMONES AND VACCINES.

By Colonel R. H. Firth.

If Heberden, Mead, Abernethy and other leading doctors of the comparatively recent past could revisit this world and note the practice of the consulting rooms and hospitals of our day, probably nothing would impress them more than the existence amongst us of what we may call substitution therapy, or the administration of substances in order to either replace or supplement a pathological deficiency. It is well known to all that this therapy is of recent growth, and finds its expression essentially in the administration of the substances called hormones and vaccines. The purport of this article is to review the present position of their therapeutic value.

By hormones, one means the active agents contained in the internal secretions of certain glands, some of which are ductless. The secretion of these glands contains one or more special hormones and there is much which suggests that one hormone differs from another in the particular effect it can produce. That this is the case may be due to the fact that many of the ductless glands consist of two parts, apparently endowed with different functions; well-known examples are the thyroid and parathyroid, the anterior and intermediate lobes of the pituitary, the cortex and medulla of the suprarenals. Similarly, one portion of the ovary, testis and pancreas supplies an external and another portion an internal secretion. In therapeutics, extracts are employed prepared from the whole of the glands, and it is questionable whether we know the exact properties of the hormones supplied by each member or part of the glands, or are employing them otherwise than empirically. The term hormone really means a stimulator of metabolism, but many of the so-called hormones control or even inhibit metabolism. They are thus the chemical means of correlation of the activities of different parts of the body; their action may be either the increase or diminution of function and the alteration of nutrition or rate of growth. A complication arises from the fact that the external secretion of these glands contains different ferments and, just as one ferment such as trypsin under proper conditions can replace another such as pepsin in the digestion of protein, so it is not unreasonable to suppose that one hormone may, to a certain extent, be able to supplement or replace another of similar but not identical properties. Another difficulty is that there is much to suggest that
Hormones and Vaccines

some of the hormones, like those from the pancreas, are not obtained or administered in a physiologically active condition. In spite of these defects of knowledge, considerable evidence exists that the hormones have a therapeutic value in one or other of the following ways. Their most obvious use is in the treatment of those diseases due to destructive lesions of the gland by which they are secreted; in this true substitution treatment the hormones are obviously used rationally. Again, the hormones are of use when there is a physiological demand for an increased secretion which the glands of the patient are unable to meet, and in this manner we may employ hormones which not only excite but those which restrain functional activity in other organs. Further, the hormones can be used where their known physiological action may be of use quite apart from any defect in activity of the patient’s own glands; this constitutes their empirical use.

These various uses are well illustrated by the therapeutic employment of the thyroidal hormones. Myxœdema is the result of diminution or loss of the normal supply of these hormones in man; yet, by the constant and regulated use of heterogeneous thyroidal hormones prepared from a lower animal, all the symptoms of myxœdema in man can be removed and do not return as long as an adequate supply of these hormones is maintained. The same may be said of cretinism, provided treatment is commenced early and continued throughout the full period of developmental growth. Similarly, the simple parenchymatous enlargement of the thyroid which occurs in young women is a goitre arising in response to a demand for a greater supply of thyroidal hormones, but apt to be both excessive and persistent. If the hormones are supplied ready made in the form of one or two five-grain tabloids of thyroidal extract, the goitre subsides gradually in most cases; on the other hand, early cases of Graves’s disease, due to an already too abundant supply of these hormones, are aggravated by this substitution therapy. Again, thyroidal hormones may be used to stimulate metabolism in the treatment of some forms of obesity, and of certain types of psoriasis; their value is manifest equally in fortifying the resistance of the teeth against caries, in rickets, rheumatoid arthritis, and in nocturnal enuresis. How the hormones act in these cases we cannot explain, but it is probably by stimulating the metabolism of calcium salts.

In dealing with the therapeutic use of the hormones, it is convenient to divide the hormonic actions of the body into two classes, or the acute and the chronic. A typical example of the
former is the mechanism for secretion of the pancreatic juice, where the entry of acid chyme into the duodenum liberates in the cells of the mucous membrane a chemical substance, secretin, which, absorbed by the blood-vessels of the gut, is carried to the pancreas which it excites to secretory activity. Other examples of the same class are the production of adrenalin by the suprarenals under conditions of fright, and the chemical regulation of the activity of the respiratory centre in accordance with the metabolism of the muscles and the production of carbonic acid. Although carbonic acid and adrenalin are being produced constantly in the body, their amount may be increased largely under certain conditions; the production of adrenalin is particularly a beautiful example of refinement of means by Nature for the one great end, namely, the undertaking of active movements for offence or defence. These demand a high blood-pressure, increased blood-flow through the heart, and a mobilization from the liver of the glycogen store of that organ, whereby the muscles are flooded with the food most readily utilized by them to supply the extra energy demanded. By its extraordinary power of raising blood-pressure, adrenalin is the magician which instantaneously initiates these essential factors for sustained effort. Even the clotting of blood by adrenalin is but a further elaboration to check leakage in any chance wound of the body during action; and the very machinery employed to prepare for combative effort may, with the cowardice of civilization and by a curious antithesis of emotions, be set as powerfully in motion only to express fright.

In all these cases it is essential that the reaction take place at once, and cease as soon as the exciting cause is removed. The hormones associated with these reactions must, therefore, be capable of rapid disappearance from the body, either, as in the case of secretin or adrenalin, by oxidative destruction, or, as in the case of carbonic acid, by elimination. Owing to the ready destructibility of both secretin and adrenalin, their employment in a substitution therapy is limited, and their administration by the mouth practically useless. Similarly, their only use is as drugs, because, though we can evoke the physiological action of these substances by introduction into the blood-stream, it is difficult to control or grade their action, as must be the case under normal or natural conditions. Adrenalin we constantly use for its local effects on the blood-vessels; personally, one employs it as an excellent and rapid means of stopping bleeding after a cut during shaving, but it is practically useless to replace the functions of
an absent suprarenal medulla. We know it to be the most
efficient cardiac stimulant, but its employment in a case of failing
heart is discounted by our inability to dissociate its power of
vascular constriction, and increasing the resistance to the blood-
stream, from its action on the heart. Although secretin is an
infallible excitant of pancreatic secretion it is doubtful whether we
can expect good results to follow its use; we need to remember
that this alkaline juice enters the duodenum immediately after a
certain amount of acid chyme, and the secretion of the pancreatic
juice lasts only so long as the duodenal contents are acid. Cases in
which secretin has been given to healthy animals have resulted
in symptoms of acute collapse produced by the entry and non-
neutralization of the highly alkaline pancreatic juice and degradation
changes in the intestinal mucous membrane.

When we pass to the second or chronic class of hormonic
reactions we find better chances of successful substitution therapy.
In this group are the action of the thyroid on nutrition, metabolism,
and on the functions of the central nervous system; also, the
action of the anterior lobe of the pituitary body on the growth of
bone, the action of the sexual glands on the development of
secondary sexual characteristics, and the action of the corpus
luteum on the growth of the mammary glands. To this list, one
might add the apparent influence of the pancreas in regulating
carbohydrate metabolism. In them all the chemical product of
some organ passes into the blood-stream and exercises a slow or
chronic effect upon some distant organ or group of organs. The
weakness of our position lies in the fact that we cannot in all cases
be sure that there is not a vulnerability of the hormone from the
destructive actions of the body juices or of oxidation. This explains
why we do not get therapeutic results always by the oral adminis-
tration of hormone-producing organs in cases of their deficiency.
The only certain result has been attained by the administration
of the thyroid, and that this is so results from adherence to two
conditions which are essential if success is to follow administration
by the mouth; these are, that there is a storage of the active
substance in the gland, and that the substance is not destroyed
in the alimentary canal. In connexion with these essentials is the
interesting point that at one period in our evolution the thyroid
was a gland opening into the anterior part of the alimentary canal.
Unfortunately, all efforts to reproduce the action of the testes, the
ovaries or of the corpora lutea, and of the anterior lobe of the
pituitary by oral administration or by the subcutaneous injection
of extracts have resulted, so far, in failure or indefinite results.
In the case of any gland of internal secretion, it is evidently necessary for the success of substitution therapy that the gland in question must act as a storehouse for the active elements of its secretion, and must hold them in quantity much in excess of the immediate needs of the body. Further, those active elements must be of a relatively high stability, retaining their potency in artificial solution or surviving the death and drying of the parental gland tissue. Again, if there is to be any success from the administration of hormones under the ordinary conditions of practice, their action must be such that the introduction of large doses at long intervals can replace the slow constant secretion, by which we presume they reach the circulation under physiological conditions. In the case of thyroid treatment, we know that these conditions are met, but in respect of the other ductless glands the evidence is in the other direction. Certain hormones, like secretin, adrenalin, and the active constituent of the posterior lobe of the pituitary body are relatively stable substances, but their use is rather as drugs than in the sense of the true substitution therapy; we cannot say they cure, at the most they relieve somewhat the conditions associated with pathological defects of their glands of origin. We know little or nothing of the active principles of the suprarenal cortex and of the anterior pituitary lobe, except that they are not the stable hormones recognizable in the other portions of those glands. It is true that benefits are reported from relatively large doses of ox pituitaries, but the evidence does not warrant our assuming that, either in its power of storage or in the stability and absorbability of its principles, the pituitary gland is in the same class as the thyroid.

The relations of adrenalin to chloroform anaesthesia are of some importance. Direct and careful observations made upon chloroform anaesthesia, produced under conditions militating against exact and scientific methods of administration, show that in fatal cases it is the heart which failed and not the respiration. The factor at work would seem to be ventricular fibrillation, due to an irritable ventricle or ventricle giving rise to frequent extra systoles and sometimes tachycardia. The intimate relation of such to fibrillation suggests that the latter is merely a further advance upon the former. The administration of adrenalin favours both the ventricular irregularities and the onset of fibrillation. The lesson is obvious that chloroform administration is contra-indicated after local adrenalin application. Recent research suggests that this unfavourable action of adrenalin is due to simultaneous stimulation
of the extracardial nerves, the vagus and the sympathetic. The sensitiveness of the vagus to adrenalin appears to be heightened by the chloroform. The cardiac irregularities under chloroform anaesthesia with adrenalin seem to follow a definite plan. It is a plan explainable by synchronous vagal and accelerator stimulation. A remedy is forthcoming by a previous injection of atropine which, by cutting off vagal effects, lessens the liability to cardiac irregularity.

Of all the hormones, adrenalin stands out prominently as having furnished a fascinating chapter in recent physiological literature, and nowhere more than in its effects after acute fevers and diphtheria, when the suprarenals are depleted of their store, does it show itself as essentially a therapeutic substitute. Pituitrin obtained from the pars intermedia or from the posterior lobe of the pituitary body, we must regard as a drug. The clinical results of pituitary atrophy are familiar under the name of adiposo-genital dystrophy; in this rare condition, improvement in the obesity and sexual power has followed treatment with the pituitary extract. The same extract is useless in acromegaly, as this condition is due probably to a hyper-secretion of the gland, though in the later stages there appears to be a failure of pituitary hormones, against which the giving of large doses of the extract affords some relief of symptoms. Recent work indicates the great value of pituitrin as a stimulant of plain muscle, whereon it acts by increasing its sensitiveness to normal stimuli rather than by acting as a direct stimulant. In the normal person, it causes no rise of blood pressure, but in the experimental animal with high blood-pressure may cause a fall; yet, when the vasomotor centre is impaired and the blood-pressure lowered artificially, the tonic effect of pituitary extract on the arteries is great and prolonged. The heart is not affected directly, but, in shock and the anemia caused by general relaxation of the arteries, the restored tone of the latter following the administration of pituitrin improves the heart-beat. The physiological action of pituitary extract upon the uterus has been beneficial in post-partum haemorrhage, but many regard it as inferior to ergot. In amenorrhoea and mal-development of the mammae or backward sexual functioning in young women, the use of the pituitary extract has given good results, while, in those curious and undefined neurotic or neurasthenic conditions of some women, the empirical use of this extract has been known to act as a charm. Again, in cases of pneumonia with low blood-pressure an injection of one cubic centimetre of pituitary extract every six
hours is a resource worth remembering; similarly, it may be of value in tympanites due to paresis of the intestinal muscular coat.

At the present time, the chief interest of pituitrin centres round its action on the uterus, where its therapeutic action appears to depend more on increasing the sensitiveness of that musculature to normal stimuli than on direct stimulation. If the extract be injected during pregnancy it does not induce labour; but when labour has commenced and the normal physiological stimulus is presumably present, but the uterine muscle inert or deficient in response, then pituitary extract intensifies and prolongs the uterine contractions and hastens the completion of the second stage of labour. Current literature indicates that its use has obviated the employment of forceps in many cases, without entailing harm to mother or child. The other defined effects of pituitary extract on the excretion of urine and secretion of milk have not found so far a wide therapeutic field, but as accessories to its other actions in obstetric practice they have an obvious value. Doubts exist as to whether one or more principles are concerned in the activity of the extract, but, from the practical aspect, there is no known method of separating the activities, neither has the presence of any one of them imposed any limit on the use of the extract for the sake of the others. To the hypercritical, the pituitary extract is not a hormone, in that our anatomical knowledge does not support the view that the pituitary body secretes a principle or principles producing its effects upon the circulation during life. Whether it is a hormone or not, the probabilities are all in favour of the view that it is, and it is difficult to explain the presence of such a potent principle in the body on any other assumption; the most we are prepared to admit is that our present ignorance of its nature compels us to use it in therapeutics as a drug rather than as a true hormone.

The hormones produced by the interstitial cells of the ovary and testis have definite physiological actions, but their real use in medicine is still empirical. Symptoms due to the normal climacteric and those induced in a premature climacteric, following removal of both ovaries, have been and are relieved by the administration of ovarian extract. The writer knows also of a case, which may best be termed as one of climacteric in the male, in which curious neurotic symptoms disappeared after a course of testicular extract, called didymin. Since so many of the symptoms in both classes of case are subjective, it is difficult to appraise correctly the effect of any treatment, and it is wiser to suspend judgment as to the
Hormones and Vaccines

real value of either ovarian or testicular extract. An intimate knowledge of the pathology of diabetes, and a recognition of the part which a loss or deficiency of the internal secretion of the islands of Langerhans in the pancreas play in carbohydrate metabolism suggests that could we obtain the pancreatic hormones in an active form and maintain an active supply of them, we should have a powerful means of controlling cases of pancreatic diabetes. So far, this addition to our therapeutic armament is not available. Enough has been said to show that the use of the hormones of a single gland is complicated, but the questions at issue have been made more difficult by attempts to employ combinations of hormones in the treatment of conditions thought to be due to polyglandular insufficiency. We know too little of the actions and real values of the individual hormones to attempt to dogmatize or prognosticate as to polyglandular therapy, but it is interesting to note that a therapeutic mitrailleuse, called hormotone, and said to contain several active hormones, is on the market and alleged to be successful in the kind of neurasthenic cases referred to as benefiting by pituitary extract. One is tempted to close this section of the article by saying, that while the therapeutic value of thyroidal, suprarenal and pituitary hormones is undoubted, the evidence available as to the other hormones suggests caution or reserve in advocacion of their value in the treatment of disease.

We can now pass to the consideration of the so-called vaccines as therapeutic agents; in respect of this nomenclature, one cannot refrain from the expression of a regret that the term "vaccine" was ever applied to preparations which are neither derived from nor have the remotest connexion with the cow, that classical and familiar beast rightly and honourably associated with the discovery and efficacy of Jennerian vaccination. As the term has passed into current use, one employs it in this article as meaning those preparations or emulsions of killed micro-organisms which, if injected into the body fluids, by virtue of their associated toxins stimulate the formation of antibodies protective or antagonistic to the particular infection in which they are employed. The administration of these preparations constitutes what may be called a specific therapy, in contradistinction to the substitution therapy as typified by the administration of hormones. The evolution of this therapy is recent and of interest, as it marks the intrusion of the skilled bacteriologist into the sphere of clinical medicine and the cooperation between the laboratory and the clinique. The existence and genesis of this particular specific therapy appeals much to us,
as its inception and placing upon a non-empirical plane was the outcome of the work and advocacy of a one-time colleague of the writer's, Sir Almroth Wright, who in the old laboratory at Netley worked laboriously in perfecting technique for the practice of a therapeutic method which, if not giving all the results at one time expected of it, has come to stay and contains much promise of greater development. Like other new methods, vaccine therapy suffered from the over-zeal of its earlier advocates and their failure to appreciate that its value is in direct proportion to the care and judgment bestowed upon the diagnosis of the case in which it was proposed to employ it. The initial error on the part of professional advisers was accentuated by the enthusiasm of the lay public in resorting to and desiring inoculations, an attitude which appeared at one time to have reached almost the belief that the inoculating syringe was the panacea for all ills. The result, for some years at least, was a situation of rampant empiricism which has left a record of vaccine therapy at once unsystematized and unreliable, so much so that it has gone perilously far towards bringing the whole procedure into disrepute. The original inception of Wright and his pupils for the employment of a strictly appropriate or autogenous vaccine was gravely lost sight of and, in the course of time, a supply of stock vaccines was put upon the market by enterprising pharmacists. Admitting the logic of the inference that there is an actual necessity for stock vaccines in certain cases, in which no material is available for the making of an autogenous vaccine or in which experience makes the nature of the infection highly probable, it follows that stock vaccines, if prepared at all, should be prepared with a view to their being polyvalent, or at least made from a mixture of strains of the particular micro-organism concerned. A later demand has been for substances of more questionable value, and pharmacists now supply stock preparations which, under the name of phylacogens, are mixtures of the endotoxins of several different micro-organisms. The evolution of vaccine therapy has led, therefore, to the production of three grades of the particular reagent emanating from the laboratory; namely, autogenous vaccines, stock vaccines, and phylacogens. There can be little doubt but that these three grades correspond with three degrees of efficiency, and the merits of vaccine therapy as a curative measure rest almost entirely upon the results obtained by the use of the autogenous vaccines prepared, after careful investigation, from materials obtained from the patient. The use of either of the other kinds of preparation must be regarded as partaking of the nature of
a pseudo-scientific gamble, or a medical practice on the hit or miss principle. For these various reasons, there can be no doubt that vaccines have been employed improperly in many ways, a fact which makes it all the more difficult to form a sound opinion as to their true value as therapeutic agents.

In attempting to appraise the value of vaccines, we need to remember that patients do recover from the bacterial infections without any very direct assistance from the doctor; this is a fact that makes it clear that they have natural powers of resistance thereto, independent of the physician's drugs. We know that this power of recovery is due to the fact that the tissues can form antibodies to any foreign albuminous substance which is soluble in the tissue fluids. Exponents of vaccine therapy have, therefore, the advantage of a logical claim that they are guided by a definite principle; that is, they use a substance which can produce a certain physiological effect and, moreover, use it with greater rational support than is possible with most drugs available for oral administration. For success, three conditions must be observed; they are (1) that the correct micro-organisms be used for the vaccine, (2) that suitable doses be injected, and (3) that the patient's tissues are capable of responding. Errors are only too easily made with regard to the first two, but they are capable of correction; unfortunately, the third condition remains an unknown quantity. In the matter of using only the correct micro-organism for the preparation of the vaccine, too much importance cannot be attached to the proper collection of infected material from which that micro-organism is to be isolated. Not infrequently, this is relegated to the patient or the nurse; this leads to many errors and increases difficulties that are quite sufficient already. The material collected must come from the actual lesion suspected as the cause of the infection and, here it may be remarked, it matters much that the process shall be one of proved infection. To isolate a micro-organism from some part of a patient's body and to assume that his disease is therefore due to its activities is, in the sphere of diagnosis, but the analogue of the phylacogen in the sphere of treatment. Once the material is collected, it must be dealt with promptly, for many of the failures to make efficient vaccines are failures in eliminating contamination rather than failures in tapping the true centres of infection. Of methods of preparing the vaccine, one need not consider in this article beyond saying that it seems immaterial whether it be prepared by heat, by autolysis, or by the use of antiseptics; on sensitized vaccines, some remarks follow subsequently.
Of the question of dosage and of interval between doses of a vaccine it is difficult to say very much or to be dogmatic, as our knowledge is at present inexact as to both these factors; our chief guides are tradition and personal experience. Without producing untoward results, the range of effective dosage in man is probably considerable for the greater number of everyday vaccines. Of the various systems of dosage, that which begins with a presumed subminimal dose and increasing to a dose beyond which it is thought or found that bad effects follow, seems to be the method in most general use. In chronic infections that tend to recur, like furunculosis, it is often better to graduate the dose in a reverse order; on the other hand, in acute infections, a stoppage system of dosage by which three doses of increasing size are given at short intervals, followed by a pause, the second series beginning with the final dose used in the first series, and so on; this method appears best adapted when employing sensitized vaccines in the acute infections. By intervals is meant from seven to ten days in chronic cases, and twenty-four to forty-eight hours in acute cases. On these points, one is not prepared to be dogmatic, as intervals must be determined by the course of the disease and by the apparent effects produced. Some people are very susceptible, especially to pneumococcal vaccine, and in many instances it may be necessary to continue treatment over long periods with gradually increasing intervals, because the duration of immunity varies greatly as to particular micro-organisms in different individuals. For example, the more acute infections of the upper air passages are due generally to streptococcus or pneumococcus, either of which may be rapidly fatal from a general blood poisoning. In these cases, experience indicates the value of a large dose of the vaccine given early and repeated; this practice is especially suited to the sensitized vaccines, as these are less likely to make the patient worse than non-sensitized preparations. In the acute streptococcal infections doses of 100, 500 and 1,000 million can be given boldly on three successive days and often with the best of results. In the acne class of cases the doses may and should be comparatively small; weekly doses of from 2 to 10 or 30 to 90 million are usually sufficient, as anything over 90 million seems, more often than not, to aggravate the symptoms.

The practical or clinical use of vaccines appears to be confined to the treatment of such diverse ailments as acne, boils, seborrhoea oleosa, sycoses, staphylococcal infections of the scalp, folliculitis, certain types of alopecia areata, influenza, colds in the head,
chronic nasal discharges, chronic bronchitis, asthma, pneumonia, arthritis, endocarditis, colitis, bacilluria and the general septicemic infections by various streptococci and staphylococci, as in puerperal sepsis. The value of vaccines in all these diseases is most unequal; the most consistently good results appear to have been obtained in the skin cases of chronic pustular infection, from which it is relatively easy to isolate the active micro-organism and from it to prepare an autogenous vaccine. It is otherwise with many of the generalized infections, and especially with malignant endocarditis, from which it is obvious that the preparation of a true autogenous vaccine is extremely difficult; occasionally, in streptococcal septicæmia a few doses of a sensitized stock coccal vaccine produce a result which is little short of magical and, now and again, a pneumococcal case, similarly treated, gives a brilliant result; obviously, these are shots in the dark and savouring of pure empiricism. The treatment of enteric fever by autogenous vaccine has, so far, been disappointing, but, here and there, one meets with encouraging reports of severe cases improved and assisted by vaccine therapy. In the same category of failures for the most part must be placed cases of colitis and bacilluria; the difficulties in the way of making a true autogenous vaccine from this class of patient are enormous, but the experiences gained do not warrant our total abandonment of efforts to treat these cases by a vaccine; by its means we can reduce the number of pus cells and micro-organisms in the urine, reduce the fever and relieve pain and other local symptoms. One writes from a personal experience of a pyelitis in a near relative, in whom a vaccine, although unable to cure, most certainly helps to make life more bearable for the patient. The case teaches the important fact of a need to examine the urine from time to time to ascertain if the same micro-organism is the cause of the trouble; in the particular case one has in mind no less than three different organisms were isolated from the urine in the course of eighteen months, and respective infections by each were the apparent cause of the acuter symptoms, as vaccines made from the respective cultures were markedly beneficial; the particular micro-organisms isolated and so used were a streptococcus, the Bacillus proteus and B. coli communis.

Some of the most encouraging results follow the treatment of pyorrhoea alveolaris, accompanied by a general sepsis, when an autogenous vaccine is used. In these and analogous cases it is necessary to remove or drain the focus of infection. There is also a large group of cases which respond excellently to vaccine therapy,
classed under such headings as colds, pharyngitis, laryngitis, and chronic infection of the upper air passages. The active organisms are the pneumococcus and *Micrococcus catarrhalis*, or the pneumococcus and the influenza bacillus in combination; many of the patients are feverish in the early stages and not a few are suspected of tuberculosis. There is abundant evidence that suitable vaccines will often cure them; the corollary suggests itself why, when a severe catarrhal or influenzal epidemic is prevalent, should not the bold employment of a stock vaccine be a means of protecting individuals against an insidious, prostrating and most unromantic affection? Reports indicate that some much up-to-date practitioners have succeeded in demonstrating the value of the idea. Of course, the real value of vaccine therapy is the relief of toxic symptoms, and this explains why we find it giving good results in somewhat unexpected kinds of case. Asthma is often due to the presence of infection in the nose, tonsils, or upper air passages; a vaccine prepared from an infecting organism isolated from the focus will in most cases diminish the severity and frequency of the attacks; technical literature is full of reports of such cases. Rheumatoid arthritis is also a condition in which a focus of infection is to be found frequently; if it cannot be completely removed, vaccines will often assist the surgical treatment, when employed either for a short time before or for a long time afterwards. This suggests the cognate idea of using a vaccine before operations in which there is a danger of septic infection, say, for example, in obstetric practice as a prophylactic against puerperal sepsis. In the development of this notion, the value of the sensitized vaccines is pre-eminently indicated.

The utility of vaccines in pneumonia has been the subject of considerable attention, but the difficulties are great in arriving at an accurate estimate of the procedure, owing to the constant change in type of pneumonia and the varying intensity of virulence displayed by the pneumococcus in different seasons. We recognize that a vaccine to be potent ought to be autogenous and used early; but this is a matter of great difficulty, as the disease, being of such acute and short duration, has either subsided or terminated fatally before the vaccine can be prepared. In these cases, therefore, recourse must be made to a stock vaccine or a homologous vaccine prepared from a pure culture of pneumococci isolated from the blood of a patient suffering from lobar pneumonia. This means a disadvantage, because the strains of pneumococci vary much in their virulence and characteristics, so that there is no certainty
that a vaccine is being used and prepared from the same type of infection as that from which the patient is suffering. In spite of this, the results with stock vaccines in acute pneumococcal infections are encouraging, but they must be used on the first or second day, as once a general blood-stream pneumococcic infection has been established the vaccine is of little value, and seems to exert little or no influence on the course of the attack. The effective dose is not less than fifty million, followed in twenty-four hours by another of one hundred million; it seems to be mere trifling to give smaller doses, as the effective action must be prompt and vigorous. Making all due allowance for the optimism of workers in this field, one cannot resist the conclusion that in a pneumococcus vaccine we have a valuable aid in the treatment of pneumonia and, although not a specific remedy, it should be used in those cases of a virulent type which threaten the life of the patient.

Mention has been repeatedly made of sensitized vaccines, and their value emphasized in the acute infections by streptococci and pneumococci; it may not be time wasted if we recall briefly the main facts with regard to this particular kind of vaccine. The procedure adopted usually in the preparation of sensitized vaccines is similar to the method originally employed in 1902 by Besredka, when he first introduced them. Pure cultures of the indicated organism are allowed to remain in contact with homologous immune serum for a sufficient time to permit of the adsorption by the bacteria of the specific antibodies present in the serum. When this has taken place, the bacteria are centrifuged down and the supernatant fluid removed and replaced by normal salt solution. The deposited bacteria are then shaken up and the process is repeated until the last trace of serum is removed from the bacterial bodies. Besredka favours the use of living sensitized vaccines, but with us the general practice is to kill the bacteria, after sensitization, by the addition of one per cent phenol to the terminal washing. The advantages of a sensitized vaccine are that it is less toxic than the ordinary whole vaccine and confers a more rapid and more permanent immunity. The mechanism of the immunity conferred is probably that, during sensitization, the bodies of the bacteria become covered over with specific agglutinin and opsonin, and the bacteria, thus sensitized, are so readily taken up by the polymorphonuclear leucocytes that bacteriolysis occurs in the interior of the phagocytes and endotoxin is liberated, and the production of antibody much stimulated by the endotoxin thus set free in the interior of the leucocytes. The essential factor in
the process appears to be a shortening of the preliminary work of the phagocytes. There has accumulated a large body of evidence that these sensitized vaccines are a very great advance upon the earlier or whole vaccines; Continental workers favour the use of living vaccines, but taking into consideration the fact that our knowledge of the factors which influence the variation of bacterial virulence is still rudimentary, the indiscriminate use of living vaccines in treatment would seem undesirable. Another difficulty is the question of the best antiserum for sensitization of the bacilli; this appears to be largely a matter of individual opinion. Some use polyvalent antiserum, others use autogenous serum, and so on. The sensitized vaccines in common use are derived either from stock vaccines, or are prepared from the causal organism isolated from the patient; here again there does not seem to be any well-marked uniformity of opinion, though everything points to the superiority of an autogenous source.

In attempting to cast up a balance-sheet in respect of this question of vaccine therapy, we must admit that the failures are undoubtedly more numerous than its successes; curative vaccine treatment must be admitted to have disappointed the high hopes with which it began, and in this respect its history resembles that of most remedies. The problem of immunity is so complex that it is highly probable that the technique or practice, rather than the principle, of vaccine therapy is at fault, and that in time this may be so perfected as to establish the status of vaccines as a reliable remedy. For the present, their use appears to be justified only when trustworthy therapeutic methods have failed or do not exist; anyhow, few will argue that the specific action of vaccines is as certain as that of such drugs as mercury, arsenic, digitalis, or the iodides, bromides and salicylates. In spite of this we are not precluded from recognizing that we have in vaccine therapy a weapon of great value against the infective diseases. Too much uniformity of results has been and is expected from vaccine treatment by many, who forget the complexity of the causal factors in many of the infective processes, and the variations even in the natural course run by them. The critic must remember also the difficulties there are in ensuring the proper correlation of the vaccine used with the pathological condition under consideration and, above all things, patience is necessary in order to determine the best mode of calling out the specific response. In connexion with all kinds of disease, the therapeutic argument is notoriously difficult, and nowhere is it more so than in relation to the infective
processes. Most of us have had cases under our notice in which the patient has made a specific response to inoculations and thereby been cured of his infection by a vaccine; even one positive case of the kind must outweigh many cases of apparent or real failure. So much are we still in the dark as to the inner facts of recovery from an infective process, that our position may be well described as though we wandered up and down a long passage, into which many locked doors opened, with a key in our hands trying each door with it. Owing to the key not fitting, many locks refuse to open, but then there comes one in which the key turns and the door opens. The simile of a lock and key illustrates the specific stimulus and response of a vaccine given in a successful case; our problem is, does any key fit any door and how frequently are we able to find the proper key?

In this search for a proper key or proper lock, and this quest for a specific response to a specific stimulus, it must be borne in mind that the object is not to see from what depths we can raise the patient by a specific stimulus, but rather to supplement those general measures that have raised him or her already to a certain level, at which he or she now remains, until the extra leverage of the vaccine completes the process. This conception makes it necessary, in all cases, not to neglect attention to non-specific points in treatment, as the general condition of the patient is a factor of vital importance in getting the best effect from a vaccine. Too often, this elementary point is overlooked or ignored while, in other cases, failures to use vaccine therapy successfully are to be explained by the want of a rudimentary knowledge of the practical application of bacteriology to disease on the part of practitioners. It is obviously futile to order a vaccine to be prepared from the urine or faeces for a case diagnosed as myocarditis, or to suggest that the treatment for lumbago is a vaccine prepared from an organism isolated from the pharynx; equally misleading would it be to say that a vaccine has failed to do any good, when it is eventually shown that the patient was suffering all the time from cancer of the rectum. These are not fantastic examples quoted to score a point or be facetious, they are typical of everyday experiences by those in technical practice, and have an obvious lesson for us who are not.

Some personal experience prompts the opinion that vaccines are valuable in mitigating symptoms and causing the disappearance of infections in some acute and chronic cases, but not in all. The present state of our knowledge is so incomplete that we can neither
account for failures nor predict success in vaccine therapy. There is still much to learn, but the following points need emphasizing; they are: (a) Vaccines are to be regarded and employed essentially as supplementary therapeutic agents, and not as substitutes for established methods; (b) where a disease is attributable to a focus of infection, that focus should if possible be eradicated, or treated by recognized procedure and, if necessary, by the employment of a vaccine; (c) in many cases, the focus of infection remains and relapses ensue; it is in these cases that a vaccine may relieve symptoms but without curing the disease; (d) in the acute infections the use of vaccines is contra-indicated as a general rule; if used in acute cases, the dosage should err on the small side, whereas in chronic cases increasing doses of a vaccine may be pushed often with confidence; (e) all experience indicates that, though a vaccine may do no good, a vaccine does no permanent harm.

The general conclusion is, therefore, permissible that vaccine therapy is still on its trial; startling and brilliant cases of success have been recorded, but there remains still the doubt whether the success can be attributed to the vaccine alone. The plain truth is, we need more knowledge and the necessity is brought home to us for a closer co-operation between pathological inquiry in the laboratory and clinical noting in the ward, for it is only by the test of clinical experience that the value of any remedy in disease can be decided ultimately. We cannot overlook the fact that the disappointments in the use of vaccines have been many, but the future holds out definite promise. The present methods may be crude and often misdirected, yet practice and research may improve them and give them the precision they now lack. In hopeful confidence of the arrival of that day, we must leave the subject.