ADAPTATION AND ADAPTIVE DYSFUNCTION.

A THESIS

submitted for the Degree of Doctor of Medicine

by

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1.

INTRODUCTION.

It is universally acknowledged that all the marvels of modern medicine and surgery would not be of the slightest use were it not for those vital forces, which, even to-day, are still referred to as the 'vis medicatrix naturae'.

Apart from their role in recovery, these forces are also responsible for the maintenance of health. The only satisfactory manner in which health may be defined is as a state of perfect adaptation to the environment. From this point of view, therefore, all diseases may be regarded as a manifestation of partial failure to maintain adaptation, which becomes complete in the event of death.

Whilst the pressing problems presented by the sick must occupy the forefront of our minds, it is clear that it is worth while to pause to consider the greater puzzle of the healthy, and why they should remain so, despite the destructive influences which surround us from the cradle to the grave.

The power of the forces which act unseen to maintain life is illustrated by the most remarkable fact that disease is the exception rather than the rule, and that many of us live to a ripe old age. Indeed, that we should continue to live is a far greater enigma than that we should die, and that we recover is often a greater miracle than that we should not.

There can be no doubt that the power of adaptation to adverse internal or external environmental
circumstance is the most potent influence determining our survival, and it is with these mechanisms of adaptation, and the possible manner in which they may become deranged, that this thesis is concerned.

This work is the result of an exhaustive analysis of all the available published work which appears to have any possible application to the subject. It is not a review, but an attempt to correlate and interpret this miscellany of data, so as to build up a composite picture of the adaptive processes as a whole.

The extreme diversity of the fields of medical endeavour from which the data has been derived has necessitated the discussion of highly specialised subjects with which the writer has not formerly been familiar. It is felt, however, that any risk of misinterpretation is offset by the possible value of providing a unifying concept of this most important subject.
A GENERAL DISCUSSION OF ADAPTATION.

The ability to become adapted to adverse conditions in the internal or the external environment is a property common to all forms of life in greater or in lesser degree. From the very lowest to the very highest form of life the struggle for survival demands that the organism become, and remain, adapted to those environmental circumstances which are inimical to the survival of the individual, and therefore of the species.

Even at the lower end of the evolutionary scale, among the bacteria, the phenomenon of adaptation to adverse conditions can be observed. Here, as in all other forms of life, adaptation can be achieved as long as the change in the environment is not too sudden to allow time for adaptation to take place, nor so severe that the state of adaptation cannot be maintained without ultimate breakdown and death.

It is very well worthy of note that adaptation only takes place to adverse environmental circumstance. Crile (1916) expressed this point in a manner which cannot be bettered when he wrote—"There exists abundant and reliable evidence of the fact that whenever man has been subjected to the stunting influences of an unchanging environment fairly favourable to life, he has shown no more disposition to progress than the most stolid animals. Indeed, he has usually retrogressed. The need to
fight for food and home has been the spur which has ever driven man forward to establish the manifold forms of physical and mental life which make up human existence today." The loss of virulence which occurs if the environment of a bacterium is too favourable is proof of the general biological significance of this statement.

The adaptive mechanisms which will now be discussed briefly are all completely non-specific in character, and are therefore of the most general application.

The power to adapt to adverse environmental circumstance must be of the most fundamental importance in relation to the evolution of the species, for without this power it is obvious that evolution could never have taken place at all. It is therefore correct to state that the power to adapt is the driving force behind the process of evolution, and that the process of evolution may equally well be termed the consequence of adaptation to the various circumstances of the environment.

From the very bottom of the evolutionary scale upwards all the species except man have become sidetracked into one form of physical specialisation or the other. Man, on the contrary, has not become specially adapted to live in the sea, or fly in the air, or to be fleet of foot and long of limb in order to hunt his food or escape from his enemies. In no
way can he be said to be truly specialised except in his cerebral development. As a result he is able to adapt himself to almost any task or mode of life, and to bend all else to his will. His supremacy clearly depends upon his extraordinary cerebral development, allied with the lack of specificity and the adaptability of his relatively puny bodily structure.

The present form and functions of man, and of his various organs and tissues, must represent the end-result of biological and anatomical mechanisms which were adopted or discarded as they were found to be advantageous or otherwise to the body during the age-long struggle of evolution. As a consequence of the law of natural selection only those structures and mechanisms found to be of assistance in the struggle for existence have survived. It is obvious that many of these mechanisms must be of the nature of a compromise, and indeed obvious flaws, such as vestigial and useless remnants of discarded structures like the vermiform appendix, still exist to remind us of arrangements which were discarded far back in the process of evolution.

From a general point of view it may therefore be said that, despite his many imperfections, man is the result of this evolutionary process of trial and error, and that it is only very recently in the history of mankind that the processes of natural selection have been interfered with to any extent by
medical science and public health measures.

A somewhat analogous process of adaptation and evolution may clearly be discerned to have occurred within living memory in the gradual development of the automobile, the aeroplane, radio, and so on. From their first humble and imperfect beginnings these devices have also evolved through a painful process of trial and error in which many imperfect mechanisms have been discarded and better ones adopted, until they have now reached their present peak of perfection as regards structure, function, and reliability. For example, the jeep may perhaps be called the most adaptable form of mechanically propelled vehicle, though lacking in the comfort provided by its less adaptable counterpart, the ordinary saloon car; and from the jeep one may distinguish the various types of transport which have been developed for one specific purpose, and which are virtually useless for anything else. In these machines, as in nature, specific adaptation to one particular purpose limits its general usefulness, just as the overspecialisation of the prehistoric monsters determined their extinction.

The last century has seen advances in applied science and in civilisation on an unprecedented scale, and in consequence civilised life has become a much more complicated and stressful existence than it was formerly. At the same time, the advance of medical science has been instrumental in preserving
and prolonging the lives of many individuals who would otherwise have died out because of mental or physical inadequacy, and has thus enabled them to procreate others who inherit these defects. Though the healthy fit individual can now look forward to a much longer life span than before, this interference with the process of natural selection must also have resulted in the preservation of an increasing number of those who have some physical or mental weakness. The result must be the existence of an increasing number of persons who are mentally or physically unable to completely adapt themselves to the conditions of life today.

This nihilistic point of view is, of course, completely unjustifiable when the other side of the ledger is examined, for there is no doubt that untold millions of perfectly fit individuals owe their lives directly to the progress in the war against disease and death, and even more are alive as an indirect result of measures which have reduced the incidence of, or the susceptibility to, disease. The dilution of the human stock is indeed a small price to pay for such benefits, though wars have also tended to reverse the law of nature, and to bring about the survival of the unfittest.

The process of the moulding of the form and functions of the human body by the forces of environmental circumstance and survival of the fittest is
known to have occupied an untold number of years. It follows that this process must occur very slowly indeed, and that the impact of modern civilisation upon the human organism must constitute a very recent event, which might be said to represent but the last sentence in the latest chapter of the history of man. It does not seem unlikely, when the matter is regarded from this point of view, that we cannot possibly have become adapted to life under the conditions of civilisation, and that many years will yet be required for this readjustment to take place.

It may therefore be true that the impact of the civilised mode of life may, in many cases, be of such intensity that the individual fails to become adapted to the strain, or is not able to maintain adaptation to it for more than a limited period. The manifestations of such failures of adaptation to the civilised environment are currently termed the "stress diseases", and, as would be expected, their incidence is increasing with the intensification of the strain and complexity of modern life today.

Though civilisation originated in the east, modern "civilisation" is a western development, so that its impact on the western peoples has been more gradual and they may be said to have had more chance to become adapted to it. There is a good deal of evidence to suggest that the more primitive peoples, upon whom its impact has been recent and sudden, are
much less able to stand the strain. For example, there are many surveys showing that the American Negro, despite many generations who have lived and died in America, is much more liable to develop essential hypertension than the American White, who is of European origin. It has been suggested that the more primitive peoples are constitutionally unable to adapt themselves to civilised conditions. We may therefore ask whether it is the case that the impact of civilisation on the human race has been so acute in the last hundred years or so that an increasing number of individuals are unable to adapt themselves to the conditions of life today. While the majority are able to withstand the hurly-burly of everyday existence, the minority develop some disorder which is a manifestation of dysfunction of the adaptive processes, a defect which varies from one to the other, just as it is the weakest link in a chain which breaks.

The supreme development, adaptibility and versatility of the human mind is allied with the flexibility of function of the body. Neither can function without the other to any extent, and to act as one, both must be perfectly co-ordinated. Though it is possible to divide mind and body in an arbitrary manner, they are clearly indivisible, and form what may be called a psycho-somatic whole. In this thesis it is with the physical or somatic mechanisms of adaptation that we are chiefly concerned, but at
no time can we afford to lose sight of the interdependence of psyche and soma.

Via the nervous system, the body carries out the orders given to it by the brain. The process does not end there, however, as the body has also to adapt itself to the level of activity demanded of it. For example, if intense muscular activity is required, the whole body becomes adapted, for the time being, to this purpose. All the metabolic processes must be speeded up, and many physiological adjustments made, in order to maintain the level of activity demanded. In running a hundred yards, for example, an oxygen debt is incurred, because the body is unable to completely adapt itself so suddenly to such a level of activity, and the necessary re-adjustments have to take place after the race. On the other hand, in an individual suffering from "effort syndrome" the co-ordination between body and mind is so disturbed that severe exertion is impossible. The failure of adaptation has affected both the soma and the psyche.

Under basal conditions, as in sleep, all the functions of the body are at their lowest ebb. The primitive part of the nervous system acts to maintain the vital functions, rather like a night-watchman; the parasympathetic, the more vegetative division of the autonomic nervous system, being predominant. The activity of the tissues is at the lowest level, the endocrine glands secrete the minimum amount of hormones necessary to maintain the internal environ-
ment and the metabolic processes, and the only demands on the powers of adaptation in health are those of the physical environment.

During the hours of wakefulness a very different state of affairs exists. The external environment not only influences the body directly, but also through the special senses, the impressions from which may profoundly influence the cerebral cortex by giving rise to emotion, or by causing it to make some direct demand on the body, such as muscular activity. By exercise of the will the cerebral cortex may also make any sort of demand on the body, independently of the impressions received from the outside world.

In order to ensure that the soma and the psyche work hand in hand at all times as a perfectly coordinated whole, it is obvious that a sensitive system must exist whereby the body may quickly adapt itself to the demands made upon it by the mind. One such adaptive mechanism, the sympathetic nervous system, is already well-known, particularly as a means of extremely rapid adaptation in an emergency. This mechanism is one which is only able to act for a short time at a high level of activity, though it can be over-active to a lesser degree for prolonged periods.

Should a situation which imposes stress of longer duration on the body require to be dealt with, it is now known that increased activity of the endocrine glands as well as of the sympathetic nervous
system is necessary, in order not only to maintain the constancy of the internal environment, but also to increase the activity of the metabolic processes and of the cells of the body to a level adequate to cope with the stress. It has recently been found that increased activity of the endocrine system may be caused, at least in one way, by the peripheral action of adrenaline in increasing the rate of utilisation of certain hormones in the tissues, which, by a mechanism which is fully described later, causes an increased supply of these hormones to meet the demand.

The main glands involved in stepping up the metabolic activities of the body to the level demanded are the adrenal cortex and the thyroid, under the control of the anterior pituitary. Evidence has been obtained that the adrenal cortex responds to the situations of daily life like a well-oiled machine, and that its activity declines to basal levels during sleep. This co-ordination between the nervous and endocrine systems has been found to be severely impaired or absent in mental disease, once again emphasising the indivisibility of the soma and the psyche and the fact that a disturbance in one must lead to a disturbance in the other. Similarly, endocrine dysfunction of the gonads, the adrenal, the thyroid, or the pituitary can cause mental disorder.

While it is apparent that both the mind and the body are capable of a remarkable degree of adaptation
to adverse mental or physical circumstances, it is equally evident that adaptation cannot be maintained indefinitely. There is a limit, which differs for every individual, after which adaptation breaks down. Whether this happens sooner or later clearly depends on the intensity of the strain which is imposed on the body or the mind, and the ability of the individual to adapt himself to it. For example, a man can only tolerate a job, or a life situation, which imposes an uncomfortable strain on his powers of adaptation, for a varying period, after which adaptation breaks down. Such a failure of adaptation might take the form of a psychoneurosis in one individual, but might equally well manifest itself as a peptic ulcer or hyperthyroidism in another. The results of failure of the adaptive powers of the mind are therefore not of purely psychiatric interest, and may be manifested in an almost entirely somatic way.

From the purely physical, or somatic, aspect the first step in the study of the mechanisms of non-specific adaptation was probably the realisation by Claud Bernard that the fundamental difference between the cold-blooded reptile and the warm-blooded mammal is the ability of the latter to maintain the internal environment of the body fluids, in which each individual cell must live, relatively constant in spite of even extreme changes in the external environment. Relative independence of the physical environment, which is probably found at its highest
level of development in man, clearly depends on this simple fact. It is also clear that this is predominantly an endocrine responsibility, and that the survival of the specialised cells of the body, which, by reason of their being specifically adapted to various special purposes have at the same time lost much of their adaptability, is secured by the creation of this constant environment which is necessary to their survival and function.

The maintenance of constant conditions in which the cells of the specialised organs can live and work is, however, but a relatively small part of the responsibilities of the endocrine glands, as the hormones which they secrete not only have a marked influence over the activity, functions, and health of the target organs upon which they exert their effects, but are also responsible for the supply of essential nutriments to them, and to the body as a whole. It would appear to be the case that in the absence of the anterior lobe of the pituitary gland all the endocrine functions except those which maintain the constancy of the internal environment are abolished, and that the latter is also somewhat impaired and unable to cope with adverse conditions. Under such conditions most of the active and adaptable, but non-vital, endocrine influences are in abeyance.

So far the non-specific adaptive mechanisms
have been considered only in relation to physiological adjustments, but the work of Hans Selye and many others has now made it clear that these mechanisms also play a vital and essential part in the production of non-specific resistance to all forms of severe bodily stress, and are largely responsible for survival under these conditions. In severe stress these endocrine mechanisms, especially the anterior pituitary and the adrenal cortex, do not only maintain the constancy of the internal environment of the body fluids within the limits compatible with survival, but also act so as to raise the resistance of the body to all forms of destructive agency with which it may come into contact, whether it be bacterial, physical, or of any other nature. It is by means of these mechanisms that the body is enabled to survive under extremely adverse conditions, and they are completely non-specific in their nature.

The range of action of the non-specific endocrine adaptive mechanisms is therefore very wide, as, though they are activated by the very slightest bodily activity, they are at the same time capable, by means of a maximal effort, of ensuring the survival of the body during severe stress of any sort. These endocrine mechanisms are, though of the utmost importance, but a part of the other non-specific adaptive mechanisms, and are co-ordinated with all the other physiological adjustments which take place in accordance with the needs of the body at any
moment. It is obvious that a very wide range of physiological adjustment to increased activity must be concerned in ensuring that the body is at all times perfectly adapted to the environment and to the task on hand, and that all the mechanisms of circulatory and respiratory regulation, of the autonomic nervous system, and a vast number of other major and minor adjustments, must also be included among the non-specific adaptive mechanisms, both under normal conditions and in stress. Indeed, it may be truly said that man is an agglomeration of adaptive mechanisms, so that he himself constitutes a perfectly co-ordinated adaptive mechanism.

It is therefore true that the non-specific adaptive mechanisms are the means whereby we are able to go anywhere in the world, endure untold physical hardship under the most adverse environmental conditions, resist the onslaughts of disease, trauma, and all other destructive agencies which we may encounter, and yet survive to tell the tale.

Turning briefly to a consideration of specific adaptation, it is at once obvious that man has not only an almost limitless capacity for specific adaptation to perform a specific task, but that everyone has acquired a vast number of specific adaptive mechanisms, such as speech, writing, reading, and so on. Such adaptive mechanisms almost always involve the intimate co-ordination of mind, body, nervous system, muscles, endocrine glands, and many other mechanisms.
In relation to purely somatic specific adaptation, apart from such phenomena as the development of a muscle through constant use, we come to a most important defence mechanism, the power of the body to acquire specific immunity to the attacks of pathogenic bacteria.

It is obvious that man, or indeed any other living species, would be extinct had the capacity to resist the onslaughts of pathogenic bacteria and viruses not been acquired to some extent during the evolutionary process. In consequence, we all possess some degree of natural immunity, particularly to diseases which have been endemic in the race for a long period, and at the same time have marked ability to acquire specific immunity when we come into contact with a pathogenic organism. The capacity to develop specific immunity depends upon a great many factors, which may be summed up as the two great factors of the virulence of the seed and the resistance of the soil. As would be expected from the general principles of adaptation, it is to the most virulent form of a pathogenic organism that the highest and the most lasting degree of immunity is developed, provided that the individual survives.

From the point of view of specific adaptation, and leaving aside questions of virulence and of the varying capacity of the body to become immune to different species of organism, it is possible to
regard any disease which is brought about by infection with bacteria, or viruses, as a manifestation of failure to become specifically adapted to resisting the attack of that particular organism without developing the disease which it causes. Thus the development of the disease may be called a partial failure of adaptation if recovery ensues, while death represents a complete failure of adaptation. A speedy recovery may be said to represent the accomplishment of specific adaptation after a slight set-back, especially if lasting immunity is acquired.

It is therefore correct to state that an individual who is immune to a specific organism is one who, because of acquired, active, or passive immunity, is specifically adapted to resist the attack of that organism on the body. On the other hand, in chronic disease specific adaptation has only been partly successful, and it is often the case that a certain amount of mutual adaptation between the host and the organism takes place, with the result that a sort of war of attrition is waged for many years. In the carrier state there is no doubt that there has been mutual adaptation, in this case without the development of chronic disease.

Specific adaptation to resist any pathogenic organism may therefore be developed so rapidly and to such a high degree that no disease results, may be sufficient to ensure a speedy recovery, or only
enough to keep the disease in check so that it becomes chronic.

It is evident that the development of a disease signifies that specific adaptation has been developed too slowly, or to an insufficient degree, or that the infection has been too virulent or the dose too large to be dealt with by the immunity mechanisms. It is, of course, true that human susceptibility to different diseases varies most widely, but this argument is still valid. Specific adaptation having failed to prevent the disease, it is clear that some means must exist whereby the survival of the patient is assured until such time as recovery or the final acquisition of a degree of specific immunity which is adequate to deal with the infection can take place.

There is no doubt that the requisite assistance in this situation is supplied by the non-specific adaptive mechanisms, particularly the anterior pituitary and the adrenal cortex. Non-specific adaptation, therefore, makes up for the failure of specific adaptation, and if it also fails death is the result.

During the course of a chronic disease it is clear that a considerable degree of specific adaptation has been acquired against the infection, and that, after a varying length of time, either cure or death will result. Just as in every other form of adaptation, there may finally come a day when the strain proves too much, and specific adaptation breaks down.
The result is once more the intervention of the non-specific adaptive mechanisms to attempt to save the situation, but in chronic disease the end is usually not far off, non-specific adaptation also fails, and death ensues.

There can be no doubt that the adaptability of man, or of any other living thing, is the most potent factor determining survival of the individual or of the species. If this argument is carried to its logical conclusion it becomes apparent that were any individual capable of completely adequate adaptation to any adverse circumstance which might occur, and of maintaining this state of perfect adaptation indefinitely, that individual would be immortal except in the event of accidental death. It is also possible to attribute much accidental death to failure of adaptation to the environment, as for example meeting an untimely end through inability to maintain adaptation to the fact that stepping into the street without taking the precaution of looking both ways is liable to be fatal.

It follows that while we are alive we must be constantly and automatically adapting ourselves to the continuously varying influences of all manner of environmental circumstance, whether affecting the internal or the external environment, whether chemical, physical, bacterial, mental, or of any other nature. It may be said, with truth, that to cease to adapt is to die, and that to die is to cease to adapt, for we must adapt continuously from the moment of conception.
to the moment of death. It is notable that it is to adverse circumstance that we are forced to adapt, and that if the environment is notably free from adverse circumstance we tend inevitably to retrogress instead of to progress. This truth was realised many years ago by Shakespeare, though certainly not in its present connection.

It may be felt that this discussion has been reduced to absurdity, but it has served to emphasise the complete universality of application of the concept of adaptation and the fundamental principles which govern it.

Although almost every branch of medical science is involved in the study of the adaptive processes, a major part lies in the field of endocrinology, with the difference that it is not so much with the normal relationships between the endocrine glands, but with their reactions to applied stress, that we are concerned here. In consequence it is necessary at the outset to review and to integrate much recent data concerning the adrenal cortex, the thyroid, and the anterior pituitary, before it is possible to consider the adaptive processes.
THE HORMONES OF THE ADRENAL CORTEX.

This short and inadequate review regarding the hormones of the adrenal cortex has been included for the purpose of providing an up-to-date background for the discussions which follow, and in order to draw attention to recent observations which seem to be of significance.

The preparation of the first satisfactory extract of the adrenal cortex by Swingle and Pfiffner in 1931 began a new era in adrenal physiology. Since then some twenty-eight or more steroid compounds have been isolated from the adrenal cortex, and the chemistry of these hormones of the cortex, and of the sex glands, has become an extremely complex branch of organic chemistry.

Only a few of these compounds have been found to be of any physiological importance, and only some of them have been synthesised; and, though these sterboids have been isolated from the gland, there is no proof that they are actually secreted in these forms by the gland during life. Vogt (1943) has shown that the amount of hormone contained in the blood of the adrenal vein of the anaesthetised dog is so great compared with the quantity of hormone which can be extracted from the adrenal cortex as to make it highly probable that the hormones are stored in the gland in the form of inactive precursors. By the methods used it was also found impossible to detect any quantity of the hormones in the peripheral blood, indicating that they vanish very quickly indeed in the tissues.
It is well known that those hormones of importance may be roughly divided into three groups. Firstly, those mainly concerned with carbohydrate metabolism, the sugar hormones or 11 oxysteroids, and comprising those compounds which, for brevity, have been named by Kendall compounds A, B, E, and F. Secondly, those which are mainly concerned with the control of the electrolyte balance of the body, the electrolyte-controlling and life-maintaining hormones; and thirdly, the androgenic hormones of the cortex, which affect sex characteristics and to some extent protein metabolism. There is good reason to believe that the electrolyte-controlling hormones are secreted by the zona glomerulosa, the sugar hormones by the zona fasciculata, and the androgens by the zona reticularis.

As Reichstein and Shoppee point out in their review (1943), the sum of the activities of all the crystalline compounds isolated from the gland is but a fraction of the total life-maintaining activity of the extract, the major portion of which remains in the mother liquors, from which the so-called "amorphous fraction" can be isolated. The hormones contained in this fraction, the composition and even the numbers of which are unknown, have very marked ability to maintain the electrolyte balance of the body, and therefore the life of the adrenalectomised animal.

The only hormone of the electrolyte-controlling group which is known and has been synthesised is
desoxycorticosterone, but the results of both chemical
and physiological investigations suggest that only
traces of this substance are to be found in the gland,
(Kendall 1948). Despite the extensive use of its
acetate in the treatment of Addison's disease, Selye
(1948), and several others have expressed doubt as to
whether this hormone is normally secreted by the cortex
in any quantity.

As desoxycorticosterone acetate, or DOCA, is
available in the pure state, it has been used as a
standard for the comparison of the life maintaining
potency of the various amorphous fractions which have
been isolated. These products have varied considerably,
that prepared by Grollman (1939) being found to have
about 100 times the potency of DOCA, while that of Wells
and Kendall (1940), from 2.5 to 5 times as potent, and
Kendall (1941) reported that from one to two microgrammes
per kilogramme would maintain an adrenalectomised dog.
Kendall's fraction was said to be free from any trace
of the crystalline sugar hormones, and Wells and Kendall
(1940a) found that even when doses of this fraction
several thousand times those which sufficed to maintain
the adrenalectomised animal in health were given to an
intact animal it did not cause a rise in the sodium or
a fall in the potassium of the blood, nor any other
apparent effect. As there is now no doubt that large
doses of the adrenocorticotropic hormone in man will
cause the same effects on the electrolytes as DOCA, it
is clear that this observation should now be regarded with grave suspicion. Hartman and Spoor (1940) prepared a fraction which had a specific effect on sodium alone, but further reports have not appeared. It is apparent from this brief survey that our ignorance of the composition and functions of the hormone or hormones of the cortex which control the body electrolytes via their influence on the renal tubular epithelium is very great indeed.

DOCA being readily available, its effects in man and in animals have been closely studied by many investigators. In the treatment of Addison's disease, though it has been of great use, it is now well recognised that over-dosage may result in excessive retention of salt and water, lack of potassium, oedema, cardiac failure, and hypertension, when given with excessive amounts of salt. This hormone acts almost wholly on electrolyte balance, any effects on carbohydrate and protein metabolism are probably mediated by its effects on the electrolytes.

It is now agreed that this hormone affords only partial replacement therapy, and that whole cortical extract is essential in conditions of stress.

There is complete agreement that in normal men or animals the administration of DOCA causes an increase in the sodium, the alkali reserve, and the volume of the blood, with a fall in the potassium and a relative decrease in the chlorides. The weight
increases and the potassium content of the tissues falls while the sodium rises.

It is firmly established that, if optimal amounts of sodium, potassium, and chloride are supplied to an adrenalectomised animal, such as the dog, it may be maintained for months in a comparatively normal state. This fact is one of great importance in relation to adrenal cortical physiology, as many previous investigators have omitted to allow for this factor in the interpretation of their results. Kendall (1948) has recently reviewed this aspect of adrenal physiology, and has pointed out that under these conditions renal function is almost normal, the absorption and metabolism of proteins, fats and carbohydrates is not seriously disturbed, and the animal appears normal. Similar results were obtained in the treatment of Addison's disease before the introduction of specific therapy, but, as in the animal, life was precarious because the slightest alteration of the intake of these elements or any form of stress was liable to produce a crisis.

The blood urea can be held to almost any desired level in such an animal by alterations of the salt intake, and Kendall believes that this phenomenon cannot be wholly explained by the low plasma volume and low blood pressure which results. It would seem that this contention is supported by the well recognised effects of lack or severe loss of sodium and chlorides on renal function in states other than adrenal insufficiency. He also emphasises strongly that the fundamental defect
in adrenal insufficiency is the loss of control of the transport of ions through cell membranes, and that until we discover the reason for this defect we will not be able to understand fully how the adrenal cortex governs the distribution of the body electrolytes.

Correction of the electrolyte imbalance which results from the absence of the adrenal cortex, by restoring the internal environment to normal, therefore corrects the results of the absence of the cortical hormones, but only to a low level. Even the use of DOCA is unsatisfactory, as the control is not labile, and the absence of the sugar hormones lowers the resistance of the body to stress. The correct view seems to be that, apart from the vital control of the electrolytes, the cortical hormones can be done without except under conditions of stress or when increased metabolic activity is required. In their absence the metabolic processes which they accelerate can proceed, but slowly and at a low level, and are incapable of being increased in response to increased needs.

It is clear that one remarkable fact emerges from this work - that, in the presence of the correct concentrations of electrolytes, the metabolic processes which are affected by the sugar hormones are still able to function. Therefore the electrolyte balance of the body must also have an effect on all the metabolic processes, as they are seriously upset by any gross disturbance of this balance. It is not clear, however, if disturbances of the electrolytes within physiological
limits have any effect on metabolism.

Those hormones of the cortex which have pronounced effects on carbohydrate metabolism, namely, compound A (11 dehydrocorticosterone), compound B (corticosterone), compound E or "cortisone" (17 hydroxy 11 dehydrocorticosterone), and compound F (17 hydroxy corticosterone), are the only crystalline hormones which have been found to be of importance so far.

Kendall (1942) has pointed out that the amounts of compounds A, B, E, and F, which can be isolated from the whole extract of the cortex are very small, and that the effect on carbohydrate metabolism of the whole extract is many times that which would be produced by the administration of that amount of these compounds which would be contained in the same amount of extract. He has produced evidence that this discrepancy is probably due to synergism between these compounds when they are actually secreted by the gland, and not to a further unknown compound or compounds.

It is, however, notable that a decrease in the amount of ascorbic acid in the cortex has been found to be a reliable and sensitive indication of the discharge of hormones from it, (Long 1947a). Though the evidence regarding the matter is somewhat controversial (Long 1947b) the large amount of this vitamin in the cortex has always suggested that it may play an important part in the formation of the hormones. Vogt (1948) found that no rise in the ascorbic acid content of the adrenal vein took place under conditions which cause the
secretion of large quantities of the cortical hormones, suggesting that the hormones may be combined with ascorbic acid under natural conditions. Though so far unconfirmed, Lowenstein and Zwemer (1946) claim to have isolated a new compound from the cortex which incorporates ascorbic acid in its molecule.

In this connection the recent empirical discovery by Lewin and Wassen (1949) that a simultaneous injection of ascorbic acid and DOCA, which has since been clearly shown by Le Vay and Loxton (1950) to be due to an \textit{in vivo} combination of the two substances in the circulation and not in the adrenal cortex, can produce an effect similar to that of compound E in rheumatoid arthritis, is clearly of great interest.

The above considerations justify re-emphasis of the statement that we still do not know the exact form in which the hormones are secreted by the gland \textit{in vivo}.

It is notable that the amorphous fraction, DOCA, and compounds A and B, in that order, have progressively less power to retain sodium in the body, while compounds E and F have been found, under certain conditions, to promote the excretion of both sodium and potassium. The action of compound E on the excretion of water and electrolytes is discussed later, as it is somewhat paradoxical. The metabolic activity of these hormones is in the reverse order, E and F being very active, B occupying an intermediate position affecting both metabolism and electrolyte balance, and DOCA and the amorphous fraction acting on electrolyte balance only.
These points are illustrated in Table I. It is now apparent that the chemical structure of the hormones determines their action on the electrolytes or the metabolic processes.

Kendall (1945) showed that compounds A and B can produce excessive deposition of fat in animals similar to that found in Cushing's syndrome, and Bergner (1943) has reported that compound A causes a marked reduction of the faecal fat excretion in the adrenalectomised animal and in two patients with Addison's disease.

Deposition of fat in the liver has been repeatedly observed not to occur in the adrenalectomised animal maintained in good condition with sodium chloride. This has been confirmed by Barnes et al. (1941), while Baker et al. (1948) found that ACTH will cause fatty infiltration of the liver in the rat. Hartman (1947) claimed to have found a new hormone of the cortex which will cause the deposition of fat in the liver, but no further report has been made.

There is no doubt that compounds E and F are very active in relation to the metabolism of carbohydrate. They antagonise the peripheral effects of insulin like the diabetogenic hormone of the anterior pituitary, and according to Golowick, Cori, and Slein (1947) both the pituitary and the adrenal hormones do this by inhibiting the hexokinase enzyme system.

The action of the sugar hormones in increasing the deposition of glycogen in the liver is so well established as to be used as a method of bio-assay of the excretion.
of corticoids in the urine (Venning, Hoffman & Browne-1944). The rise in the blood sugar produced by them was thought by Wells and Kendall (1940b), Wells (1940b), and by Long et al. (1940) to be probably due to the breakdown of protein to form glucose. Wells and Kendall used phloridzinised adrenalectomised rats, and came to the conclusion that such animals could manufacture carbohydrate from exogenous, but not from endogenous, protein. When compound E was given to these animals, however, it was found that the nitrogen excretion, in the absence of protein intake, was markedly raised. They therefore thought that endogenous protein was now being used to make glucose. Thorn et al. (1949) state that the latest view is that the extra glucose which is mobilised by these hormones is not derived from body protein, but rather by diverting amino-acid radicles to pyruvic acid and glucose. Ingle (1948) was unable to account for more than a small amount of glucose as coming from protein, and suggested that decreased utilisation of sugar is also a large factor in the production of a high blood sugar. Engel (1949) has produced evidence from experiments on nephrectomised animals that the action of cortical extract on protein depends upon the availability of glucose, as the rise in the blood urea which followed the administration of cortical extract to these animals was exaggerated by insulin hypoglycaemia and prevented by glucose. On the other hand Conn et al. (1948, 1949) have shown that the temporary diabetic state which can be produced by
large doses of ACTH in man is intimately connected with the disturbance of purine metabolism produced by the sugar hormones liberated. They also noted that the "diabetic state" bore no relation to the nitrogen excretion. It would appear that the origin of the glucose which is mobilised by these hormones is by no means clear and is, to say the least of it, controversial.

It is also of interest that the administration of compound E to a patient with Addison's disease and diabetes, maintained with DOCA and salt, but deprived of insulin and food for twenty-four hours, produced a very marked ketosis, glycosuria, and increased nitrogen excretion, even though very small doses of the hormone (Balfour and Sprague 1949) were given. This observation would seem of some interest in relation to the causation of diabetic ketosis, and is remarkably similar to the findings of Kendall (1945) in the partially depancreatissed, adrenalectomised dog.

ACTH, or compounds E or F, have been repeatedly shown in many species of animals to cause a fall in the lymphocyte and eosinophil counts, a rise in the polymorph count, and involution of the thymus and lymphoid tissue. In the rabbit these hormones have been reported to cause a rise in the antibody titre and gamma globulin as well, and have therefore been thought to act as part of the non-specific defence mechanism of the body by releasing stores of preformed antibody which...
are said to be contained in the lymphocytes, (Dougherty and White, 1944, 1945, 1947; White and Dougherty 1945, Chase, White and Dougherty 1946). These changes in the blood, with the exception of the gamma globulin, have been confirmed in man by the injection of compounds E, F, and ACTH. (Forsham and Thorn 1948, Hench et al. 1949a, Hill et al. 1948). In the rat, Li and Reinhardt (1947) found that pure ACTH caused a rise in the albumin fraction, but had no effect on the total or gamma globulins. Hench et al. (1949a) found that in man compound E corrected a reversed globulin ratio. Furthermore, the use of even huge doses of ACTH in man has failed to produce any effect on the gamma globulin or antibody titre (Forsham et al. 1948, Mason et al. 1948, Herbert and De Vries 1948, 1949, Sayers et al. 1949). In the cat, Thatcher et al. (1948) found that adrenalectomy has no effect on antibody production.

It would appear that the role of the adrenal cortex in immunity mechanisms is very problematical in man.

The lymphocyte counts in Addison's and Simmond's disease have been found to be, on the average, above normal, and in Cushing's Syndrome below normal, and it has been observed that the differential count in Addison's disease does not alter in severe stress. (De la Belze et al. 1946, Baez-Villasenor et al. 1943).

The percentage drop in the lymphocytes or the eosinophils from previous levels following conditions causing increased cortical secretion, or the adminis-
tration of ACTH, has been suggested as a test of cortical function. The increase in uric acid excretion which results from the administration of compounds E, F, or ACTH, is thought by Forsham and Thorn (1948) to be partly due to the breakdown of the nuclei of the lymphocytes, and as the uric acid of the blood also falls these hormones also appear to increase the uric acid clearance. Conn et al. (1949b) have reported that the intravenous injection of reduced glutathione causes a dramatic transitory reversal of all the effects of ACTH on the blood cells and on carbohydrate metabolism. This remarkable finding has not been confirmed or elucidated so far.

Wells (1940a) showed clearly that compound B, and especially compound E, have a marked inhibitory effect on the growth of the experimental animal. This apparent antagonism between the growth and the sugar hormones has also been found to hold for ACTH in respect of bone, cartilage, and marrow growth by Baker and Ingle (1948), and the evidence regarding its retarding influence on somatic growth as a whole has been summarised by Li and Evans (1947). The many ways in which these two pituitary hormones oppose each other are further illustrated in Table I.

Taubenhaus and Amromin (1949) have recently reported that in the experimental animal the administration of DOCA causes accelerated formation of granulation tissue, a marked fibroblast response, and laying down of collagen. Ragan et al. (1949) have found that
the administration of ACTH in man causes marked delay in wound healing because of tardy formation of granulation tissue and laying down of collagen, and have found (1949) that compound E has the same effect in the rat. It is significant that the same defect is found in cases of Cushing's syndrome.

The androgenic hormones of the cortex exert effects similar to the testicular androgens, such as testosterone, produce masculinisation in the female and virilism in the male, as in the adreno-genital syndrome, have a definite protein anabolic effect, very slight power to retain sodium, and do not appear, so far, to play such a prominent part in the adaptive processes as the electrolyte-controlling and sugar hormones. In the female these hormones are mainly from the cortex, but in the male one-third is thought to be of testicular origin. It is not improbable, however, that abnormalities of secretion of these hormones may play a part in the causation of certain diseases which are associated with a marked sex incidence. For example, in anklyosing spondylitis, which is almost exclusively a male disease, Davison et al. (1947, 1949) have found that the 17-ketosteroid excretion is increased, that X-ray therapy causes a further rise followed by a fall to lower levels accompanied by clinical improvement, and that the administration of pregnenolone causes marked and striking relief accompanied by a return of the 17-ketosteroid excretion to normal. Gout would also seem to be
associated with cortical dysfunction, as Robinson et al. (1948) have found that ACTH will abort an attack, and Wolfson et al. (1949) have reported that gout is characterised by abnormally low 17 ketosteroid excretion with normal androgenic function, and suggested that an abnormal steroid may be secreted by the cortex in this affliction.

Table I is included in order to supplement this brief summary.
<table>
<thead>
<tr>
<th>EFFECTS ON</th>
<th>CORTICAL HORMONES IN MAN OR RAT</th>
<th>ACTH IN RAT 1 dose of 25 mgms.</th>
<th>ACTH IN RAT 100 mgms. for 8 or more days</th>
<th>GROWTH HORMONES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sugar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot; sodium</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>&quot; potassium</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>&quot; ph.</td>
<td>0 mg</td>
<td>0 mg</td>
<td>0 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>&quot; uric acid</td>
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<td>0 mg</td>
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<td>0 mg</td>
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<tr>
<td>&quot; alk. phosphatase</td>
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<td>0 mg</td>
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<tr>
<td>&quot; inorganic phosphate</td>
<td>0 mg</td>
<td>0 mg</td>
<td>0 mg</td>
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</tr>
<tr>
<td>&quot; eosin. &amp; lymphos.</td>
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<td>0 mg</td>
<td>0 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>&quot; neutrophils</td>
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<td>0 mg</td>
<td>0 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>Urinary sodium</td>
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<td>0 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>&quot; potassium</td>
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<td>0 mg</td>
<td>0 mg</td>
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<tr>
<td>&quot; nitrogen</td>
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<td>&quot; calcium</td>
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<tr>
<td>&quot; inorganic phosphate</td>
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<td>0 mg</td>
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</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sodium retention</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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</tr>
<tr>
<td>Pituitary inhibition</td>
<td>100%</td>
<td>100%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Resistance to stress and work capacity</td>
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<td>0%</td>
<td>0%</td>
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</tr>
<tr>
<td>Liver glycogen</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Liver and body fat</td>
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<td>Absorption fat</td>
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<td>Insulin resistance</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>Thymus</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Body and bone growth</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>lymphoid tissue</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Wound healing, fibroblastic proliferation</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Connective tissue, skin, sebaceous glands</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Legend:

- ↑ = increase
- ↓ = decrease
- 0 = no effect
- m = marked effect
- s = slight effect
- x = no data
- 1 = probably
- - = not applicable

*Note: The effects on electrolytes are not shown in the table.*

(1) Any effects of DOCA on the metabolic processes are probably assisted by its action on the electrolytes.

(2) The effects of these hormones on the electrolytes are somewhat paradoxical, and are referred to in the text. In intact animal or man the initial doses only cause a rise in sodium excretion. ACTH acts in a similar manner.

(3) These effects of DOCA in the intact animal are probably due to pituitary inhibition, resulting in a deficiency of sugar hormones.
PITUITARY-ADRENAL-THYROID INTER-RELATIONSHIPS.

The Secretion of ACTH

Before proceeding further it is necessary to consider the available evidence regarding the interrelationships which exist between the anterior pituitary, the adrenal cortex, and the thyroid gland.

Though it appears to be generally believed that the adrenocorticotrophic hormone is secreted by the basophil cells of the anterior pituitary, this question is by no means settled, and has recently been discussed by Albright (1948). On the other hand, as it has become firmly established that the anterior pituitary profoundly influences the size and function of the adrenal cortex and that the production of ACTH is dependent on the concentration of the cortical hormones in the circulating blood, the question of exactly what cells secrete ACTH is not really pertinent to the present discussion.

Li (1948) has shown that pure ACTH is a heat-stable protein with a molecular weight of about 20,000. It was found that peptic digestion of the hormone did not destroy its activity, which was still present in a peptide with a molecular weight of about 1,200. Morris and Morris (1950) have also isolated this peptide, and report that its association with the protein is apparently reversible. Luft et al (1949) and Hakanson and Luft (1949) have shown that the peptide has the same clinical effects as ACTH on rheumatoid arthritis.
Sayers and Sayers (1948) have expressed the opinion that ACTH may act as a catalyst in the transformation of the adrenal cholesterol and ascorbic acid into hormones.

Sayers and Sayers (1947) (1948) have suggested that any cause of increased demand for, or increased utilisation of, the cortical hormones in the tissues causes a fall in the concentration of these hormones in the blood, thus releasing the inhibition of the pituitary and allowing it to secrete more ACTH, with the result that the cortex secretes more hormones to supply the demand. They have, therefore, added the factor of tissue utilisation of the hormones in the control of the secretion of the hormones of the cortex. Though there is no proof that the cortical hormones are actually used or inactivated in the tissues in accordance with metabolic requirements, the views of Sayers and Sayers seem to the author to be very logical indeed, as there can be no doubt that it is for the purpose of supplying the tissues of the body with hormones that the endocrine glands exist at all. Some support is provided by the finding of Vogt (1943) that the hormones disappear very rapidly indeed from the circulation.

The evidence for this self-controlling mechanism, which is similar to that which has been found to control the thyroid and the gonads and closely resembles a thermostat, is very firmly established, as is the
observation that large doses of cortical hormones cause atrophy of the cortex because of inhibition of the production of ACTH, just as atrophy follows hypophysectomy because of absence of ACTH.
The Pituitary-Adrenal Relationships.

The isolation and close study of the properties of the pure hormones has shown that the matter is not quite so simple as would appear. Sayers and Sayers (1947) investigated the power of the various pure hormones to inhibit the production of ACTH by the pituitary in the rat. They showed clearly that the power of a hormone to control the electrolytes is in inverse relationship to its power to inhibit the production of ACTH and its metabolic activity. Though DOCA had a marked effect on the electrolyte balance, it had little power to inhibit the production of ACTH. Compounds E and F, on the other hand, had little or no influence over the electrolyte balance, but very marked power to inhibit the production of ACTH, and these compounds possess very great metabolic activity. Compound B was found to occupy an intermediate position, and it is very probable that Compound A also does so. Thorn et al. (1949) have stated that Compound E has about one-thirtieth of the power of DOCA to retain sodium, so that large doses are required to maintain a patient with complete adrenal insufficiency.

This work at once leads one to suspect that, while the elaboration of the sugar hormones must be strictly under pituitary control in the rat, forming a labile and adaptable system well suited to the ever-changing demands of the metabolic activities of the body, the elaboration of the electrolyte-controlling
hormones cannot be to any extent under pituitary control. If they were, it is obvious that the secretion of the electrolyte-controlling hormones could be very considerably in excess before they would inhibit the production of ACTH. The secretion of these hormones must, therefore, be controlled in some other way.

Swann (1940) in a review of the relationship between the anterior pituitary and the adrenal cortex, expressed the opinion that the evidence available at that time was strongly in favour of the view that the electrolyte-controlling hormones of the cortex are secreted by the cells of the zona glomerulosa, or outer zone of the gland, and are only slightly under pituitary control, and that the sugar hormones are secreted by the zona fasciculata, or middle zone, and are under strict pituitary control. He emphasised that while death invariably resulted from removal of the adrenals because of the disturbance of the electrolyte balance, the removal of the anterior pituitary was not fatal, and had not been shown to cause any disturbance of the electrolytes, the only defect being an impairment of the ability to excrete excess water, and furthermore, that the zona fasciculata atrophied after removal of the pituitary, while the zona glomerulosa did not.

Since then Swann's views have received the most striking confirmation. Sarason (1943a) showed that the atrophy following hypophysectomy in the rat was limited
to the fasciculata, and that atrophy of the zona glomerulosa as well could be produced by the administration of DOCA, which, when administered to the intact animal, produced selective atrophy of the zona glomerulosa alone. Carnes et al. (1941) using large doses of DOCA, produced atrophy of both the fasciculata and the glomerulosa, which was particularly striking in the latter, and numerous other observers, notably Selye, have noted adrenal atrophy as a result of the administration of DOCA. Deane and Greep (1946), confirmed that hypophysectomy in the rat produced selective atrophy of the zona fasciculata alone, and produced cytochemical evidence of cessation of hormone production there. Greep and Deane (1947) confirmed that small doses of DOCA produced atrophy and cessation of hormone production in the zona glomerulosa. Ingle et al. (1946) reported that while the administration of ACTH to the rat produced all the phenomena associated with the secretion of the sugar hormones, it had no significant effect on the electrolyte balance, and it has become firmly established that the atrophy of the fasciculata which follows hypophysectomy can be restored by ACTH, and can be used as a means of biological assay of the hormone.

Knowlton et al. (1946) found that the selective atrophy of the glomerulosa which follows the administration of DOCA was prevented by sodium restriction, and incidentally the renal lesions which were produced by the hormone were also prevented. Finally, Deane,
Shaw, and Greep (1948) showed conclusively that severe sodium restriction produced hypertrophy of the zona glomerulosa alone in both normal and hypophysectomised rats, and Bergner and Deane (1948), showed that the administration of ACTH had a powerful effect in stimulating the zona fasciculata, but had no effect on the zona glomerulosa.

The evidence that the electrolyte-controlling hormones of the zona glomerulosa are not under pituitary control in the rat is therefore quite conclusive, and as hypophysectomy has not been shown to have any effect on electrolyte balance in the dog (Swann 1940), it would appear that it is also the case in the dog.

Since purified ACTH became available in larger quantities it has been used in a number of studies in man, and in the treatment of rheumatic and other diseases. The most comprehensive study was by Forsham and Thorn (1948) where it was stated clearly that the hormone was free from any trace of gonadotrophic or thyrotrophic hormones, contained a variable amount of pituitrin, and was not a homogeneous substance. The same preparation (Armour) has been used by other recent investigators. Forsham and Thorn ruled out the possible effect of pituitrin, but though electrophoretically pure ACTH has been used in animal experiments it has not yet been used in man. Bergner and Deane (1948) used the Armour product in the rat, and found that it had no effect on the zona glomerulosa. As this product is derived from hog
pituitaries there is also a possibility of a species difference in the hormone, though the evidence suggests that this is most unlikely.

Forsham and Thorm showed that, in normal man, a single injection of ACTH produced increased excretion of sodium, potassium, and uric acid, a marked fall in the lymphocytes and eosinophils, and a rise in the polymorphs, these effects being maximal in about four hours. A normal response was obtained in a patient with no thymus and no spleen. Subjects suffering from Addison's disease showed no response, but an injection of compound F produced a more marked response than normal, while compound A, DOCA, and testosterone were shown to have no such effects. From these results it is clear that a single injection of ACTH produces effects characteristic of the secretion of the sugar hormones.

When the injections were prolonged over several days the excretion of 17 ketosteroids, corticoids, phosphates, urates, uric acid, and potassium in the urine increased, and sodium chloride decreased. In the blood the sugar, sodium and CO₂ combining power increased, while potassium and inorganic phosphate, and the eosinophil and lymphocyte counts, decreased. In the tissues intra-cellular sodium increased, and potassium decreased. A diuresis followed cessation of the administration of the hormone. A similar result was obtained by Prunty et al (1949), and more prolonged administration by Hench et al (1949) in the
treatment of rheumatoid arthritis showed the same electrolyte changes plus a rise in the blood pressure in one case. McAlpine et al. (1948) produced sodium retention and glycosuria by the administration of large quantities of ACTH within 24 hours. It is notable that these changes in the electrolytes are similar to those produced by the administration of DOCA. Conn et al. (1948) (1949) produced a temporary diabetic state in man by the use of large doses of ACTH, and pointed out that, in addition to the above, the blood uric acid and glutathione are depressed, while the excretion of uric acid is markedly increased. This temporary diabetic state was found to be somewhat insulin resistant.

The repeated demonstration that in man ACTH can cause increased secretion of all the hormones of the adrenal cortex, and therefore stimulation of all its known functions, has resulted in the prevalence of the view that all the functions of the cortex are under pituitary control in man. Though it was formerly thought that there might be a separate pituitary hormone responsible for the control of each of the three groups of hormones which are secreted by the adrenal cortex, it is now thought that there is most likely to be only one, which stimulates the production of all.

Closer analysis of the evidence for this concept of one adrenocorticotropic hormone exposes a very probable fallacy, which has been brought about by the use of doses of ACTH, which must be grossly unphysiological.
Forsham and Thorn (1948) showed clearly that a single dose of ACTH produced all the effects which have been established to be characteristic of the sugar hormones within a few hours, including an increase in the rate of excretion of sodium and potassium. It was only after some days of continuous administration that salt and water retention became notable. It is possible that the effect of an increase in the secretion of the electrolyte-controlling hormones would not become evident for some time, but in view of the very prompt response of the cortex by production of the sugar hormones it is clear that, even if the production of both types of hormone was simultaneously increased, the response in respect of the sugar hormones was much more immediate and much greater than that of the electrolyte controlling hormones. Only on prolonged administration does salt and water retention appear, while the hypersecretion of the sugar and the sex hormones of the cortex continues unabated.

This work, therefore, gives a definite impression that the secretion of the sugar hormones is much more easily increased by ACTH than that of the electrolyte controlling hormones, and that the initial response is on the part of the sugar hormones alone. That this should be so seems quite logical, because, as the sugar hormones are intimately concerned in many aspects of metabolic activity, the manufacture of these hormones
must be capable of being varied rapidly in accordance with requirements. To fulfil their functions the secretion of these hormones in man, as in the rat, must be under strict pituitary control. On the other hand, it appears that only prolonged over-activity by the pituitary can affect the secretion of the electrolyte-controlling hormones, activity which must result in simultaneous secretion of very great quantities of sugar hormones.

Certain cases of Cushing's syndrome have been reported, most recently by Kepler et al. (1948), in which the electrolyte balance has been found to be disturbed in the same manner as by prolonged administration of ACTH or DOCA. It is, however, significant that such cases are not common, and that both in these cases and in those in which there is no such electrolyte disturbance the main symptoms are clearly referable to over-production of the sugar or the sex hormones or both.

These rare cases would appear to correspond to the effects of the doses of ACTH which are in use at the present time. The secretion of the electrolyte-controlling hormones being relatively insensitive to the action of ACTH compared to the sugar hormones, an excessive amount of the latter must inevitably be secreted at the same time.

From this point of view it is obvious that the pituitary cannot possibly be in control of the secretion of the electrolyte-controlling hormones in man, and
that the dosage of ACTH which has so far been used in these experiments and in the treatment of rheumatic disease must be greatly in excess of the amount of hormone which is normally secreted by the anterior pituitary. There can be no doubt that, if the human pituitary normally secreted such quantities of the hormone, the whole human race would inevitably be afflicted with Cushing's syndrome.

The fact that it is possible for the anterior pituitary to take a hand in the control of the electrolytes in man may simply be a consequence of the pre-eminent position of man in the evolutionary scale, and constitute a further safeguard of the internal environment under conditions of stress, when extra amounts of electrolyte-controlling hormones as well as sugar hormones may be necessary.

Mason et al. (1948) did not find that prolonged administration of ACTH produced sodium retention in man. As they were using a pure ACTH (Li's preparation) this would suggest that some other hormone in the Armour product might be responsible. However, Albright et al. (1948) have shown that both forms of ACTH have a similar effect on sodium excretion in man. The ACTH peptide has also been found to act in this way (Luft et al. 1949, Hakanson and Luft 1949).

The view that only the sugar and sex hormones are under complete pituitary control in man is also supported by the clinical evidence. It is well established that the person suffering from failure of the anterior
pituitary gland does not come under medical care because of an Addisonian crisis, but because of the effects of lack of the sugar and the androgenic hormones of the cortex and failure of the thyroid gland. Though Stephens (1940) has shown that there is some impairment of electrolyte balance in hypopituitarism, a finding which has been repeatedly confirmed, it is notable that the assistance of the laboratory has to be sought in order to demonstrate this abnormality. It is true that some cases have been found to lose all control of the electrolytes, but close perusal of the literature reveals that these patients have usually been treated with thyroid extract, a procedure which is well known to precipitate an Addisonian crisis in this disorder. Others have been treated with DOCA, which must clearly have had the effect of suppressing the electrolyte-controlling functions of the cortex, which must still be intact. Furthermore, as compounds A and B have been shown to have quite an appreciable effect on electrolyte balance, it is possible that the loss of these factors, which have their main action on the metabolic processes, may be responsible for the slight degree of loss of control of electrolyte balance. The absence of a possible trophic effect of ACTH on the zona glomerulosa in man may also be a factor. The fact remains, however, that the degree of impairment of electrolyte control in these cases is slight.

This view is well supported by the case of hypopituitarism which was studied by Cluxon, Bennet, and
Kepler (1948). They found no serious disturbance of the electrolytes, and at postmortem found that while the zona fasciculata was markedly shrunken the zona glomerulosa was prominent and contained plenty of lipoids. This is the only case which has been found in the literature in which a careful histological examination has been done, and in which there is a good microphotograph. That the excessive secretion of ACTH in stress may cause hypersecretion of the electrolyte-controlling hormones is also supported by the recent observation of Wilkinson et al. (1949) that salt and water retention follows surgical operations in man.

It is well established that the hypophysectomised or the adrenalectomised animal cannot excrete excess water normally, and is in consequence very susceptible to water intoxication. This fact is the basis for the water test for adrenal insufficiency devised by Robinson, Power, and Kepler (1941). It is significant that this test has been found by Levy et al. (1946) to be also positive in hypopituitarism, anorexia nervosa, and hyperthyroidism. In this connection the finding of Eversole, Gaunt, and Kendall (1942) that in the adrenalectomised animal DOCA and the amorphous fraction were less effective in protecting against water intoxication than whole cortical extract, Compound E was at least three times as effective as DOCA, assumes added significance. It would appear that the sugar hormones are concerned in the excretion of water, and that the
electrolyte-controlling hormones play little part in the excretion of water. This point is discussed more fully elsewhere.

Thyroid extract has been repeatedly shown to cause hypertrophy of the adrenal cortex in the experimental animal, and Davis and Creep (1947) have carried out a careful and highly significant investigation into the nature of this phenomenon in the rat.

Thyroidectomy or thiouracil treatment causes a progressive decrease in the cytochemical signs of activity in the zona fasciculata and infundibulum of the adrenal gland. The zona glomerulosa was also affected by thyroidectomy, as the signs of activity showed a tendency to increase, but the significance of this change is doubtful because the zona glomerulosa was removed. Thiouracil treatment quickly produces exhaustion in the zona glomerulosa, but smaller doses of thiouracil this exhaustion could be reversed. The interpretation of these results is also not clear.

The increase in the zona glomerulosa is also due to adrenal feeding under a market condition. The role of the zona fasciculata in this case is not completely understood.
Thyroid-Adrenal Relationships, and their influence on the balance of water and electrolytes.

In discussion of the pituitary-adrenal relationships the role of the thyroid gland is commonly overlooked. A relationship between the thyroid and the adrenal cortex has often been postulated, but it is only very recently that the nature of this relationship is becoming clear, not only in respect of the metabolic functions of the sugar and the thyroid hormones, but also in relation to the balance of water and electrolytes.

Thyroid extract has been repeatedly shown to cause hypertrophy of the adrenal cortex in the experimental animal, and Deane and Greep (1947) have carried out a careful and highly significant investigation into the nature of this phenomenon in the rat.

Thyroidectomy or thiouracil treatment caused a progressive decrease in the cytochemical signs of activity in the zona fasciculata and involution of the zone. The zona glomerulosa was also affected by thyroidectomy, as the signs of activity showed a tendency to increase, but the significance of this change is doubtful because the parathyroids were also removed. Thiouracil treatment caused exhaustion of the zona glomerulosa, but smaller doses showed that this exhaustion could be recovered from in time. The interpretation of this effect is also not clear.

The induction of a hyper-thyroid state by thyroid feeding caused a marked increase in the activity of the zona fasciculata, with widening of the zone, which
eventually proceeded to exhaustion. The zona glomerulosa became thinner, and cytochemical evidence of activity eventually ceased. This change is more indicative of depression of the zone than of stimulation to the point of exhaustion.

These observations are surprisingly in accord with and Daughaday et al (1948), the results of Talbot et al. (1947) who found that the urinary excretion of corticoids was either normal, increased, or markedly decreased in human hyperthyroidism. In some cases, especially in a thyroid crisis, the level approached that found in adrenal or pituitary insufficiency. In myxoedema the corticoid excretion was low, and was increased by treatment with thyroid extract.

The involution of the cortex caused by thiouracil has also been observed by Baumann and Marine (1945) and by Zarrow and Money (1949) who also observed that the adrenal cortex in the cretinoid rat was very small. Owing to the difference in size, it is difficult to determine the relative magnitude of the dosage used in rats, but it would appear to be much greater than that used in man.

Gaunt et al. (1944) showed that the administration of thyroxine to the rat produced an increased diuretic response to water, increased resistance to water intoxication, and adrenal hypertrophy. They also noted that an excessive dose of water caused a reduction in the cholesterol content of the gland, a phenomenon which is now well-known to indicate that there has been an abrupt increase in hormone output, mainly from the
fasciculata, which is relatively much larger than the glomerulosa. On removal of the adrenals these animals were found to be just as susceptible to water intoxication as normal adrenalectomised rats.

In man thyroid extract is well-known to cause a diuresis in both normal and in myxoedematous subjects, especially in the latter, and Blotner and Cutler (1941) have reported that thyroidectomy in man markedly reduces the polyuria and polydipsia in diabetes insipidus, though others do not agree with this view. Certainly this observation is in line with animal experiments in which a similar result has been repeatedly observed. Byrom (1933), in a well controlled balance experiment, found that in normal man an intravenous injection of thyroxine produced a marked rise in the excretion of sodium, potassium, nitrogen, and water. This result is remarkably similar to that which follows the administration of a single dose of ACTH, though somewhat more prolonged.

On the other hand, Levy et al. (1946) found that the water excretion test for adrenal insufficiency was not only positive in hypopituitarism, but also in hyperthyroidism. In conjunction with the data which has been reviewed above it is clear that hyperthyroidism may be associated with either hypertrophy or exhaustion of the fasciculata, and lack or excess of sugar hormones, so that the presence of excess of thyroxine may not cause a diuresis or increased capacity to excrete water, but will have the reverse effect if the zona fasciculata is exhausted.
The apparent relationship between the thyroid and the zona fasciculata can best be explained by application of the concept of increased tissue utilisation of cortical hormones suggested by Sayers and Sayers (1948).

It seems reasonable, therefore, to suggest that the increase in the rate of tissue metabolism caused by the secretion of more thyroxine should necessitate a concomitant increase in the supply of sugar hormones. In excess it is clear that thyroxine could produce hypertrophy and finally exhaustion of the zona fasciculata, as appears to be the case in hyperthyroidism.

This concept is supported by the observation of Koelsche and Kendall (1935) that thyroid increased the requirements of the adrenalectomised animal for cortical extract, and Wells and Kendall (1940b) and Wells and Chapman (1940) have shown clearly that in the hypophysectomised phloridzinised rat the administration of thyroxine or thyrotrophic hormone was necessary as well as compound E before the excretion of glucose and nitrogen could be made to equal that of the intact phloridzinised animal.

Under normal conditions it seems probable that thyroxine and the sugar hormones work in partnership in their metabolic activities. The sensitivity of the Addisonian patient to cold would support this concept.

Further evidence which has been obtained by Reiss
et al. (1949) and Soffer et al. (1947) is very strongly in favour of a most intimate relationship between these hormones. It is not discussed here because it would be somewhat out of its context, and is dealt with in the section regarding the psycho-somatic links.

Several authorities have previously remarked on the various points of similarity between hyperthyroidism and adrenal insufficiency, and it now appears that this clinical observation has been provided with good experimental backing.

In the myxoedematous subject the diuretic action of thyroid extract has been popularly supposed to be due to the action of the hormone in increasing the metabolic activity of the cells of the renal tubules, in common with the rest of the body. That some such action should take place seems most probable, but there is no doubt from the above that the stimulation of the zona fasciculata and a great increase in the secretion of the sugar hormones, which were not needed in any great quantity owing to the low level of metabolic activity, must also play a part which is very likely to be by far the major one. The deficiency of the sugar hormones produced by the low metabolic rate may also play a part in allowing the retention of excessive amounts of fluid in the body in myxoedema.

While the data which has been reviewed above appears to provide a satisfactory explanation for
the action of thyroxine in promoting the excretion of water, it does not explain the action of this hormone on electrolyte balance.

It is a well substantiated observation that the administration of thyroid to a patient suffering from pituitary insufficiency is liable to cause the onset of an Addisonian crisis, and that a thyroid crisis is remarkably similar to an Addisonian crisis in many ways. As good reasons have been given for the belief that the zona glomerulosa is intact in the patient with hypopituitarism, it would appear that the thyroid hormone is capable of having an effect on the functions of this zone of the adrenal cortex. Whether this action is indirect, so that thyroxine acts on the kidney to promote the excretion of sodium, or directly on the zone itself, is not clear, but this evidence certainly indicates that the influence of the thyroid on electrolyte balance can be considerable.

It would appear that in myxoedema the zona fasciculata is likely to be dormant; in hyperthyroidism, hypertrophied or exhausted, especially in a crisis; and in hypopituitarism atrophic. In all three conditions there is lack of sugar hormones from one reason or the other. In hyperthyroidism there is excess of the endogenous thyroid hormone, and there is excessive loss of salt and water in a crisis, while the administration of thyroid extract to both myxoedema and hypopituitarism tends to cause excessive loss of salt and water.
Byrom (1933) showed that a dose of intravenous thyroxine given to a myxoedematous patient caused very marked loss of both water and salt, with relative retention of potassium, which persisted for some days. In a normal subject, on the other hand, more potassium was lost than sodium, and the effect was not as marked. Though there does not appear to be any data on this point, it seems likely that thyroid extract will cause a similar loss of salt and water in the patient with pituitary insufficiency, but while in myxoedema the zona fasciculata is only dormant, here it is atrophic. The secretion of the sugar hormones is probably capable of increasing to normal within a fairly short time in myxoedema, so that the hormonal imbalance is of short duration, and so, incidentally, is the loss of salt and water.

On the other hand, there is slight impairment of the control of the electrolytes in hypopituitarism, and it is possible that the addition of thyroid extract is enough to tip the balance the wrong way. In myxoedema there is an excessive amount of retained salt and water just waiting to be excreted, so that the similarity of the hormonal imbalance produced in the two conditions may not be of significance. The evidence suggests, however, that excess of thyroxine in the presence of deficiency of the sugar hormones will result in excessive loss of salt and water. Though it is not possible to rule out a direct action of thyroxine on the kidney, it may be significant that Deand and
Greep (1947) noted changes in the zona glomerulosa as a result of thyroid feeding which were indicative of depression of the zone. It is clear that if thyroxine promoted excretion of sodium by direct action on the kidney the zona glomerulosa should tend to hypertrophy, and not atrophy, so that a direct depressant effect on the zone is a possibility.

In general, it appears that the influence of the thyroid on water and electrolytes under normal conditions is closely allied with its effects on metabolism and its apparent partnership with the zona fasciculata. It seems unlikely to be directly concerned under normal conditions, and to be more of the nature of a maintenance influence. The possibility of an effect on the zone glomerulosa is perhaps one way in which the pituitary may exert some influence on the balance of the electrolytes, but much more evidence is necessary before the true relationship becomes clear.

The probable relationships between these glands are illustrated in Fig. 1. It will be readily seen that there are really four main components - the tissue cells, the pituitary, the zona fasciculata, and the thyroid - and that this system is ideally adapted to supply exactly the amount of the hormones required.
Fig. 1.

Pituitary-Adrenal-Thyroid Relationships.

- Increased tissue oxidation for any reason whatever
- Increased utilisation thyroxine
- Synergism between these hormones
- Increased utilisation sugar hormones
- Release of pituitary inhibition according to rate of utilisation
- Anterior Pituitary
- Thyrotrophic hormone
- Thyroid gland
- Some direct reciprocal relationship?
- Zona fasciculata of Adrenal cortex
- Thyroxine
- Synergism
- Sugar hormones
- Increased demands for hormones in the tissues satisfied
GLUTATHIONE AND ITS RELATIONSHIP TO THE ENDOCRINE SYSTEM.

Though the tripeptide glutathione has been known for many years to be a constituent of the blood and the tissues, and to be found in particularly high concentration in the adrenal cortex and the thymus, the physiological role of this substance is only beginning to be elucidated. Very briefly, the glutathione of the blood exists almost entirely within the red cells, the bulk of it being in the reduced form which, by virtue of its sulph-hydryl group, may play a part in many enzyme systems.

Leech and Bailey (1945) showed that the diabetogenic substance, alloxan, also causes a marked decrease in the reduced glutathione of the blood. Acting on the hypothesis that its diabetogenic action might be concerned with inactivation of enzyme systems which require sulph-hydryl groups in the pancreatic islets and elsewhere, Lazarow (1946, 1947) found that the injection of glutathione, cysteine, or B.A.L., just before the alloxan prevented the production of diabetes. Even five minutes after the alloxan these substances had no inhibitory effect. He also found that ascorbic acid potentiated the diabetogenic affect of alloxan, a finding which may be related to the report by Prunty and Vass (1943) that large doses of ascorbic acid cause a reduction of the reduced glutathione of the blood in man.
Lazarow, Patterson and Levy (1948) have adduced further in vitro evidence that the protective action of cysteine may be due to its ability to reduce alloxan to dialuric acid, and to retard the opposite change. This substance, which is roughly midway between alloxan and uric acid, is thought by Bruckmann and Wertheimer (1947) not to be diabetogenic per se, but because it can be converted into alloxan in the body. Lazarow et al also found that reduced glutathione converts alloxan into another unspecified compound.

By feeding rabbits on a diet lacking in methionine and cysteine, thus reducing the blood glutathione to about half the normal, Griffiths (1948) found that the injection of a quantity of uric acid intraperitoneally resulted in changes in the blood sugar analogous to those which follow a dose of alloxan.

This work would appear to suggest that the diabetogenic action of alloxan is due to its effect on the availability of sulph-hydryl groups, and that the production of alloxan or similar substances from uric or dialuric acid may play a part in the causation of human diabetes. That this cannot be the whole story seems clear from the work of Bruckmann and Wertheimer (1947), who found that the non-diabetogenic substance, ninhydrin, had about twice the power of alloxan to lower the blood glutathione, and that several other non-diabetogenic derivatives of alloxan also lowered the blood glutathione.
Glutathione has become of great interest recently from a totally different aspect. In a series of investigations in which a temporary diabetic state was produced in man by means of very large doses of ACTH, Conn et al (1948, 1949a, 1949b) have shown that the hyperglycaemia, lowered renal threshold for sugar, and glycosuria, which is produced, is closely associated with a marked fall in the reduced glutathione of the blood and a marked increase in the excretion of uric acid. The administration of reduced glutathione intravenously brings about a dramatic reversal of these changes (1949b). The hyperglycaemia, glycosuria, and the lowered renal threshold produced by ACTH are abolished for some hours, and the changes in the peripheral blood cells are also temporarily reversed. As the cessation of the loss of glucose in the urine was not associated with a rise in the blood glucose, it was deduced that the rate of utilisation of sugar in the tissues was increased. As the renal threshold for glucose also rose, it was thought that the glutathione had improved the performance of these enzyme systems in the renal tubules which are concerned with the reabsorption of glucose. They believe that the metabolic activities of the cortical hormones are not blocked by the glutathione, but that this substance improves performance in those enzyme systems which require free sulph-hydryl groups for normal activity.

It was also noted that increased loss of nitrogen
in the urine bore no relation to the intensity of the diabetic state. In those who reacted to the hormone by a marked increase in both urinary corticoids and 17 ketosteroids the nitrogen excretion was increased, while in those in whom the corticoids rose to a greater extent than the 17 ketosteroids the nitrogen excretion was not affected. This observation suggested that the production of a negative nitrogen balance depended on the relative proportions of sugar and androgenic hormones which were produced by the adrenal cortex.

They found that the diabetic state produced by ACTH was markedly resistant to insulin, and that insulin had no effect on the low blood glutathione. They have suggested that permanent diabetes might be produced by ACTH because the lack of glutathione might allow alloxan-like substances to be produced.

It is notable that the various lots of ACTH used by these investigators varied in diabetogenic potency. The possibility of contamination with another pituitary hormone being responsible for the diabetogenic effect of ACTH by potentiating the diabetogenic action of the sugar hormones cannot, therefore, be ruled out until the effects of pure ACTH can be demonstrated in man. It is also possible that the different batches of the hormone had varying power to liberate a specific hormone of the cortex which was responsible for the production of the diabetic state. Glycosuria has not been reported
as an effect of the treatment of rheumatoid arthritis by means of compound E, but the fact that these remarkable experiments showed a clear relationship between the increase in the excretion of uric acid in the urine, and the temporary diabetes, which is definitely an effect produced by compounds E and F, indicates that the sugar hormones of the cortex certainly play a prominent part in the production of this diabetic state. The significance of these observations, however, would appear to be somewhat vitiated by the use of huge doses of ACTH, well out of the possible physiological range. It is, therefore, possible that a false impression has been given.

A search of the literature for further information regarding the changes in the concentration of glutathione in the blood in various conditions has been made. Claims and counterclaims to have observed significant changes in the concentration of this substance in the blood have been made in a great many conditions, and in consequence it is difficult to attach much credit to all but the most recent reports, in which it is to be presumed that the chemical estimations are more likely to be accurate.

The question of sulphur metabolism and glutathione has been reviewed by Goldziéher in his monograph on the adrenals (1944), but unfortunately most of the literature quoted has not been available. It has been reported that adrenalectomy causes a drop in the glutathione of
the blood and tissues to about a third of the pre-operative level, and that the administration of cortical extract restores both to normal. The administration of cortical extract to the intact animal has been found to raise the blood glutathione; and cysteine, and also glutathione, have been reported to have a beneficial effect on Addison's disease. The sulphur of the blood, skin, tissues, and urine, has been observed to increase following adrenalectomy, and to decrease following the administration of cortical extract.

The occasional reports which exist in the literature in the last ten years seem to agree that the reduced glutathione is decreased in Addison's disease, a finding which seems to be at variance with Conn's work.

Sandberg et al. (1940) found that the removal of the thymus of the rat caused a marked decrease in the amount of reduced glutathione in the blood, with a concomitant increase of the oxidised glutathione, which persisted for some months. This finding seems to suggest that the effect of the sugar hormones in causing atrophy of the thymus should not be overlooked as a possible indirect way in which the blood glutathione might be influenced by the adrenal cortex.

Ralli and Sherry (1948) have shown very clearly that the injection of insulin into the normal or diabetic dog or man has the effect of causing a remarkable redistribution of ascorbic acid from the blood to the
tissues. The ascorbic acid content of the blood and the urine drops abruptly, only to return when the effect of the insulin has worn off. From this finding it seems reasonable to suppose, from the findings of Prunty and Vass (1943) that the reduced glutathione of the blood might rise at the same time. Rosenberg (1938) observed that large doses of insulin caused a fall in the blood uric acid even when hypoglyceamia was prevented.

It is accepted that reduced glutathione exerts a protective influence over ascorbic acid by preventing it from irreversible oxidation. It would seem that either too little or too much glutathione could possibly effect the availability of the vitamin, and thereby adversely affect collagen tissue and play some part in the causation of the diseases of collagen. Previous investigations of the blood glutathione in rheumatoid arthritis, osteoarthritis, fibrositis, and rheumatic fever have already been made (Schultz 1939, Senturia 1934) and no significant changes found. Though it would appear unlikely that a gross change would have escaped notice, there is no doubt that the whole question of the blood glutathione in relation to rheumatism and other diseases should be reopened, in view of the prevailing confusion in the literature and recent developments.

The preliminary report by Conn, Louis and Johnston (1949b) that the changes in the blood cells which are produced by ACTH are temporarily reversed by an injection of glutathione is a most unexpected finding. It is much too early to draw any conclusions, but it is, perhaps,
significant that there is substantial agreement that the blood glutathione is markedly increased in the leukaemias. The most recent report (Bichel 1946) states that the high reduced glutathione in leukaemia is decreased at the same time as the white count by X-ray treatment. It appears that, though normally almost all the glutathione is in the red cells, it is also contained in the leucocytes, so that in leukaemia the blood glutathione is raised.

Dougherty and White (1946) have shown that, though small doses of X-rays will cause stimulation of the adrenal cortex, thymic atrophy, and the typical blood changes, larger doses will produce the same changes in the adrenalectomised animal. The effect of X-rays would, therefore, appear to be both direct and via the adrenal cortex. The administration of glutathione has been reported to be of benefit in radiation sickness, and though in view of the remarkable number of remedies for this condition scepticism is unavoidable, it would appear that there might be some foundation for this claim. Further support is given by the work of Patt et al. (1949) who found that the administration of cysteine before exposure to a large dose of X-rays had some protective effect. They also refer to recent work in connection with atomic research which showed that these enzymes which rely upon sulphydryl groups for their activity are oxidised by irradiation, but can be re-activated by glutathione.

It would seem that this field is one in which much
rapid development is to be expected, and that it is, perhaps, not so purely biochemical as would at first appear to be the case. There is every indication that glutathione is a substance of great physiological importance, and that it is affected by the endocrine system. It would, therefore, be surprising if this substance did not play some part in the adaptive mechanisms, and perhaps in those diseases which may be caused by adaptive dysfunction.
THE ENDOCRINE GLANDS AS THE GUARDIANS OF THE INTERNAL ENVIRONMENT.

**Introductory**

Though it is many years since Claude Bernard realised the vital importance of the maintenance of constancy in the internal environment of the body fluids, it is only comparatively recently, with the elucidation of the causation and the consequences of lack or loss of salt, or water, or both, that the importance of disturbances of the balance of the body water and electrolytes has gained the widespread recognition it deserves.

The magnitude of the task performed by the body in maintaining a state of relative constancy in the composition, volume, and distribution of water and electrolytes is exemplified by the quotation of a few well-established facts and figures which, because they are seldom quoted together, are worth recalling here, viz:-

The body of a man weighing 70Kilos. contains about 50 litres of water and 175 Grammes of sodium chloride. About 170 litres of colloid-free plasma is filtered through the glomeruli every day, and all but about 1.5 litres reabsorbed again, while at the same time 8 or 9 litres of water and about 50 Grammes of sodium chloride is poured out into the gut and reabsorbed again. It is at once apparent that the maintenance of any sort of balance in the face of the movement of such enormous
quantities of fluid and electrolytes in health is, perhaps, a greater marvel than that the balance should tend to be disturbed in disease, and that the mechanisms which maintain the constancy of the internal environment must indeed be robust and flexible.

Peters (1935) has aptly described the kidneys as not just excretory organs, but as the ultimate guardians of the constitution of the internal environment, which they maintain with uncanny accuracy under the most unfavourable circumstances. On the other hand, it is equally true that the kidney is not adapted to maintain the constancy of the internal environment by itself, but through the various factors which modify and control its functions. Though considerable modification of renal function can take place as a result of nervous, humoural, or pathological influences upon its specialised vascular arrangements, it is evident that the major part of the control of renal function takes place in the tubules. That the control of tubular reabsorption is predominantly an endocrine responsibility is emphasised by the effects of absence of the secretions of the adrenal cortex or of the posterior lobe of the pituitary respectively, on the balance of electrolytes and water.

Progress in endocrinology in the past few years has been so rapid that, though we now possess much new information which concerns the influence of the endocrine glands upon the balance of water and electrolytes, this data has not yet been correlated and fitted
together to form any sort of pattern. That this should be so seems to the author to be due to the existence of what appear to be definite misinterpretations of the data which has been obtained.

Though it has been obvious for many years that endocrine factors play a very large part in the maintenance of the constancy of the internal environment, most recent advances in our understanding of disturbances of the internal environment have been gained by the application of physico-chemical methods. As this aspect of the problem has been very adequately dealt with elsewhere, it has been left alone as far as possible, and attention here focussed on the role of the endocrines. It must be made clear at the outset that the importance of these physico-chemical mechanisms is not minimised here by the emphasis on the endocrine factors, but that these endocrine factors are the means of modifying these fundamental processes in such a way as to maintain constancy in the internal environment in the face of the continuously varying conditions imposed by the external environment, and by the continuously varying activity of the body.
The Control of Electrolyte Balance.

At the present time it is fortunate that recent research by Deane, Shaw and Greep (1948) has provided us with some very significant data regarding the manner in which the secretion of the electrolyte-controlling hormones by the zona glomerulosa is controlled in the rat.

These hormones, by retaining sodium and excreting potassium in accordance with the needs of the body, maintain the balance of electrolytes. Deane et al., however, contend that the alteration of the ratio of sodium to potassium in the plasma determines the activity or otherwise of the zone. They suggest that should this ratio decrease, as a result of lack of sodium or excess of potassium, the zone becomes hyperactive, as more hormones are needed in order to excrete potassium or retain sodium and restore the ratio to normal. Conversely, any rise in the ratio, such as would be produced by an excess of sodium or lack of potassium, would depress the production of these hormones, allowing sodium to be lost and potassium to be retained, thus lowering the ratio to normal.

The writer is unable to agree with this view on simple arithmetical grounds. The normal figure quoted for serum sodium is 315 - 340 mg.% and for potassium 16 - 22 mg.% . It is obvious, without even calculating out the ratio Na/K that a small alteration in the
potassium concentration must cause a much larger alteration in the ratio than that produced by an equivalent, or even a much larger, alteration in the sodium concentration. For example, if the serum sodium is assumed to remain constant at 320 mg.%, the ratio Na/K for various potassium concentrations is as follows:

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<tr>
<th>Potassium Concentration (mg.%)</th>
<th>Ratio Na/K</th>
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<tr>
<td>25</td>
<td>13</td>
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<td>20</td>
<td>16</td>
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<td>21</td>
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<td>10</td>
<td>32</td>
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The ratio is scarcely disturbed by changes in the sodium concentration of the same magnitude, if the potassium is assumed to remain constant, and to produce changes in this ratio of the same degree by alteration of the sodium concentration necessitates very large changes, quite incompatible with life. The use of milli-equivalents does not alter the situation appreciably.

It is, therefore, obvious that this ratio cannot be the controlling factor, as if it were the potassium concentration of the blood would be in control of the secretion of the hormones of the zona glomerulosa, and even a gross alteration of the sodium concentration would have almost no effect. There can be no doubt that this cannot be the case, and that the concentration of sodium in the blood must, directly or indirectly, be the main factor affecting the rate of secretion of these hormones. The following summary of the observations of Deane et al. has, therefore, been written from this viewpoint.
They found that a diet very low in sodium produced broadening of the zona glomerulosa and enlargement of its cells, which became filled with fine lipoid droplets. After from 38 to 70 days the hypertrophy of the zone became very marked, the cells very large, and they became completely depleted of all lipoids. These changes had been previously shown by these authors to be indicative of intense activity followed by exhaustion, when observed in the zona fasciculata as a result of the prolonged administration of ACTH (Bergner and Deane 1948), and the administration of thyroid (Deane and Greep 1947).

Lack of sodium, therefore, caused hypertrophy of the zone and signs of increased output of hormones, as more hormones were required in order to retain sodium in the body. As the lack of sodium was extreme, exhaustion of the zone was finally produced. Exactly the same sequence of events was observed in the zona glomerulosa of hypophysectomised rats. A sudden rise in the potassium concentration of the blood, produced by the injection of potassium chloride, caused, in those animals which survived this procedure, complete discharge of all the cortical lipoids within a few hours, with rapid enlargement of the cells. Within 24 hours fine lipoid droplets reappeared, and the zone gradually returned to normal. These changes are obviously connected with the sudden
demand for excessive quantities of the hormones of the zona glomerulosa to promote the excretion of the toxic amount of potassium which had been injected.

A diet containing adequate sodium, but practically no potassium, produced evidence of decreased hormone production. The zone became narrower, the cells smaller, and the lipoid droplets larger. As there was an adequate sodium intake, large amounts of the hormones of the zona glomerulosa were not required, so that hormone production could decrease in order to allow the potassium to be retained. Enlargement of the kidney was noted, but not examined. It is of interest that Durlacher, Darrow and Winternitz (1942) have shown that potassium deficiency produces a work hypertrophy of the collecting tubules, no doubt in an attempt to reabsorb more potassium.

A diet lacking in both elements produced the same hypertrophy and signs of hypersecretion of the zona as sodium lack alone, but complete exhaustion did not occur even after ten weeks. It seems clear that sodium lack took priority over potassium lack, but that the latter prevented the appearance of exhaustion. Lack of sodium being more important to the body than lack of potassium, more hormones were produced, despite the potassium deficiency, in order to prevent sodium loss.

Administration of DOCA to animals on an adequate intake of both elements caused marked involution and
almost atrophy of the zone, which was more extreme than that produced by lack of potassium alone. Though the authors interpret this effect as the result of raising the ratio Na/K, they point out that the alteration of the ratio produced by potassium deficiency is almost as great, and that other factors may be operative. It may be pointed out here that DOCA not only tends to cause the retention of sodium, but also the excretion of potassium, so that while the potassium falls the sodium also rises. Both a rise in sodium and a fall in potassium obviously tend to suppress the production of hormones by the zone, in an attempt to restore the body fluids to normal by allowing loss of sodium and retention of potassium. The combined effect of both these factors is, therefore, a much more likely explanation of the difference between the effects of DOCA and the effects of potassium deficiency. Signs of slightly decreased activity of the zona fasciculata were also noted, probably from pituitary inhibition.

Administration of DOCA to rats on a sodium deficient diet failed to prevent the hypertrophy of the zone as a result of sodium deficiency except to an insignificant degree. They point out that this result can be interpreted in two ways. The dosage of DOCA may have been insufficient to retain enough sodium to depress the zone, or that the kidney may have already been con-
serving sodium to the limit of its ability, so that no extra amount of DOCA could succeed in retaining more sodium in the face of such marked sodium deficiency. The sodium concentration could not rise, so that no inhibition of the production of hormones by the zone could result. The latter interpretation is most likely to be correct, as the dose was quite large, and the same effect had already been noted by Knowlton et al. (1946) using a slightly larger dose of DOCA.

This paper has been quoted freely not only because of its importance, but also in order to elucidate the fundamental misconception contained in it. Furthermore, as the sodium concentration is by far the major factor in the maintenance of the osmotic pressure of the plasma, it is reasonable to suggest that the effect of the sodium concentration on the osmotic pressure may be the main factor controlling the activity of the zone.

In the light of the foregoing it appears justifiable to suggest that the zona glomerulosa performs the same functions in man, except that the anterior pituitary is able to exert some control in an emergency. This concept could be confirmed by the histological examination of the adrenal cortex of a patient who had died suddenly while being treated for hypertension by drastic restriction of the salt intake over a long period.

Selye (1946a) has repeatedly demonstrated the action of ammonium chloride and other acid chlorides
in preventing the production of lesions by means of excessive doses of DOCA and sodium chloride or other sodium salts. It is unfortunate that there is no data regarding the effect of ammonium chloride on the zona glomerulosa, but it would seem very probable that it prevents the suppression of the zone by DOCA and excess salt. Whether it may do so by virtue of its action in promoting the excretion of sodium or via its effect on the acid-base balance of the blood is a matter of some interest, and it is also notable that the prevention of the suppression of production of the hormones of the zona glomerulosa should coincide with the prevention of the production of lesions.

While the evidence available at present indicates that the sodium concentration is the major factor affecting the secretion of the electrolyte-controlling hormones, it seems possible that the acid-base balance of the blood may also be a factor. Whether any such influence may be direct or indirect is conjectural. The possibility of an effect of the thyroid on the activity of the zone has already been considered.
The excretion of sodium chloride.

It has recently been demonstrated by Reforze-Membrives et al. (1945) that not only is the patient suffering from adrenal insufficiency unable to excrete excess water, but that there is also diminution in the power to excrete excess sodium chloride. This observation has previously been made in animals, and confirmed recently by Roemmelt et al. (1949).

These observations would appear to indicate that the adrenal cortex is not only responsible for the retention of sodium and chloride, but for the excretion of any large excess. The sugar hormones appear to be the most likely agency through which this function is performed.

Forsham and Thorn (1948) showed that one injection of ACTH promoted the excretion of sodium and potassium, and reasons have been given for the belief that the initial effect of this hormone is on the zona fasciculata and the sugar hormones. Data regarding the effects of compound E on the excretion of electrolytes is scanty, but Thorn et al. (1941) reported that this compound caused excretion of sodium and chloride in the dog, and Thorn and Clinton (1943) reported the same result in man in response to one dose, though the patient was also suffering from diabetes mellitus and adrenal insufficiency. Ingle, Li and Evans (1946) found that large doses of ACTH had no consistent effect on the excretion of sodium and chloride in the rat. Ingle,
Sheppard et al. (1946) found that large quantities of compound F will cause a definite increase in the excretion of sodium chloride in the rat, and that compound B, which in smaller amounts causes some sodium retention, caused an increase in sodium excretion when given in large doses.

Thorn et al. (1949) have reported that the administration of compound E to a patient with complete adrenal insufficiency who had been given excessive doses of DOCA and salt resulted in an increase in salt excretion, while 20 mgms. of compound E daily had enough salt retaining effect to maintain a case of adrenal insufficiency. It would appear that compound E is capable of promoting the excretion of salt in the presence of the electrolyte-controlling hormones or DOCA, while in the absence of either it can have a mild salt-retaining effect.

Perera et al. (1949) administered 80 mgms of compound E daily to several cases of hypertension for a few days. They found that slight retention of salt and water was produced, with some haemodilution and a slight decrease in the serum sodium. The changes observed were not very convincing, but would appear to suggest that more water than salt was retained. It is clearly unsafe to draw any conclusions from this small series, but it must be pointed out that the administration of an amount of compound E four times that
necessary to maintain a case of adrenal insufficiency must have rather far-reaching effects on the endocrine system. It could be postulated that the hormone suppressed the pituitary, and thus substituted compound E for all the secretions of the zona fasciculata but on the other hand it is not clear how long it would take for such an effect to be produced, and it is possible that within the period of administration both endogenous and exogenous hormones were exerting their effects. In the presence of an intact cortex it is, therefore, very difficult to determine the effect of one hormone of the cortex.

The argument may seem rather tenuous, but it is worthy of note that Hillarp (1949) noted that the acute or the chronic administration of excessive amounts of saline resulted in the production of demonstrable histological changes not only in the supra-optic nuclei of the hypothalamus, which have been definitely connected with the secretion of the anti-diuretic hormone of the posterior lobe of the pituitary, but also in the paraventricular nuclei. This observation seems to be of more than passing significance when it is pointed out that Heinbecker (1944) has produced good presumptive evidence that this particular nucleus of the hypothalamus may be concerned with the control of the corticotrophic activity of the anterior pituitary, or of the response of the adrenal cortex to ACTH. (Vide p. 116). As the administration of an excessive amount of salt is probably capable of producing an
"alarm reaction", with hypertrophy and hypersecretion of the sugar hormones of the cortex, it is possible that the excretion of the excess is promoted in this way.

Many investigators have postulated that the antidiuretic hormone of the posterior pituitary not only promotes the retention of water, but also the excretion of sodium and chloride. This question is discussed separately.

The scanty evidence which is available seems to indicate that, though the sugar hormones may oppose the action of the electrolyte-controlling hormones, this action is of little or no significance under normal conditions. As these hormones are mainly concerned in the metabolic processes, it is not logical to expect that their output should also be altered in accordance with the need to excrete sodium chloride, and potassium, except when a gross excess has to be excreted. It is apparent that the alteration of the output of the hormones of the zona glomerulosa in accordance with the needs of the body to conserve salt or otherwise must be the main mechanism which is normally concerned in the control of the excretion of sodium chloride, and that only when the need to excrete an excessive amount of sodium chloride arises do the sugar hormones take a hand, because of the general "alarm" produced.
The excretion of water.

The evidence indicating that the sugar hormones play a dominant role in the excretion of water has already been discussed in connection with the relationships between the anterior pituitary, the zona fasciculata of the adrenal cortex, and the thyroid. It was concluded that the sugar hormones, in conjunction with the effect of the thyroid on the zona fasciculata and possibly through a direct effect of thyroxine on renal function, are mainly responsible for the excretion of water. In effect, they are the diuretic hormones, and are opposed to the antidiuretic hormones of the posterior lobe of the pituitary.

The similar effects of the absence of the adrenals or the anterior pituitary on the capacity to excrete excess water in both animals and man clearly indicate that the electrolyte-controlling hormones of the zona glomerulosa cannot play any significant part in the excretion of water. The reports that DOCA has a marked power to promote the excretion of water are dealt with elsewhere.

Joseph et al. (1944) showed clearly that the delay in water excretion in the hypophysectomised rat is not due to delayed absorption of water, and could be almost completely corrected by the administration of cortical extract or DOCA. As Gaunt (1946) has emphasised, this observation is of interest because in neither man nor animals does the administration of these hormones correct the defect in water excretion,
or the diminution in renal function which has been observed in adrenal insufficiency in man by Talbott et al. (1942).

These findings would suggest that in the absence of both electrolyte-controlling and sugar hormones neither renal function nor the capacity to excrete water can be restored completely to normal, and that it is possible that some sort of synergism may exist between the two groups of hormones.

The role of the adrenal medulla in the excretion of water is rather controversial, as while Stein and Wertheimer (1944) found that the removal of the adrenal medulla caused diminution of the capacity to excrete water, Gaunt et al. (1945) found that this procedure was without effect on water excretion. However, Gaunt et al. observed that the effect of adrenaline, which is a powerful stimulus to the excretion of excess water in the normal animal, is much reduced in the absence of normal adrenal function. Gaunt (1946), in discussing this point, mentions that adrenaline has been found to be unable to restore the ability of the patient with adrenal insufficiency to excrete water.

It would appear that the recent demonstration of the effect of adrenaline in increasing the secretion of ACTH and therefore of the sugar hormones is likely to be the explanation of this action of adrenaline. This concept is further supported by the observation
of Liling and Gaunt (1945) that exposure of animals to stress, a procedure which is now well known to result in hypertrophy of the adrenal cortex and hypersecretion of the sugar hormones, also raises the resistance of the animal to water intoxication and enhances the diuretic response to water.

It is well established that the removal of the anterior pituitary or the adrenals has the effect of depressing renal function both in man and in animals. White et al. (1949) in the latest of a series of papers on this subject, have shown that the growth hormone of the anterior pituitary acts as a stimulant of renal function, and that the renal function of the hypophysectomised animal cannot be restored to normal without it. It is not clear, however, whether this hormone is involved in the excretion of water or not.
The regulation of water excretion.

Verney (1947) has demonstrated very clearly that the concentration of sodium in the plasma, which is by far the main factor in the maintenance of the osmotic pressure of the plasma and the extra-cellular fluid, controls the output of the antidiuretic hormone via hypothetical osmo-receptors situated somewhere in the vascular bed supplied by the internal carotid artery. He showed that a fall in the sodium concentration, by causing a fall in the osmotic pressure, inhibits the secretion of the antidiuretic hormone by the posterior lobe of the pituitary gland, thus allowing water to be excreted in order to raise the osmotic pressure to normal again. Conversely, a rise in the sodium concentration of the plasma causes secretion of the antidiuretic hormone, so that water is retained in the body to dilute the plasma, and the extra-cellular fluid, and reduce the osmotic pressure to normal again. He showed that the sensitivity of this control is such that an alteration in the plasma osmotic pressure of about 1% will cause an alteration in the rate of water excretion in the region of 1000%.

It is apparent that this hormone is in direct opposition to those hormones which promote the excretion of water, and which are controlled by the anterior lobe of the pituitary. It is evident that the secretion of these diuretic hormones cannot vary to any marked extent in response to alterations in the salt or water
intake, except when a very excessive amount of either has been ingested, as both the sugar hormones and the thyroid hormone are so intimately concerned in the metabolic processes that it does not seem reasonable to propose that the output of these hormones should also vary in accordance with the need to conserve or excrete water or salt. On the other hand, there is no doubt that the control over the rate of water excretion by the posterior lobe of the pituitary is extremely labile, and that this mechanism is almost exclusively concerned with the control of water balance. It therefore seems reasonable to suggest that the diuretic influence of the sugar hormones and thyroxine acts as a basis upon which the labile control of water excretion by means of the antidiuretic hormone can be exerted. Furthermore, the degree of control exercised is such that all except gross variations in the output of these diuretic hormones could easily be compensated for by an increase or decrease in the output of the antidiuretic hormone. From this point of view the diuretic influences can be largely disregarded as a variable factor under normal conditions.

In diabetes insipidus it is found that, though the water balance is seriously disturbed, the electrolytes are not. This is good presumptive evidence that the control of electrolyte balance is vested in the zona glomerulosa, and that, as long as the fluid balance is maintained through the sensation of thirst
and the adequate satisfaction of it, the electrolyte balance can take care of itself. In the absence of both lobes of the pituitary both the diuretic and the antidiuretic factors are lost, and as ingested water does not cause a diuresis pituitrin has no demonstrable effect (Chen and Geiling 1943, Joseph et al. 1944), while electrolyte balance is not seriously impaired.

The fact that, though the electrolyte balance in diabetes insipidus is liable to fluctuate in accordance with the wild variations in the water intake, which is vainly trying to keep up with the constant loss in the urine, no serious disturbance has been found in the electrolytes in this disorder, indicates clearly the importance of the sensation of thirst in the maintenance of water balance. It is a most commonplace observation that even a slight increase in the salt intake will cause thirst, and it would appear that this sensation is extraordinarily sensitive to any tendency for the osmotic pressure of the plasma to rise, or at any rate to any tendency for the sodium concentration to rise.

The importance of thirst as a protector of the internal environment is exaggerated in diabetes insipidus, as the normal control of water excretion has been lost and this sensation has to take its place, but it is clear that the supply of the right quantity of fluid is equally important in the normal person. Peters (1944) has reviewed recent work on the mechanism of thirst, and it appears that removal of the salivary
glands, the olfactory, gustatory, or trigeminal nerves, and many other procedures, do not abolish this sensation. It has been suggested that the stimulus to thirst is the water content of the cells, but the exact routes by which the sensation travels to the consciousness is obscure. What does seem definite, however, is that a rise in the osmotic pressure causes thirst, while a fall does not.

The administration of large doses of DOCA has been found by Ragan et al. (1940), Mulinos et al. (1941), and by others, to result in the development of a diabetes insipidus-like syndrome, especially in the dog. Mulinos et al. also noted that the polyuria and polydipsia increased in proportion to the salt intake.

Corey and Britton (1941) also observed this phenomenon, though it is notable that they used enormous doses of DOCA, and they suggested that the antidiuretic hormone and DOCA are physiological antagonists as far as the balance of electrolytes and water is concerned. McGavack et al. (1946) showed that the administration of DOCA to a case of craniopharyngioma whose diabetes insipidus had disappeared as the anterior as well as the posterior lobe became slowly destroyed, resulted in the reappearance of mild diabetes insipidus, and they therefore thought that this result supported the concept of Corey and Britton. Anderson and Murlin (1942) found that cortical extract, which contains sugar hormones as well, could aggravate diabetes insipidus.
in man. The dosages of hormones used in these investigations were, of course, more reasonable than those which have been used in the experimental animal, but there can be no doubt that an effect must be much easier to produce in the absence of the secretions of the posterior lobe.

It has already been mentioned that Eversole, Gaunt, and Kendall (1942) found that, though DOCA did protect the adrenalectomised animal against water intoxication, compound E was three times as effective.

Skahen and Green (1948) have shown that, in the rat, an increase in the salt intake will cause an increase in both the fluid exchange and in the output of antidiuretic hormone in the urine. That salt causes thirst is a most commonplace observation. The administration of DOCA without the addition of extra salt in the drinking water caused only a slight increase in the excretion of the antidiuretic hormone, but when extra salt was given the excretion of antidiuretic hormone and the fluid exchange increased in proportion to the amount of salt given.

This investigation would appear to be explicable in the following manner. As DOCA causes retention of sodium and a rise in the osmotic pressure when adequate sodium is given, it will cause an increase in the output of the antidiuretic hormone in an attempt to retain more water to dilute the plasma to the normal osmotic pressure. At the same time the rise in the osmotic pressure must, by causing thirst, increase the fluid
intake. Owing to the action of excess DOCA in promoting the excretion of water overcoming the retentive effect of the increase in the output of the antidiuretic hormone this water cannot be held in the body to dilute the body fluids to normal, so that the urinary output is also increased, and a diabetes insipidus-like condition produced. A further increase in the salt intake will obviously increase the thirst, and therefore the fluid intake, but the water will still be excreted by the action of the excess of DOCA on the kidney, and possibly is also aggravated by the osmotic effect of the increased salt content of the urine. As more salt is available, the excess DOCA can raise the blood sodium still further, with a resultant further increase in the output of the antidiuretic hormone, which again fails in its object.

Sartorius and Roberts (1949) have found that when more physiological doses of DOCA are given to the intact dog by the intravenous route it does not promote the excretion of water, but the significance of this observation is difficult to estimate as the animals were intact and the effects of DOCA on the endocrine system are very widespread indeed.

All this data does not detract from the evidence that the sugar hormones are the main diuretic hormones, and would appear to have been obtained by the administration of excessive doses of DOCA.
The actions of posterior pituitary extracts.

While there is no doubt whatever that pitressin can put an abrupt stop to the continuous water diuresis of diabetes insipidus and can inhibit water diuresis, it is equally well established that the hormone has relatively little antidiuretic effect on the individual who is in a normal state of hydration. Unless there is an excess of water available for excretion the hormone is without much effect.

It seems most likely that this difference is accounted for by the relative completeness of water reabsorption under normal everyday conditions.

While the daily volume of the glomerular filtrate has been established to be about 170 litres, the maximum daily water output which has been observed in diabetes insipidus is only about 40 litres. It is clear that in the complete absence of the antidiuretic hormone some 130 litres of water can be reabsorbed, and that the 40 litres represents the basis upon which the antidiuretic hormone can exert its effects. The normal daily volume of urine is about 1500 ccm. or so, of which about 500 ccm. is the "volume obligatore", so that it is obvious that under these conditions, if the figure of 40 litres is anywhere near correct, that the antidiuretic function is working at between 96.25 and 97.5 per cent efficiency. Under these conditions it is not surprising that an extra dose of pituitrin has
little effect. Furthermore, at this level of efficiency the reabsorptive powers of the renal tubules are working fairly close to the osmotic limit beyond which they cannot reabsorb more water. It is also apparent that this hormone can have no effect on a diuresis produced by excess of sodium chloride, as the osmotic effect of the salt will prevent an increase in the rate of tubular reabsorption of water, unless the water intake is grossly in excess of that required to excrete the salt.

It appears from the literature that, though many investigators have reported that pitressin promotes the excretion of sodium and chloride, many others doubt whether this effect is a true one. Dicker and Heller (1946) have produced evidence that contamination of pitressin with the oxytocic fraction of the extract is responsible for this action of commercial pitressin as far as chlorides are concerned, but the effect on sodium excretion was not ascertained. This work raises the question of what the function of the oxytocic fraction may be apart from its well-known role in parturition.

Many investigators have used doses of pitressin which are well out of the physiological range, but Sartorious and Roberts (1949) have taken care not to make this mistake. Nevertheless, they demonstrated quite an impressive effect on the excretion of sodium, and of potassium as well. Melville, and others quoted by him (1936), found that pitressin produced a diuresis
when given to an animal receiving a high salt and low water intake, and that the diuresis was in proportion to the salt intake. It seems possible that this effect may be explained by the promotion of the excretion of salt by the pitressin, thus obligating the excretion of more water with the salt in order to prevent an increase in the osmotic pressure of the urine over that limit beyond which further tubular reabsorption of water cannot proceed.

The question of the possible action of the anti-diuretic hormone in promoting the excretion of sodium chloride has recently been discussed as a possible cause of the loss of salt which is found in adrenal insufficiency.

Though it is an incontrovertible fact that there is serious depletion of sodium in adrenal insufficiency, Martin et al. (1939) demonstrated that an antidiuretic substance was excreted in the urine in the adrenalectomised animal when it was not being maintained with cortical extract, and very recently Birnie et al. (1949) found that the serum of normal rats contained a labile substance or substances with antidiuretic and chloruretic properties, which was markedly increased after the removal of the adrenals. They also state that a similar substance has been found in increased amount in human adrenal insufficiency.

These observations are most difficult to reconcile with the clear-cut demonstration of Verney (1947) that
a fall in the sodium concentration inhibits the secretion of the antidiuretic hormone. If the antidiuretic hormone is truly in excess in adrenal insufficiency it may be that it is accounted for by the loss of control over the distribution of the electrolytes, so that the function of the "osmo-receptors" is affected in such a manner that the secretion of the antidiuretic hormone is stimulated in the presence of a low sodium concentration.

The finding of Winter et al. (1941) and in several other investigations by these authors, that if a cat with diabetes insipidus was adrenalectomised the serum sodium did not fall, though the animals did not survive so long as those who were only adrenalectomised, would appear to be explicable in the following manner.

There can be no doubt that, in the absence of the adrenals, more salt than water is lost, in a relative sense. If the antidiuretic influence of the posterior pituitary is also absent it is evident that all control over both water and salt is lost. In the absence of the diuretic hormones of the adrenal cortex the water loss cannot be severe, and the absence of the antidiuretic hormone as well may be sufficient to make the salt loss and the water loss through the kidney relatively equal. The serum sodium does not fall because the simultaneous loss of water has prevented a fall, but as the animal has lost both water and salt the survival time is adversely affected. These
comments also apply to those animals from which the adrenals and the pituitary were removed, and then a fall in the sodium concentration produced by administering pitressin, thus completing the converse of the experiment.

It has been necessary to attempt to elucidate the mechanism of these experiments in view of the recent evidence suggesting that the loss of sodium in adrenal insufficiency is due to the unopposed action of the antidiuretic hormone. Whatever the magnitude of the effect on the excretion of sodium and chloride may be, there seems little doubt that this effect is a minor one in comparison to the effect of this hormone on the reabsorption of water. Whether the effect on sodium excretion is apparent or real, direct or indirect, is certainly far from clear at the moment.

There is a certain amount of rather fragmentary evidence suggesting that the fall in the blood chlorides which is a feature of overdosage with DOCA, ACTH, and is found in some cases of Cushing's syndrome may be due to hypersecretion of the antidiuretic hormone of the posterior pituitary.

Selye and Basset (1940) found that DOCA produced neither lesions nor a relative lack of blood chlorides in the absence of the entire hypophysis, though they pointed out that the significance of these findings was rather doubtful in respect of the causation of the
lesions. McQuarrie (1942) found that the administration of DOCA alone to an epileptic patient produced less marked depression of the urinary chlorides than of sodium, but when pituitrin was also given the urinary chlorides increased even further.

The demonstration of excessive quantities of anti-diuretic substance in the urine of hypertensive patients by Ellis and Grollman (1949) and other previous workers may be connected with the observation of Farnsworth and Barker (1943) that there is an increase in the excretion of chlorides in hypertension, and the demonstration of a disturbance of the blood chemistry similar to that produced by ACTH, DOCA, or Cushing's syndrome in certain cases of hypertension by Selye (1947).
The endocrine control of the balance of water and electrolytes.

Now that all the available evidence regarding the endocrine influences which may be concerned in the maintenance of the balance of water and electrolytes has been reviewed and discussed it is possible to attempt to discern the manner in which they may form an interlocking mechanism which opposes any tendency to change in the internal environment.

The antidiuretic hormone and the electrolyte-controlling hormones must play a major part in the maintenance of the constancy of the internal environment, and the third important factor is clearly the sensation of thirst. The evidence is now strongly in favour of the sodium concentration of the plasma, probably through its effect on the osmotic pressure, being the major factor which controls the activity of the posterior pituitary and the zona glomerulosa in a diametrically opposite manner.

It is, therefore, very probable that a rise in the osmotic pressure, by bringing about the secretion of more antidiuretic and less salt-retaining hormones, results in the retention of water and the excretion of salt. At the same time the fluid intake is increased in consequence of the thirst induced by the rise in the osmotic pressure, and so renders further assistance in lowering the pressure to normal. A fall in the osmotic pressure will cause exactly the opposite
reaction to take place. This concept has been illustrated by Fig. 2.

It would appear that the osmotic pressure is the physiological constant which controls all these mechanisms, and it is difficult to visualise how this constant arises. It is, of course, quite evident that physico-chemical relationships concerned in the inter-changes of water, electrolytes, and metabolites between the intracellular and extracellular compartments of the body fluids must play a large part in determining the normal osmotic pressure, but once again the influence of the hormones of the adrenal cortex on the transport of ions through cell membranes and the distribution of the electrolytes has to be taken into account. Unfortunately, this aspect of the problem remains a closed book so far.

Apart from these considerations, however, it is evident that the interplay of the influences of the zona glomerulosa and the posterior pituitary on the renal tubule in respect of salt and water respectively, plus the influence of thirst on the water intake, may be sufficient to explain to a very large extent the manner in which the internal environment is protected against change under normal conditions by the endocrine glands. These appear most likely to be the major mechanisms, and it seems probable that the other endocrine influences which may also play a part are of the nature of emergency mechanisms or fine adjustments.
Though the osmotic pressure is very jealously guarded against change, the volume of the fluids is not so critical. Many investigators have shown that quite large increases can take place without apparent effect, and Peters (1944) has reported that as much as five or six litres of extra interstitial fluid may accumulate without there being clinical evidence of its presence. Furthermore, it is abundantly clear that the volume of the interstitial fluid can fluctuate quite widely in order to accommodate extra fluid pending its excretion. In this event there is no doubt that the amount of the interstitial fluid is being increased in order to prevent a change in the plasma volume, thus acting as a sort of buffer until the excess can be excreted. On the other hand Marriott (1947) has pointed out that comparable losses of either intracellular or extracellular fluid are productive of severe symptoms, so that it would appear to be the case that an increase in the volume of the body fluids is much more easily tolerated than a decrease. The fact that isotonic saline is only slowly excreted is a good example of this tolerance to an increase in volume in the absence of any change in the osmotic pressure.

Despite these considerations, it is also true that the body weight remains remarkably constant over long periods when in health. Since the body is 70% water, there can be no doubt that this constancy of
Endocrine inter-relationships in the control of salt and water balance.

- **Increased osmotic pressure**
  - Zona glomerulosa
    - Decreased output of electrolyte controlling hormones
    - Increased salt excretion
  - Thirst
  - Posterior pituitary
    - Increased output antidiuretic hormone
    - Water retention

- **Osmotic pressure reduced to normal**

- **Decreased osmotic pressure**
  - Zona glomerulosa
    - Increased output of electrolyte controlling hormones
    - Decreased salt excretion
    - Osmotic pressure raised to normal
  - No thirst
  - Posterior pituitary
    - Decreased output antidiuretic hormone
    - Increased water excretion
weight must depend to a very large extent upon the maintenance of constancy in the volume of the body fluids by the mechanisms described above, and it is now possible to offer a probable explanation of this phenomenon.

It is now well recognised that the loss or retention of water must result in the loss or retention of the appropriate amount of salt, and that the loss or retention of salt must result in the loss or retention of the correct amount of water, in order that the osmotic pressure may remain constant. The evidence presented here indicates that while the posterior pituitary acts primarily to conserve water in accordance with the amount of salt available, the zona glomerulosa acts to conserve salt in accordance with the amount of water available.

It is obvious that the two influences must cancel out to a large extent, as the posterior pituitary allows water to escape from the body if it is in excess of that required for the maintenance of the osmotic pressure, and the zona glomerulosa allows salt to escape if it is in excess of that required to maintain the osmotic pressure. Should the amount of either salt or water be below that required, these mechanisms at once enforce rigid economy, which is clearly more efficient in the case of salt than of water, as unavoidable water loss must continue. A decrease in the volume of the body fluids is, therefore, rigidly
prevented, with the assistance of the sensation of thirst, and the reciprocal relationship between these interlocking influences on water and salt tends to prevent an increase in the volume, though not so rigidly. The loss or the accumulation of an undue amount of either water or salt in the body and an increase or a decrease in the volume of the body fluids is, therefore, prevented from occurring. It has been attempted to illustrate this mechanism by Fig. 3.
Fig. 3.

The maintenance of constancy in the volume of the body fluids.

- The fundamental constant of the osmotic pressure to maintain which:
  - Glomerulosa causes retention of just enough Na to maintain the osmotic pressure in accordance with available water, and allows excess to be excreted.
  - Osmotic pressure maintained substantially constant.
  - Accumulation of excess sodium prevented.
  - Volume of the body fluids maintained substantially constant.

- Taste and thirst:
  - Taste: appropriate sodium intake.
  - Thirst: appropriate water intake.

- Posterior pituitary causes retention of just enough water to maintain the osmotic pressure in accordance with available Na, and allows excess to be excreted.

- Accumulation of excess water prevented.

As there is no satisfactory method of estimating the output of the electrolyte-controlling hormone, no data relating to their decreased destruction have been illustrated in Fig. 4.
The causation of an increase in the volume of the body fluids.

An increase in the volume of the body fluids, particularly of the interstitial fluid and of the plasma, may be of considerable proportions without causing detectable oedema. Peters (1944) has reported that as much as five or six litres may accumulate as latent oedema, and there is no doubt that transient increases are of common occurrence as a physiological adjustment pending the excretion of the excess. Many other factors concerned in the causation of oedema have now been elucidated, but it is felt that an endocrine factor may now be added.

It is evident from the foregoing that the retention of salt and water could originate from either the zona glomerulosa or the posterior pituitary. As water cannot be retained without the appropriate amount of salt, and vice versa, overactivity of one of them must lead to overactivity of the other. Another way in which retention could be caused is by impaired destruction of either the electrolyte-controlling or the antidiuretic hormones in the liver. The possible mechanisms by which retention of primary adrenal or primary posterior pituitary origin may occur have been illustrated in Fig. 4.

As there is no satisfactory method of estimating the output of the electrolyte-controlling hormones we have no data relating to their decreased destruction
Fig. 4.

Endocrine causes of an increase in the volume of the body fluids.

- Excessive production or impaired destruction of the antidiuretic hormone
  - Retention of water
  - Tendency for osmotic pressure to fall
  - Zona glomerulosa
  - Increased production of electrolyte-controlling hormones
    - Retention of sodium
    - Fall in the osmotic pressure prevented at the expense of an increase in the volume of the extracellular fluid

- Increased production of electrolyte-controlling hormones
  - Retention of sodium
  - Rise in the osmotic pressure prevented at the expense of an increase in the volume of the extracellular fluid
or increased production, but the demonstration by Burrill and Greene (1942) that DOCA is destroyed in the liver would suggest that the natural hormones may also be inactivated in this way.

The only evidence which is at all suggestive of hypersecretion of these hormones is the report of Selye (1947) that some cases of hypertension exhibit the same relative lack of chlorides as is found in Cushing's syndrome and as a result of prolonged dosage with ACTH or DOCA. It has already been pointed out that this biochemical abnormality may be due to hypersecretion of the antidiuretic hormone, so it is not possible to decide whether the posterior pituitary or the adrenal cortex is at fault.

In the case of the antidiuretic hormone, however, we have much more information. Eversole et al. (1948) have reported that the injection of pitressin into the portal circulation is much less effective than when injected intramuscularly, suggesting that the antidiuretic hormone is destroyed in the liver. This result is in clear accord with recent observations of increased amounts of antidiuretic hormone in the urine in hepatic insufficiency.

Ralli et al. (1945) found increased amounts of what appeared to be antidiuretic hormone in the urine in cases of hepatic cirrhosis with ascites, and Kunkel et al. (1948) have since confirmed this. Labby and Hoagland (1947) have shown that during the acute stage
of infective hepatitis there is considerable fluid retention, with an increase in the volume of the blood and the interstitial fluid. The chlorides of the plasma and of the urine were decreased, and there was a tendency to retain ingested water. Labby (1949) has reported that the output of antidiuretic hormone in the urine is increased in the acute stage and declines with recovery in a manner parallel to the water retention and low chlorides. Unfortunately, there is no note of the effect of infective hepatitis on the sodium concentration, but in view of the manner in which the body preserves the sodium concentration and the osmotic pressure at all costs it would seem possible that it was not affected, and that the chlorides were relatively low. If this is so it provides further support for the concept that excess of the antidiuretic hormone causes a relative fall in the chlorides. A further factor is introduced by the work of Gilder and Hoagland (1946) who, struck by the tendency to feminisation observed in cases of chronic hepatic disease, estimated that the excretion of oestrogens in cases of infective hepatitis and found that it was markedly increased, and fell to normal on recovery. It is now well established that oestrogens are destroyed in the liver, and that they tend to cause retention of salt and water and may be responsible for the syndrome of pre-menstrual oedema.

In acute and chronic liver damage there is, therefore, a fair amount of evidence to suggest that there
is impaired destruction of the antidiuretic hormone. The retention of water resulting from this defect must tend to cause a fall in the osmotic pressure and the sodium concentration, thus stimulating the zona glomerulosa to retain the correct amount of sodium to prevent any fall, with the result that the volume of the extracellular fluid is increased. The low chlorides may be due to the action of the antidiuretic hormone. What part the impaired destruction of oestrogens and, perhaps, of the electrolyte-controlling hormones as well, may play in this retention of salt and water is impossible to define.

Robinson and Farr (1949) found an increase in the amount of antidiuretic substance in the urine in cases of acute nephritis, nephrotic syndrome, pre-menstrual oedema, and Cushing's syndrome. Ellis and Grollman (1949) have reported that the amount of antidiuretic hormone in the urine of eleven out of fifteen cases of hypertension was increased, and also in animals with experimental hypertension. This finding has been previously reported by Pendergrass et al. (1947) and by others, and Pendergrass found that deep X-ray therapy applied to the pituitary region caused the disappearance of the excess of antidiuretic hormone and had a beneficial effect on the blood pressure in a fair number of cases. It seems possible that the reduction in the output of antidiuretic hormone produced in this way may have had the effect of abolishing any tendency
to retention of water and salt, and might in a way be equivalent to a low sodium diet. It has already been pointed out that an increase in the chloride excretion has been demonstrated in hypertension by Farnsworth and Barker (1943) and that this is possibly due to excess of the antidiuretic hormone.

It is now well known that the hypertensive patient has a tendency to salt and water retention. This has been demonstrated most recently by Perera and Blood (1946), who found that the hypertensive patient does not show a rise in the urine volume as the result of withdrawal of salt, as a normal person does.

In the light of the foregoing it would be expected that the destruction of the antidiuretic hormone is impaired in congestive cardiac failure, but there does not appear to be any evidence to this effect in the literature. Parrish (1949) has found that the urine of patients with congestive failure contains an increased amount of corticoids, and that the urine of the most severely ill patients was also able to prolong the survival time of the adrenalectomised rat. This finding would suggest that there is hypersecretion of the electrolyte-controlling hormones in severe failure, a feature which would be expected to be associated with massive retention of salt and water. In this type of case, however, it is probable that salt and water retention, apart from the question of impaired destruction of the antidiuretic hormone in the liver,
is a phenomenon which is mainly secondary to the venous congestion.

It would appear that the main feature which arises from this discussion of the probable role of endocrine factors in the causation of latent or obvious oedema the is/probability that hypersecretion or impaired destruction of either the antidiuretic or of the electrolyte-controlling hormones is most likely to result in the hyperactivity of the other, in order to retain the correct amount of salt or water to maintain the osmotic pressure constant at the expense of an increase in the volume of the body fluids. It is, therefore, not possible to determine whether undue accumulation of water and salt in the body may be primarily of adrenal or posterior pituitary origin.

The evidence which has been presented indicates clearly that the methods of treatment of oedematous stages by means of low or very low sodium intakes and free or high water intake are likely to remove any such endocrine abnormality which may be contributing to the retention. If salt intake is drastically restricted the secretions of the electrolyte-controlling hormones will certainly increase to a maximum in order to prevent the depletion of the salt stores of the body and a fall in the osmotic pressure, but as there is no more than a minimal amount of salt available it is not possible for retention of more salt to occur. The osmotic pressure, therefore, cannot rise, and in the
presence of a free or large water intake the posterior pituitary must be kept more or less suppressed. Retention cannot occur under these circumstances, and the fact that the kidney cannot completely conserve salt tends to deplete the salt, and therefore the water, stores of the body as long as the intake is kept below the minimal loss of salt allowed by the kidney. The endocrine factor in the causation of retention will thus be eliminated.
Abnormal states of salt and water balance.

While the mechanisms which have been described above may suffice to maintain the balance under normal conditions, it is apparent that other endocrine influences may complicate the picture when a strain is imposed upon them by severe lack or excess of either salt or water.

Physiological experiments involving the ingestion of excessive amounts of salt or water must create conditions to which the body is not adapted, as no sane person would go against the dictates of taste or thirst to such an extent. It is, therefore, very probable that such procedures may bring about hypersecretion of the sugar hormones. As a result, the results of such experiments may be somewhat complicated and difficult to interpret.

Although the salt intake is normally in excess of requirements, there is no doubt that a gross excess is very difficult to take without causing the defence reaction of vomiting. On the other hand there can be no doubt that an excessive intake of water is much more likely to occur, and that the body can get rid of excess water very easily. On general grounds it therefore seems correct to assume that the body is better adapted to getting rid of excess water than excess salt.

The ingestion of a grossly excessive amount of salt without an increase in the water intake, by
causing the osmotic pressure to rise, will tend to cause the retention of water and the excretion of salt. The influence of the antidiuretic hormone is overcome by the osmotic effect of the increased amount of salt in the urine on tubular reabsorption of water, so that diuresis results which has been shown to cause dehydration of the intracellular compartment, just as in pure water lack.

As Peters (1944) has pointed out, the reabsorption of salt increases under such conditions, despite the need to get rid of it, this being due to the fact that the kidney is faced with the choice of excreting salt or waste products such as urea, and the waste products are preferentially excreted in the small amount of water available. In other words, the excretion of salt takes second place to that of urea, and similar solutes, when there is a need for the conservation of water. As the evidence indicates that the secretion of the salt-retaining hormones should be decreased, it is difficult to explain how the increased reabsorption of salt is effected, and furthermore, how the sugar hormones can promote its excretion under these conditions.

On the other hand it is not physiological to withhold water from an individual with a raging thirst caused by excess salt, and it is evident that if the thirst is satisfied both salt and waste products can be excreted and the rise in the osmotic pressure and intracellular dehydration prevented. Under these circum-
stances it is possible that the sugar hormones may be diverted from their predominantly metabolic activities and actively promote the excretion of salt. The observations of Hillarp (1949) that infusion of excess salt caused signs of activity in both supra-optic and paraventricular hypothalamic nuclei is of interest in this connection.

The sequence of events which results from the ingestion of excess water is naturally somewhat different. The resulting fall in the osmotic pressure, by inhibiting the secretion of the antidiuretic hormone, allows the water to be excreted in order to raise the osmotic pressure to normal again. At the same time the fall in the osmotic pressure would appear to stimulate the production of more electrolyte-controlling hormones by the zona glomerulosa so as to retain more sodium and increase the osmotic pressure.

The administration of large amounts of water has been repeatedly found to cause a rise in the chloride excretion (Peters 1944) and an increase in the glomerular filtration rate (Shannon 1938, 1942). One explanation may be that the increase in the filtration rate may decrease the time during which reabsorption may take place in the tubules, but as there is reason to believe that the sugar hormones play a part in the excretion of excess water it is also possible that this effect is due to hypersecretion of these hormones. As they also excrete sodium and chloride, and they are
unopposed by the antidiuretic hormone in this instance, it would appear possible that they may be promoting the excretion of both salt and water.

The administration of large amounts of water is once more a procedure to which the body is obviously not adapted, but the excretion of moderate amounts is clearly a situation which commonly has to be dealt with. It is therefore of great interest to find that Eggleton (1943), Eggleton and Smith (1946), and Barclay and Nutt (1944) have all found that the administration of moderate amounts of water cause a diminution in the rate of chloride excretion in man. It is therefore probable that moderate amounts of water do not call forth the emergency mechanism of the sugar hormones.

This diminution of the chloride excretion was slight, however, while the alteration in the rate of water excretion was great. It therefore seems likely that the response of the zona glomerulosa is tardy, as compared with that of the posterior pituitary mechanism. That this should be so seems reasonable, as an excessive fluid intake is clearly a much commoner occurrence than is an excessive salt intake, and as the excess of water can be got rid of so easily and quickly there is really no need to disturb the salt-controlling mechanism as well.

It is unfortunate that most of the experiments which have been carried out have been concerned with the reaction to excessive doses of salt or water, as it seems highly probable that the emergency mechanisms must be brought into play and complicate the result.
Pure Water Lack.

The mechanism by which lack of water produces depletion of the intracellular fluids is too well-known to merit description, but one or two points are worthy of discussion.

Just as in the experiments where an excessive amount of salt was given without water, the kidney is faced with the dilemma of excreting both salt and waste when there is not enough water to excrete both. As a result more water is lost than salt, with a rise in the osmotic pressure and the withdrawal of intracellular water to dilute the extracellular fluid. The rise in the osmotic pressure might again be thought to bring about a decrease in the secretion of electrolyte-controlling hormones so that the correct amount of salt may be allowed to escape through the kidney, but a further factor in addition to the preferential excretion of urea and other waste products may be the large amounts of potassium which are released from the cells. From the experiments of Deane, Shaw, and Greep (1948) it would appear that an excess of potassium may stimulate the zona glomerulosa to promote its excretion. This factor is, therefore, a possible contributory cause of the excessive reabsorption of salt.

Pure Salt Depletion.

Severe lack of salt, or loss of salt without restriction of water, will clearly bring about hyperactivity of the zona glomerulosa and inhibition of the
posterior pituitary, so that salt is held as completely as possible and water is excreted in order to prevent the fall in the osmotic pressure. The result is well-known to be loss of extracellular fluid, and a tendency for the intracellular compartment to become increased. As the osmotic pressure is falling, there is no thirst.

Another way in which the electrolyte-controlling hormones play a part in the economy of salt is by their effect on the sodium and chloride of the sweat. McCance (1938) showed that acclimatisation to heat is associated with a reduction of the salt content of the sweat, and Conn (1949) has shown that both ACTH and DOCA will cause a decrease in the salt content, which he also found to be reduced in Cushing's syndrome and markedly increased in adrenal insufficiency. Only a slight increase was observed in pituitary insufficiency.

Mixed depletion.

The result in mixed depletion manifestly depends upon which is the major deficiency, but it is possible that if the losses of water and salt are in the correct proportions there will be no disturbance of the osmotic pressure or thirst, and that loss of the volume of the body fluids might result without disturbing the posterior pituitary or adrenal mechanisms. It is obvious that such an eventuality is extremely unlikely, and it would be of interest to find out if any other mechanism comes into play to prevent it, such as thirst.
THE RELATIONSHIP BETWEEN THE HYPOTHALAMUS AND THE ENDOCRINE GLANDS.

Though the clinical and experimental effects of lesions of the hypothalamus suggest most strongly that the hypothalamus has a strong controlling influence over the function of the anterior pituitary and, directly or indirectly, over the endocrine system as a whole, the manner in which this control is exercised is still obscure. Perusal of the voluminous and often contradictory literature regarding this subject suggests that to review it would be of little profit, but certain recent work in this field is of such great interest as to be well worth recounting.

The evidence regarding hypothalamic control of the anterior and posterior lobes of the pituitary has recently been reviewed by Harris (1948). He points out that, as section of the pituitary stalk has not been found to interfere markedly with the functions of the anterior pituitary, its scanty nerve supply is unlikely to be of any great importance. On the other hand, the portal vessels of the stalk, unlike the nerve fibres, may regenerate after stalk section. Harris and others have therefore suggested that the hypothalamus may influence the functions of the anterior pituitary by means of humoral substances passing from the hypothalamus via the pituitary portal system. Lack of concrete evidence regarding the direction of the blood flow in these minute vessels has delayed acceptance of this
theory, but this point appears to have been settled recently by the direct observation of the hypophysial portal vessels of the living rat, which showed clearly that the blood flowed from the hypothalamus to the anterior pituitary. (Green & Harris 1949). As this most peculiar arrangement of vessels has been found in practically every living species it is reasonable to assume that they serve some purpose, and that if the direction of the flow is downwards in the rat this finding should also apply to man.

Keller (1948) has shown that, by removing varying amounts of anterior pituitary tissue in the dog, he could produce widely varying effects on the endocrine organs. By means of such methods he has produced dwarfing without disturbance of sexual or adrenal function, deficiency of sexual function alone, and deficiency of all the functions of the anterior pituitary without atrophy of the adrenal cortex. Total removal of the gland, without injury to the hypothalamus, was found to be incompatible with life without adrenal cortical substitution therapy, apparently on account of hypoglycaemic crises, but when the hypothalamus was intentionally injured as well all the deficits associated with the absence of the anterior pituitary, plus diabetes insipidus, were present, with the exception of atrophy of the adrenal cortex. Though such animals were able to live indefinitely and in a fair state of health, yet only a minute speck of pituitary tissue
could be found in the scar by serial sectioning. This remnant seemed to be so small as to be incapable of secreting enough ACTH to maintain the adrenal cortex in a normal state of activity.

It is very notable that carbohydrate metabolism was normal or nearly so in those animals in which the cortex did not atrophy, therefore the zona fasciculata could not have undergone any atrophic change. It is clear from the preceding discussions that the zona glomerulosa would probably not have atrophied in any case. Histological data regarding the adrenal cortices of these remarkable animals is most unfortunately not given.

The marked difference between the results of removal of part or all of the anterior lobe without coincidental hypothalamic injury, and with hypothalamic injury, has led Keller to point out that all previous work in this field must be regarded with grave suspicion, as the two organs are so close together that both may have been interfered with in many instances and thus produced the contradictory results which have been obtained by many previous workers. He has suggested that the hypothalamus may secrete hormonal substances, and quotes the work of Scharrer (1939), who showed that certain cells in the hypothalamic area contain secretory granules and may have endocrine functions. Keller suggests that the hypothalamus controls the endocrine system by means of antihormones, and that the
atrophy of the adrenal cortex following removal of the anterior lobe without injury to the hypothalamus is due to the unopposed action of the anti-corticotropic hormones. When both are injured the corticotrophic and the anti-corticotropic hormones are both removed, and the gland is left in status quo, but if only the anti-corticotropic hormone is removed by injury to the hypothalamus alone hypertrophy of the adrenal cortex and Cushing's Syndrome may be produced.

Heinbecker, White & Rolf (1944) succeeded in producing a condition closely resembling Cushing's Syndrome in the dog by bilateral destruction of the caudal paraventricular nuclei of the hypothalamus. A similar result was obtained by Ranson et al (1938) in a monkey. In five cases of Cushing's Syndrome in which none of the more commonly recognised causes of the condition were evident Heinbecker (1944) has demonstrated that degeneration of the same part of the hypothalamus was present, and he quotes an unusual case in which increased intracranial pressure due to a meningioma of the thoracic cord produced all the manifestations of Cushing's Syndrome as well as paraplegia. As the removal of the tumour was followed by the disappearance of the endocrine disorder, he has suggested that the increased intracranial pressure may have caused temporary functional impairment of these nuclei, which lie rather superficially. Heinbecker suggested that the absence of the secretions of the hypothalamus renders the anterior
pituitary much more sensitive to a fall in the concentration of the cortical hormones in the blood, thus causing pituitary hypersecretion and cortical hypertrophy. It is notable that, though Heinbecker is apparently unaware of the work of Keller, they have nevertheless come to similar conclusions. Further support for a possible hypothalamic origin of some cases of Cushing's Syndrome is provided by the recent report by Luft (1947) of endocrine disorders resembling Cushing's Syndrome following poliomyelitis in quite a large number of cases.

When this recent work is considered in conjunction with the possible role of the pituitary portal system in controlling the activity of the anterior lobe by means of humoral substances from the hypothalamus it seems probable that the function of this vascular arrangement may be to carry these antihormones to the gland. It is notable that in all Keller's animals there was a scrap of pituitary tissue left, and it is therefore possible that, in the absence of the hypothetical inhibitory hormone of the hypothalamus, this speck of tissue was capable of secreting enough ACTH to maintain adrenal function. It is well known that important organs have a surprising reserve of function, and it would be surprising indeed were an important organ like the anterior pituitary an exception to the rule.
The work of Pincus and his group regarding cortical function in schizophrenia, where they have shown that the cortex is somewhat refractory to ACTH, would suggest that the primary fault here may lie in the hypothalamus. At the same time, this work implies that a peripheral action of a possible hypothalamic antihormone on the cortex itself, and not on the anterior pituitary via the portal vessels, is also possible.

At the time of writing a preliminary report has just been published (Hume 1949) claiming that injury to a certain unspecified part of the anterior hypothalamus, or to its afferent tracts, abolishes the secretion of sugar hormones in response to stress as indicated by a failure of the fall in the eosinophil count. An extract prepared from the hypothalamus produced a fall in the eosinophil count both in normal dogs, and in those in which this response had been abolished by hypothalamic injury. Divesting the anterior pituitary of its vascular and nervous connections with the hypothalamus did not inhibit the stress response. Further confirmation is obviously essential, especially as it suggests that the hypothalamus secretes stimulating and not inhibitory substances, thus being in direct opposition to the work which has been reviewed above.

Though this recent work would appear to be of great possible significance, confirmation of these
findings and the demonstration of the effects of substances prepared from the hypothalamus must be awaited. They certainly suggest that a possible hypothalamic factor should be borne in mind in relation to disorders of the endocrine system, but further speculation on the implications of this work would be unwise in the present state of our knowledge.

Adrenaline has now been repeatedly shown to cause an increase in the secretion of the sugar hormones by the adrenal cortex. The work of Long (1941) has shown that adrenaline will cause a reduction in the blood content of the male adrenal cortex, but not in the female. Of the many substances in the blood, one of the most important is adrenaline, which increases the output of cortical hormones. This has been confirmed by Berson and Salk (1948), and it is shown also that stimulation of the adrenergic nerves...
THE "PSYCHO - SOMATIC LINKS".

Some years ago the work of Cannon firmly established the fact that emotion of fear, by activating the sympathetic nervous system, causes the adrenal medulla to secrete adrenaline, thus preparing the body for "fight or flight". This reaction might also be termed an emergency mechanism, depending on the nervous and not on the endocrine system, which enables the body to adapt itself very rapidly to sudden stress. At the same time, however, there is no doubt that lesser degrees of activation of this "sympathico-adrenal" system constantly occur in response to the stresses of everyday life.

Adrenaline has now been repeatedly shown to cause an increase in the secretion of the sugar hormones by the adrenal cortex. The work of Long (1947a) has shown that adrenaline will cause a reduction in the ascorbic content of the rat's adrenal cortex, but not in the absence of the pituitary. Vogt (1943 (1944) has obtained direct evidence, by estimations of the amount of cortical hormone in the blood in the adrenal vein of the dog, that the injection of adrenaline markedly increases the output of cortical hormone. This has been confirmed by Corcoran and Page (1948) and Vogt has also shown that stimulation of the splanchnic nerve
will not produce an increase in the secretion of cortical hormones unless the blood from the adrenal vein is allowed to return to general circulation.

Recant, Forsham and Thorn (1948) have shown that the administration of adrenaline to normal subjects produces a fall in the lymphocyte and eosinophil counts comparable with that observed after an injection of ACTH. Patients with pituitary insufficiency showed no such response, and patients with Addison's disease a response roughly equivalent to the clinical severity of the disease.

Gershberg and Long (1948) showed that, in the rat, the production of insulin hypoglycaemia produced a large decrease in the adrenal ascorbic acid, which did not occur if the insulin was covered with glucose. The administration of glucose did not prevent the activation of the adrenal cortex by cold or trauma, where the release of adrenaline is due to causes other than hypoglycaemia. Godlowski (1948) found that both insulin shock treatment and adrenaline infusion caused an eosinopenia, when these measures were employed in the treatment of asthma.

Gellhorn et al. (1941) have shown that in the rat emotion, or sham rage caused by hypothalamic stimulation, causes activation of both sympathetic and parasympathetic systems. Normally the blood sugar rises as a result of emotion, but after removal of the adrenal medulla it falls, owing to the unopposed secretion of insulin produced by vagal stimulation. Section of the vagi in
addition abolished the fall in blood sugar, so that emotion produced neither rise nor fall. This work suggests that in response to stress insulin is secreted as well as adrenaline in order to enable the body to utilise the extra sugar, and to preserve the hormonal balance.

The peripheral action of adrenaline in increasing the rate of tissue metabolism, thus increasing the need for cortical hormones and thereby causing indirect stimulation of the anterior pituitary to pour out more ACTH, has been suggested by Sayers and Sayers (1948) as the most likely manner in which the adrenal cortex is stimulated by adrenaline.

A link between the nervous and the endocrine systems has thus been demonstrated to exist, and it is clear that such a link may assist the body to act at all times as a perfectly co-ordinated whole. While any cause of increased tissue metabolism will cause an increase in the amount of cortical hormones secreted by the cortex quite independently of the nervous system, the psycho-somatic link described above may provide a fine adjustment which comes into play when activity above the level necessary for the prevailing rate of metabolism is demanded.

The thyroid gland is controlled by the anterior pituitary in a similar manner to the adrenal cortex. A study of the literature regarding the manifestations of adrenaline-secreting tumours of the adrenal medulla.
reveals that hyperthyroidism is not only a frequent accompaniment of these tumours and a common initial diagnosis, but that exophthalmos (Belt and Powell 1934), and in one case visible swelling of the gland (Bauer and Belt 1947), has been observed during an attack. Denervation of the adrenal gland was reported by Crile (1934) to be a highly successful mode of treatment of hyperthyroidism.

The partnership between the sugar hormones and the thyroid hormone which has previously been referred to has been further elucidated in connection with the investigation of the effects of adrenaline on the thyroid.

Soffer et al. (1947) administered adrenaline in oil to the dog and found that after some days hyperplasia of the gland was produced. They also found that adrenaline caused an increase in the amount of circulating thyrotrophic hormone which was maximal at between the fourth and fifth days and then declined. Reiss, Forsham, and Thorn (1949) reported that the uptake of radio-active iodine by the thyroid is decreased in Addison's disease, and that the administration of compound E or cortical extract caused a marked increase in the uptake of radio-active iodine, which reached a maximum in two or three days and then declined. The administration of adrenaline to normal subjects who also received radio-active iodine resulted in an increase in the uptake of radio-active iodine which was at its maximum between the third and fourth hour
after the adrenaline, thus coinciding with the maximum drop in the eosinophil count. No such response was obtained in Addisonian patients, nor in a case of Simmond's disease which had been found responsive to both ACTH and thyrotrophin. A similar experiment by Soffer et al (1949) in the rat produced an apparently contradictory result, which seems likely to be due to species differences.

This recent work would appear to suggest that the response of the thyroid to adrenaline runs parallel to that of the adrenal cortex, and that there may also be a mutual relationship between the two glands. It is also pertinent to note that it is firmly established that thyroxine potentiates the action of adrenaline, and that it is an old observation that adrenaline causes a marked rise in the metabolic rate (Goldzieher 1944). It is now not clear whether this latter effect is direct, indirect, or both.

It seems highly probable that the adrenal cortex and the thyroid work in close harmony in accordance with metabolic requirements, and that dysfunction of the one must produce dysfunction of the other. The evidence is at least suggestive that the sensitivity to cold which is found in the patient with adrenal insufficiency may be in part due to decreased activity of the thyroid.

In accordance with this evidence, the hormonal equilibrium in conditions which do not involve the secretion of adrenaline has been presented in Fig. 5.
and the effects of emotion on this system in Fig.6.

That this "psycho-somatic link" should be the only one is manifestly absurd, and it is quite obvious that the hormonal requirements of increased activity can be satisfied in a very simple manner. For example, in any form of muscular activity the muscles obey the orders of the central nervous system via their peripheral nerves. The increased rate of utilisation of the hormones by the tissues must result in a fall in their concentration and release of the pituitary, so that the demand is met by extra secretion by the glands involved. On the other hand, in the absence or dysfunction of the fine adjustment via the adrenaline mechanism there is no doubt that a degree of inco-ordination of the nervous and endocrine systems could occur, with functional limitation of the capacity for exertion, as in the neuroses.
The Hormonal Equilibrium at Rest.

Fig. 5.

Tissue metabolism at basal level as during sleep

- Minimum need for thyroxine
  - Inhibition of pituitary almost complete
  - Minimum secretion of thyrotrophic hormone
    - Secretion by thyroid of just enough thyroxine for basal requirements

- Minimum need for sugar hormones
  - Inhibition of pituitary almost complete
  - Minimum secretion of ACTH
    - Secretion by adrenal cortex of just enough sugar hormones for basal requirements.

Note: Under conditions which do not cause excessive secretion of adrenaline the above relationships still hold good, the rate of tissue metabolism, and therefore the rate of utilisation and secretion of these hormones, simply becoming set at a higher level.
Fig. 6. The Psycho-somatic Link.

Emotion

↓

Hypothalamus

↓

Sympathetic → Parasympathetic

↓

Adrenal Medulla

↓

Adrenaline

↓ Increased Tissue Oxidation

↓

Increased utilisation of thyroxine

↓

Decrease in blood concentration of thyroxine

↓

Release of inhibition of pituitary by thyroxine

↓

Secretion of more thyrotrophic hormone

↓

Stimulation of thyroid

↓

Production of more thyroxine

↓

Increased need for hormones in tissues satisfied

Thyroxine potentiates action of adrenaline on tissues

↓

Increased secretion of insulin

need for more insulin to promote utilisation in tissues of extra glucose produced by 'S' hormones and by adrenaline

by 'S' hormones

↓

Inhibition of utilisation of glucose in tissues
The Effects of Adrenaline on the Differential Blood Count.

Despite the recent work which has shown that the injection of adrenaline causes a marked fall in the lymphocyte and eosinophil count and some rise in the neutrophils some four hours afterwards as a result of the secretion of the sugar hormones, it is generally accepted that adrenaline brings about a marked rise in the lymphocyte count which is at least partly due to contraction of the spleen. This apparent paradox has recently been elucidated by Hortling and Pekkarinen (1949), who have shown that the initial effect of adrenaline is to cause a marked rise in the lymphocyte count, and a lesser rise in the neutrophil and eosinophil count. A few hours later the lymphocytes and the eosiniphils fall markedly, while the rise in the neutrophils persists. Michael (1949) has also shown that the sequence of events is as above, and has made an extensive review of the older literature which is of great interest in the light of recent developments. He has further shown that the differential count is affected in the same manner after shock therapy, and has reviewed the literature to show that the same sequence follows other forms of stress, such as epileptic fits.

Von Euler and Luft (1949) have reported that nor-adrenaline has no effect on the differential count, and therefore probably does not cause the secretion of sugar hormones.
The Psycho-somatic links in Mental Disorders and in Normal Subjects under Stress.

As the data indicating the existence of the links between the Psyche and the soma have just been discussed, it is logical to consider at this juncture the research which has been carried out in the last few years regarding the pituitary-adrenal response to various forms of stress in the normal subject, particularly that involved in piloting modern aircraft, and the parallel investigation which has been proceeding in respect of this response to stress in schizophrenia and in psychoneurosis. The results of these investigations have been reviewed by Pincus (1946) and by Hoagland (1947), and the results of a most exhaustive investigation in schizophrenia have just been published by Pincus et al (1949). Though the reviews quoted above are adequate, it is felt that further discussion is necessary here in relation to the significance of the data which has been obtained in relation to general medicine, the so-called psycho-somatic disorders, and adaptive dysfunction. Recent evidence which is relevant to this subject has also been included in order to bring this discussion up to date.

In 1943 Pincus had found that the 17 ketosteroid excretion in normal subjects exhibited a regular daily rhythm, being lowest in sleep, rising to a maximum shortly after waking, and then declining progressively throughout the day. Further investigation showed that a call to emergency duty was marked by a pronounced
rise in the 17 ketosteroid excretion, and that night duty brought about a reversal of the rhythm. Piloting an aircraft produced a rise in the excretion which increased in proportion to the length of the flight and the degree of anoxia and fatigue. A most ingenious device was also used by which the stress of piloting an aircraft could be applied to the subject on the ground, and similar results obtained (Pincus 1946). The response to heat was found to be similar (Pincus and Elmadjian 1946).

The lymphocyte counts throughout the day were also found to be subject to a daily rhythm, which was the reverse of that of the 17 ketosteroids, being highest in sleep, declining to a minimum shortly after waking, and then rising gradually throughout the day. (Elmadjian and Pincus 1946). An abrupt drop in the lymphocyte counts in response to the administration of glucose in man and in the rat was observed by Elmadjian, Freeman and Pincus (1946), and this has been found not to occur in the absence of the anterior pituitary (Pincus 1949).

Pincus (1946, 1949) found that both stress and the glucose tolerance test produced a drop in the lymphocyte count in the normal individual which bore an inverse relationship to the blood sugar, and in response to stress an inverse relationship to the rise in the 17 ketosteroid excretion. Pincus (1949) has shown that stress causes a rise in both 17 ketosteroid and in corticoid excretion, while the glucose tolerance test
produces a rise in corticoids only.

The 17 ketosteroids, though partly of testicular origin in the male, are thought to represent mainly the end-products of the cortical androgens. Sprague, et al. (1949) have, however, reported that the administration of compound E to patients with Addison's disease results in a rise in the excretion of both 17 ketosteroids and corticoids. As Forbes et al. (1947) and others have established that the 17 ketosteroid excretion following severe stress rises sharply and then falls to a low level until recovery, it would appear that for a short-term observation in temporary stress the excretion of these steroids may be a fair indication of cortical activity, and moreover one easily estimated. Pincus (1949) has also shown that the corticoid excretion behaves in a similar manner to the 17 ketosteroids in response to stress.

All these observations have also been carried out in schizophrenic patients, and Pincus et al. (1949) have found that they do not respond to either stress or to 25 mgms of ACTH by a rise in the excretion of 17 ketosteroids, corticoids, uric acid, sodium, and potassium, and by a fall in the lymphocyte count as does a normal person. Only about half of them responded to a glucose tolerance test by a fall in lymphocytes and an increase in the uric acid as in a normal subject, and the blood sugar curve tended to be flat.
A response to ACTH could be obtained by giving a dose of 75 to 100 mgms, so that it would appear that the cortex is to some extent refractory to stimulation. As the injection of cortical extracts has been found to cause the same changes in the blood and in the urine in the schizophrenic as stress or ACTH in the normal subject, it seems probable that the deficiency of the cortical response is one of quantity rather than quality.

Pincus (1946) has reported that some psychoneurotic subjects fail to respond to stress in a similar manner to the schizophrenic, and that they may have excessively high ketosteroid excretion in the morning followed by an abnormally low excretion during the rest of the day. This observation would appear to have a possible connection with the symptomatology of these disorders. He found that the total 17 ketosteroid excretion of the psychotic and psychoneurotic subjects per day is not markedly different from the normal, and that it is only in response to stress or after serial observations that the abnormality shows up. Shock therapy in schizophrenia has been reported by Hoagland et al. (1946) to bring about a return to the normal 17 ketosteroid rhythm if successful, suggesting that such a severe stimulus may have the effect of re-establishing normal relations between the nervous system and the adrenal cortex. So far the evidence on this point is no more than suggestive, however. It is also of interest in this connection that Hemphill et al. (1942) found that the 17 ketosteroid
excretion increased markedly following leucotomy, and that very good results were obtained in the treatment of involutional melancholia by means of ACTH.

A further aspect of the problem which has not been mentioned by Pincus and his group has been raised by the demonstration by Gellhorn et al. (1941) by means of bio-assay methods that, while the normal subject exhibits a rise in the blood sugar as a result of emotion, the schizophrenic patient secretes excess of insulin and does not have a rise in the blood sugar as a result of emotion. It would appear from this observation that it is possible that in addition to the failure of the adrenal cortex to respond to stress in this psychosis the vago-insulin system may also be over-active, and further aggravate the endocrine imbalance.

All these observations would suggest that in schizophrenia and in some cases of psychoneurosis the normal co-ordination between the psyche and the soma is disturbed, and that the adrenal cortex does not respond to the situations of daily life and work like a well-oiled machine as in the normal person. The fault appears to lie in the response of the adrenal cortex to the anterior pituitary, or that there is some influence which either inhibits this response or destroys or inactivates ACTH before it can reach the cortex.

It is, of course, not possible to estimate how big a part may be played by psycho-somatic dissociation or inco-ordination in the production of the somatic and the mental components of a neurosis, for example. It seems
to be of possible significance, however, that the commonest error in the early diagnosis of Addison's disease is to mistake it for a psychoneurosis. This clinical observation would suggest that lack of the sugar hormones may have some influence over mental activity. This is supported by the reports that one of the effects of compound E or ACTH in the treatment of rheumatic and other diseases is pronounced euphoria and a feeling of well-being. In one case mania has been reported as a result of this treatment. Forsham et al. (1949) have recently published a preliminary report that the administration of compound E to 14 cases of Addison's disease caused "a return towards normal of the electro-encephalogram."

It therefore does not seem unreasonable to suggest that, though the failure of the cortex to respond normally to stress must be an effect rather than a cause of a psychosis or neurosis, the resultant slight deficiency of sugar hormones may be responsible for setting up a vicious circle mechanism which aggravates the mental condition.

These recent developments would seem to confirm the many earlier suggestions, based on clinical observation, that there are many features of schizophrenia which suggest hypofunction of the adrenal cortex, and the early reports that cortical extracts brought about improvement in the condition. (Loehner 1938, 1940.)

Though there is not such a clear-cut body of evidence in favour of the response of the adrenal cortex
being faulty in the neuroses as there is in schizophrenia, it must be borne in mind that the methods by which these investigators have elucidated this defect are insensitive, and that dysfunction of this sort which would not be unequivocally detectable might well be actually present in many cases. There is, therefore, no bar on account of lack of evidence to the suggestion that the somatic symptoms of the neuroses and other "psycho-somatic" disorders may be largely due to partial failure of the adrenal cortex to respond to the stresses of life in a normal manner.

It is noteworthy that the average psychoneurotic patient exhibits clear clinical evidence of sympathetic overactivity, despite which Pincus has found that some do not respond to stress by an increase in the secretion of the cortical hormones. It would appear that even gross sympathetic overactivity fails to activate the adrenal cortex, while the direct effects of this overactivity aggravate the symptomatology of the disorder. It is of interest that Crile, in 1934, reported that the operation of adrenal denervation was very successful in the treatment of effort syndrome. It would appear possible that, apart from the purely mental aspect of the neuroses, sympathetic overactivity, refractoriness of the adrenal cortex to stimuli which would ordinarily cause secretion of more sugar hormones, and perhaps overactivity of the vago-insulin system as well, may all be concerned in the production of the somatic manifestations.

Though at first sight it would seem possible that
the extensive sympathectomies which are now performed for the relief of hypertension might produce some of the somatic symptoms of a neurosis, it is obvious that the relief of the hypertension will obscure any such effect.

These most interesting developments would suggest that when an individual is subjected to environmental stress of such intensity that he finally fails to maintain adaptation to it and develops a neurosis, the adaptive failure is not solely at the mental level, but also involves a degree of inco-ordination between the nervous and the endocrine systems which must play a part which is difficult to define in the causation of the somatic symptoms which are associated so commonly with the mental upset. It is well recognised that the worry occasioned by the somatic symptoms may play a prominent part in aggravating and perpetuating the mental symptoms, so that a vicious circle is formed. The psychiatric method of treatment is time-consuming and often unrewarded, especially if the underlying environmental cause of the mental breakdown of adaptation cannot be removed. It is therefore possible that, if some way of treating the somatic manifestations can be discovered, the task of the psychiatrist may be made considerably easier by breaking the vicious circle at the somatic link, thus restoring confidence and convincing the patient that he is getting better. Pregnonolone
would seem, according to the scanty reports, to be a drug of possible promise in this connection.

The relationship of cortical activity to the onset of fatigue has also been investigated by Pincus and his group of investigators, with particular reference to aircraft pilots. These stress experiments were carried out by means of the equipment previously referred to which enabled the stresses of flying to be simulated on the ground. It was found that the 17 ketosteroid excretion increased in proportion to the number of errors made in the performance of the test. Individual variation was great, but it was found that those whose 17 ketosteroid excretion did not increase markedly made much fewer errors.

While the administration of cortical extracts will not relieve fatigue because of its action in suppressing the production of the endogenous cortical hormones, it has been found that a new synthetic steroid, pregnonolone, does not suppress the pituitary and exerts a sparing action on the cortex. Hoagland (1947) has found that this steroid will delay the onset of fatigue, but this effect is, naturally enough, only demonstrable when the subject is working to the utmost of his ability. Thus when it was given to factory workers an improvement in output and in the quality of the work was only noted in those who were employed on a piece-work basis. Hoagland (1948) has shown that pregnonolone will prevent to some extent the loss of brain potassium which occurs in
rheas subjected to prolonged stress, and he has pointed out that there is much evidence suggesting that loss of brain potassium plays a part in the production of fatigue. Davison and Koets (1949) have reported that pregnonolone has a striking therapeutic effect on ankylosing spondylitis, which is accompanied by a reduction of the increased 17 ketoesteroid excretion to normal.

It is apparent from the above brief summary of this recent work that we are only beginning to understand the part which is played by the endocrine glands in the maintenance of efficient adjustment of the individual to his environment, and perhaps even over the mental make-up and personality of us all. Much more work must be done, however, before it may be possible to help the mal-adjusted individual by the administration of specific therapy, and it is to be hoped that if such therapy is finally introduced it will be used without neglecting the psychiatric aspects of failure to maintain adaptation to the environment.
THE PATHOGENESIS OF HYPERTHYROIDISM.

The clinical and experimental evidence suggesting that overactivity of the sympathetic nervous system may play a part in the causation of hyperthyroidism has already been reviewed, and the relationship between the adrenal cortex and the thyroid discussed. As the role of stress in the causation of many cases of hyperthyroidism is more obvious than in any other stress disease, it is felt that some further analysis of the possible role of the sympathetic nervous system in the pathogenesis of this disorder is necessary.

That thyroxine potentiates the action of adrenaline is a well-established observation, and one which would suggest that a vicious circle mechanism may be formed in some cases of hyperthyroidism.

Thus, if the peripheral action of excess of adrenaline increases the rate of utilisation of thyroxine in the tissues the result will be the release of pituitary inhibition, the secretion of more thyrotrophic hormone, and of more thyroxine, which will further potentiate the action of adrenaline. In this way it would seem possible that prolonged or very intense sympathetic overactivity may stimulate the pituitary and the thyroid to the point at which one or the other gets completely out of control. The report of Crile (1934) that adrenal denervation was 95% successful in the treatment of hyperthyroidism is therefore of some interest, as this procedure would cut any such vicious circle,
and would suggest that the results of the administration of one of the newer adrenolytic drugs in hyperthyroidism might be of interest, even if not therapeutically applicable. This hypothesis is based on few facts, but it would appear to be in accord with the clinical features and history of many cases.

Just as few would doubt that emotional disturbance plays a prominent part in the causation of many cases of primary hyperthyroidism, so, few would aver that the association is an invariable one. Some light has recently been shed on this aspect of the subject by the work of De Robertis (1948) who made direct assays of the thyrotrophic hormone in the blood of hyperthyroid and hypothyroid patients. His results confirm the long-standing suspicion that there may be two types of hyperthyroidism and two types of myxoedema.

He found that in some cases of hyperthyroidism the circulating thyrotrophic hormone was decreased, suggesting that the thyroid itself might have got out of control and that the excess of thyroxine suppressed the production of thyrotrophic hormone, or that the pituitary was not secreting the hormone for some reason. In others he found that the level of circulating thyrotrophic hormone was very high, in association with exophthalmos, so that the disease was primarily of pituitary origin. Likewise, he found that some cases of myxoedema had an increase, and others a decrease, in the amount of thyrotrophic hormone, just as would be expected in view of the occasional
association of exophthalmos, sometimes malignant, with myxoedema. In those with excess of thyrotrophic hormone it seems that the thyroid has failed, and in those with a decrease that the pituitary has failed. The rarity of exophthalmos in myxoedema remains to be explained, however.

It would seem from the above that the presence or absence of exophthalmos may perhaps be a rough clinical indication of the type of the disease with which the patient is afflicted, and would suggest that the common primary hyperthyroidism with exophthalmos in young subjects is of pituitary origin, while the masked type without exophthalmos in the older person is probably of thyroid origin.

No attempt has been made here to deal with the other endocrine inter-relationships of the thyroid, nor to explain the predominance of the female sex, though it is clear that there are many other factors concerned in the causation of this disease. Emphasis has been placed on the possible role of the adrenal medulla because it seems clear that in many cases this disorder represents a clear example of over-adaptation to stress, and that the frequency of this form of endocrine dysfunction indicates that there must be some weakness in the control of the thyroid which readily allows hyperthyroidism to occur. The possible significance of the rarity of Cushing's Syndrome in contrast to the frequency of this disease is commented on elsewhere.
THE ROLE OF STRESS IN THE PATHOGENESIS OF PEPTIC ULCERATION.

The frequency with which duodenal ulcer is associated with prolonged environmental stress and emotional disturbances resulting from it has resulted in the prevalent view that this disease is usually a psycho- somatic disorder in which the ulcer represents the somatic component.

It is a most remarkable fact that gastric or duodenal ulcer is very rarely found in patients suffering from diabetes mellitus. Conversely, it is now well recognised that hyperinsulinism is not uncommonly associated with symptoms simulating peptic ulcer, and sometimes with mental disturbances which resemble psychoneurosis. These facts would suggest that an element of hypoglycaemia might be associated with the pathogenesis of duodenal ulcer.

If duodenal ulcer is considered from the point of view of the associated emotional disturbance, it is of some interest to surmise how a hypoglycaemic tendency could result from such manifestations of failure to maintain adaptation to stress.

In the preceding section it was made clear that, according to the available evidence, emotion activates both divisions of the autonomic nervous system, so that the secretion of sugar hormones and adrenaline is to some extent matched by the secretion of insulin as a result of vagal stimulation. Thus, though the initial effect is a rise in the blood sugar, secretion of the insulin may prevent any such rise getting out of control. Vagal hyper-
activity may cause preponderance of the secretion of insulin as a result of emotion, while refractoriness of the adrenal cortex may result in the absence of the secretion of the sugar hormones to balance it. Such a state of affairs has been shown to exist in schizophrenia, where there is evidence that both defects may exist simultaneously, and it has been pointed out that there is no bar to the suggestion that lesser degrees of cortical refractoriness may not exist in the neuroses, or even in duodenal ulcer. In the case of duodenal ulcer, however, we have definite evidence that the vagus is hyperactive, and according to the above one might suspect that the encouraging effects of vagotomy may not be entirely due to its effects on gastric secretion and motility. Comparison of glucose tolerance curves before and after vagotomy might therefore be of some interest, though it would seem entirely probable that the control of insulin secretion via the vagus is of the nature of a fine adjustment only.

On the grounds of vagal hyperactivity and the suspicion that the emotional component may bring about a degree of dysfunction of the psycho-somatic link, it would seem that it is possible that a tendency to hypoglycaemia might be brought about in duodenal ulcer.

Hypoglycaemia, like emotion, activates both divisions of the autonomic nervous system. While it is clear that the excess of adrenaline which is secreted must be an emergency mechanism to raise the blood sugar quickly, we may now add that a secondary
effect must be the secretion of more sugar hormones in order to maintain the blood sugar at a higher level. The coincidental vagal stimulation results in gastric hypersecretion, hypermotility, and hunger. It is probable that insulin is secreted as well, but that its action is swamped by the effects of adrenaline, and would seem more likely to come into action later to balance the secretion of the sugar hormones.

While the reaction to a definite hypoglycaemia is as above, the reaction to one of milder degree would seem unlikely to involve much more than vagal stimulation, so that the intake of food is induced and the hypoglycaemia averted without much secretion of adrenaline.

It is well established that a rise in the blood sugar directly stimulates the islets to produce insulin, and indeed the fact that the amount of carbohydrate in the diet has a definite effect on the glucose tolerance curve is an excellent example of adaptation in an endocrine gland. In consequence of the work of Pincus and his collaborators we now know that the increased secretion of insulin as a result of a rise in the blood sugar is matched by a rise in the secretion of the sugar hormones, and that refractoriness of the adrenal cortex may affect the glucose tolerance curve, and the lymphocyte response.

Having summarised this evidence, it at once becomes clear that vagal overactivity or dysfunction of the psycho-somatic link can produce a tendency to hypoglycaemia, and that the fine
adjustment of insulin secretion would seem more robust than the psycho-somatic link. In view of lack of evidence regarding functional variations of its secretion the diabetogenic hormone of the anterior pituitary has been left out of this discussion, and any influence of the thyroid has also been omitted as it would not seem a major factor.

The number of endocrine and other factors which may affect the glucose tolerance curve is so great as to render its interpretation a matter of great complexity. It does seem clear, however, that those factors which respond to a rise in the blood sugar cannot come into action until the rise has taken place. In consequence, it would seem most probable that the falling part of the curve is that part which is most affected by endocrine and other factors. It is now generally agreed that the steep rise which characterises the lag type of curve is most commonly the result of rapid absorption. If all other factors are excluded from the argument, it follows that the steep fall which follows may be due to excess of insulin, or to lack of sugar hormones, and that the course of the largely blood sugar thereafter is also governed by the relationship between the two. The course of the blood sugar level after the first few hours is also of some interest as, if the cortical response is transitory the curve may be normal, but the level may drop below normal after some hours.

Though this discussion has been very hypothetical,
it has perhaps served the purpose of illustrating the manner in which a hypoglycaemic tendency may arise in any psycho-somatic illness. It does not explain why duodenal ulcer is not common in schizophrenia or in many other states, so that it is clear that it can only be one possible factor to add to the large number already known to play some part in the causation of duodenal ulceration. Having gone thus far, it is now possible to consider the evidence which has been obtained from investigations of the metabolism of carbohydrate in duodenal and gastric ulcer.

Abrahamson (1945) carried out an investigation of the possible role of hyperinsulinism in a small series of cases of gastric ulcer, duodenal ulcer, and some patients who had the symptoms of ulcer but negative radiological findings. Though this investigation cannot be regarded as significant on account of the small number of cases and the absence of controls, it is of some interest on account of the type of glucose tolerance test which was used and the uniformity of the results. The test consisted of 100 Gms. of glucose given when fasting, followed by six-hourly blood sugars. This test was later modified so that the glucose was taken in the early morning and only the sixth hour sugar was taken. In all 31 cases, though the fasting sugars varied widely, the sixth hour blood sugar was below 70 mgms. This test had to be stopped on account of pain in a few cases only.

An extensive investigation of the relationship between carbohydrate metabolism and gastric secretion,
with particular reference to duodenal ulcer, has recently been carried out by Muir (1949). Many aspects of this work, which includes a review of many previous observations regarding the subject, are relevant to the present discussion. In brief, Muir has confirmed previous findings that about 15% of patients with duodenal ulcer have a "lag" type of glucose tolerance curve, and that a few of these patients have gastric symptoms of hypoglycaemic origin. He concluded that there is a tendency to hypoglycaemia in patients with duodenal ulcer, and that under conditions of physical work this tendency might be more prominent. It was found that insulin hypoglycaemia had a greater stimulatory effect on gastric secretion and motility in a small series of patients with duodenal ulcer than in normal individuals.

He found, however, that the typical ulcer pain was not commonly associated with hypoglycaemia, and was not relieved by glucose, though often by alkali. The hypoglycaemic symptoms occurred later, were not relieved by alkali but by glucose, and could be differentiated in many ways from the typical ulcer pain. Finally, in ten patients with duodenal ulcer who had not complained of hypoglycaemic symptoms it was found that insulin hypoglycaemia caused no discomfort of any kind, and in others who were liable to hypoglycaemic pain the induction of insulin hypoglycaemia on a fasting stomach just after a large dose of alkali produced the hypoglycaemic symptoms. It was,
therefore, thought that the mechanism of production of the two varieties of pain was unlikely to be identical, and that the hypoglycaemic pain was not due to its effect on gastric secretion, but to some direct effect of the hypoglycaemia.

Not only is the interpretation of this recent evidence a matter of great difficulty, but it also clearly suggests that hypoglycaemia only plays a part in a minority of cases. On the other hand, the rarity of peptic ulcer in the diabetic, and the demonstration that hyperglycaemia inhibits gastric secretion, still suggests that a tendency to hypoglycaemia may predispose to ulceration. It would seem probable that, though hypoglycaemia is seldom associated with the production of symptoms, a tendency for the blood sugar to be low might act as a factor which could cause chronic hyperchlorhydria and predispose to ulceration if the other contributory factors are also present. It is perhaps unfortunate that the six hour glucose tolerance test was not used in this investigation, as it might have shown up any such tendency to hypoglycaemia.

Barclay and Bentley (1949) while carrying out an investigation of the vascularisation of the human stomach, have made observations which may have some application to the problem of peptic ulcer. By means of the injection of radio-opaque material they have succeeded in demonstrating that there are large arterio-venous shunts in the sub-mucous connective tissue of the stomach wall, and have produced evidence that these shunts are opened by the sympathetic,
so that the mucosa may be starved of blood.

In the well-known studies of Wolf and Wolff (1943) on the influence of the emotions on the gastric mucosa as observed in a subject with a gastrostomy, it was noted that fear or depression produced pallor of the mucosa, hyposecretion, hypomotility, and decreased mucin production. It would appear that the effects on the colour and secretion noted were most probably due to the opening of these shunts. They also found that resentment, anxiety, and anger were associated with hypersecretion, hypermotility, hyperaemia, and increased mucin production. According to Zane (1947) the type of mental conflict which is most commonly found in peptic ulcer patients is a combination of fear and resentment, and states that according to Wolf fear and resentment cause hypersecretion, hypermotility, and decreased mucin. As mucin has been shown to have the property of protecting the mucosa from the action of the gastric juice, this type of response would seem particularly liable to result in ulceration.

All these observations have been entirely concerned with the gastric responses to emotion, and we are completely in the dark regarding the effects of emotion on the duodenum, in which ulceration is much commoner and has a clearer relationship to stress. Nevertheless, it would seem very probable that, even if the effect is in the duodenum, the cause lies in the hypersecretory and hypermotile stomach.

This discussion has, as would be expected, thrown
little light on the factors which may combine to promote the occurrence of gastric or duodenal ulceration, except in that it is suggested that the associated emotional disturbances may cause a degree of endocrine imbalance as well as of autonomic imbalance, and that the combination of these two factors may be of some importance in pathogenesis.

As a result of the work of Selye and others it has become firmly established that the reactions of the body to prolonged stress caused by any sort of damaging agent follow a well-defined sequence of events which constitute the "General Adaptation Syndrome" of Selye. In the initial and in the final stages of the adaptation syndrome the leading part is played by the autonomic system, particularly the adrenal cortex and the anterior pituitary, and this endocrine reaction to stress is completely non-specific and totally irrespective of the nature of the damaging agent which is causing the stress.

Selye has defined the General Adaptation Syndrome as: "the sum of all the non-specific reactions of the body which occur under exposure to stress. It is distinct from the specific response to the nature of the stress".
THE GENERAL ADAPTATION SYNDROME.

General Review
During the past fifteen years or so the reactions of the body to a great variety of damaging agents have been closely studied, particularly by Hans Selye, whose most comprehensive review (1946a) is the basis of the following brief outline of the subject, though differing from it in many respects. This outline has been couched in general terms as far as possible in order to give a clear conception of the adaptation syndrome without becoming confused by a mass of detail.

As a result of the work of Selye and others it has become firmly established that the reactions of the body to prolonged stress caused by any sort of damaging agent follow a well-defined sequence of events which constitutes the "General Adaptation Syndrome" of Selye. In the initial and in the final stages of the adaptation syndrome the leading part is played by the endocrine system, particularly the adrenal cortex and the anterior pituitary, and this endocrine reaction to stress is completely non-specific and totally irrespective of the nature of the damaging agent which is causing the stress.

Selye has defined the General Adaptation Syndrome as: ... "the sum of all the non-specific, systemic reactions of the body which ensue upon long continued exposure to stress. It is distinct from the specific
adaptive reactions, such as the development of the musculature following prolonged muscular exercise, the allergic and immunologic phenomena elicited by foreign proteins or micro-organisms, etc. These latter reactions usually endow the body with a great deal of resistance against the particular agent to which it has previously been exposed, but both the manifestations of these adaptive reactions and the resistance which they confer upon the body, are specific to the agent which elicited them."

It is felt that, though the above definition is correct in so far as the sequence of events and the initial and final stages of the adaptation syndrome are completely non-specific, it is not in any way justifiable to exclude specific adaptive reactions, particularly those of an immunological nature. The correctness of this point of view will appear as the present discussion develops, and will be fully clarified later.

The adaptation syndrome has been divided by Selye into three distinct stages; namely, the "alarm reaction," the "stage of resistance," and the "stage of exhaustion."

The alarm reaction comprises all the phenomena which result from sudden exposure to any form of stress to which the body is not adapted. Such stresses are, of course, extremely diverse, and include all forms of trauma, cold, heat, burns, histamine, poisons, bacterial toxins, X-rays, infectious diseases, haemorrhage, anoxia, and even severe muscular exercise, rage,
fear, and loud noises. All these, and many more, produce the same non-specific reactions on the part of the body to resist the effects of the stress, and the intensity of the reaction varies according to the intensity of the stress and the ability of the body to withstand it. From this list it is obvious that any sudden change in the environment, internal or external, of sufficient severity to produce "alarm", brings the non-specific adaptive processes of the body into action. If the type of stress is very severe, such as burns or trauma, the alarm reaction consists of two distinct stages, "shock" and "countershock." If the exposure to stress is not very sudden, or the stress is relatively mild, the phenomena of the countershock phase become evident without any preceding shock phase. In the shock phase the first reaction is on the part of the sympathetic nervous system. The adrenal medulla pours out adrenaline, with all its well-known effects, but this is only a temporary short-term adaptive mechanism, which only operates in the first few minutes and is speedily exhausted. The stores of cortical hormones in the adrenal cortex are discharged completely, but are insufficient to cope with the situation, so that the cortex becomes completely depleted of its lipoids. The resistance thus produced is soon overcome, and the manifestations of the shock phase set in. In this phase it is probably true to say that the endocrine system, having been caught unprepared and
shot its bolt by the discharge of all the cortical hormones, is temporarily knocked out, and that the resistance of the body to stress in the shock phase does not depend on endocrine factors. It is evident that death may occur in this phase before the adaptive processes which depend on the anterior pituitary and the adrenal cortex can recover from the onslaught and begin to reverse the changes which are characteristic of this phase. Should death not occur, these processes begin to recover and the countershock phase begins.

In the countershock phase the manifestations of the shock phase are reversed, and indeed over-corrected, and the animal begins to recover. In this phase the adrenal cortex and the anterior pituitary play a leading part, as in the absence of either gland the shock phase is not only very severe, but the countershock phase is negligible or absent, and slight degrees of stress cause severe symptoms or death. If such an animal survives the initial shock, the subsequent stages of the syndrome can still be distinguished, but they are "telescopied" into a much shorter period of time before death occurs. Some form of adaptation can, therefore, take place in the absence of the adrenals or the pituitary, but the resistance to stress is very low.

In the countershock phase there is rapid hyper trophy of the adrenal cortex, with greatly increased production of its hormones. The atrophy of the thymus and lymphoid tissue and the fall in the lymphocyte
count which is characteristic of this phase is clearly due to the excessive amounts of sugar hormones which are being secreted. At the same time the disturbance in the electrolyte balance which occurs in the shock phase must have the effect of increasing the output of electrolyte controlling hormones by the zona glomerulosa in order to correct it.

The many changes characteristic of the shock and counter-shock phases of the alarm reaction are best summarised together, as follows:

The body temperature, the urine output, and the blood volume, chlorides, and sodium, all fall in the shock phase, and rise above normal in the countershock phase.

The blood pressure and the blood sugar, after an initial rise due to the secretion of adrenaline, fall markedly in the shock phase and rise above normal in the countershock phase, especially the blood sugar.

The blood non-protein nitrogen, potassium, and phosphate, all rise during the shock phase, and fall again during the countershock phase. The shock phase is accompanied by acidosis, and the countershock phase by alkalosis.

During the countershock phase the clotting and bleeding times are diminished, the lymphocyte count falls while the neutrophil count rises, and the thymus and lymphoid tissue involute. In the experimental animal ulceration of the gut is common during the shock
phase, and persists into the countershock phase.

The changes occurring in each phase are also given in tabular form in Table II, but it is felt that even a very brief description makes the relationships between these stages much clearer than a table can ever do.

This very brief summary is sufficient to show that the manifestations of the shock phase are so similar to those found in an Addisonian crisis, or in severe shock in man, that this phase can be regarded as temporary adrenal failure as the result of the application of stress of such severity as to cause relative adrenal insufficiency. The demand for the cortical hormones has exceeded the supply to such an extent that some time must elapse before the cortex can react and become adapted to produce an amount of hormones which will correct the disturbance in the internal environment.

If the stress is very severe, or the animal less resistant, the countershock phase may be transitory, and fail in its object, the symptoms of the shock phase recurring after a short interval and ending in death. It is thought by some that this sequence of events may explain the occurrence of primary and secondary shock in man. If the stress is mild the shock phase does not occur, and only the manifestations of the countershock phase become manifest.

In the countershock phase the non-specific resistance of the animal against any agent whatsoever is at
### TABLE II

The General Adaptation Syndrome

(modified from Selye 1946a)

<table>
<thead>
<tr>
<th></th>
<th>SHOCK</th>
<th>COUNTER-SHOCK</th>
<th>RESISTANCE</th>
<th>EXHAUSTION</th>
</tr>
</thead>
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<tr>
<td>Blood volume</td>
<td>↓ ++</td>
<td>↑ or ↑</td>
<td>↓</td>
<td>? ↓</td>
</tr>
<tr>
<td>&quot; clorides</td>
<td>↓ ++</td>
<td>↑ +</td>
<td>↓</td>
<td>? ↓</td>
</tr>
<tr>
<td>&quot; sugar</td>
<td>↑ then ↓ ++</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>&quot; N.P.N.</td>
<td>↑ ++</td>
<td>↑</td>
<td>↓</td>
<td>? ↑</td>
</tr>
<tr>
<td>&quot; pH</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>? ↓</td>
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<tr>
<td>&quot; clotting time</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>? ↓</td>
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<tr>
<td>&quot; Thym lymphocytes</td>
<td>↓ ++</td>
<td>↑</td>
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<tr>
<td>&quot; eosinophils</td>
<td>↑ ++</td>
<td>↓</td>
<td>↓</td>
<td>? ↑</td>
</tr>
<tr>
<td>&quot; neutrophils</td>
<td>↑ +</td>
<td>↓</td>
<td>↓</td>
<td>? ↑</td>
</tr>
<tr>
<td>Thymus and lymphoid tissue</td>
<td>↓ ++</td>
<td>↑</td>
<td>↓</td>
<td>↓ ++</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Gonads</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nitrogen Balance</td>
<td>neg ++</td>
<td>positive tendency</td>
<td>neg ++</td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>&quot; 17 K.S.</td>
<td>↑ then ↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>&quot; Corticoids</td>
<td>↑ then ↓ ++</td>
<td>↑ +</td>
<td>↑ ++</td>
<td>↓ ++</td>
</tr>
<tr>
<td>Cortical lipoids</td>
<td>↓ ++</td>
<td>↑</td>
<td>↑</td>
<td>↓ ++</td>
</tr>
<tr>
<td>Ulcers of gut</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Legend**

↑ = increase  
↓ = decrease  
◇ = unaltered  
? = probably, but no data.
a very high level. As this does not occur to any extent in the absence of the adrenals this high non-specific resistance is clearly due to the large amounts of cortical hormones, especially the sugar hormones, which are being poured out into the circulation in this phase. As DOCA has been found to have little power to combat shock, it appears that apart from the correction of the electrolyte disturbances, the hormones which control electrolyte balance have little part in the production of non-specific resistance. If the animal has previously been exposed to the same damaging agent the specific resistance acquired from this previous exposure rises to an even higher level than the non-specific resistance in the countershock phase.

If the application of stress ceases at this point the manifestations of the countershock phase gradually disappear, and the animal recovers. Daily application of sublethal "doses" of the same damaging agent, however, results in a further series of changes which are characteristic of the "stage of resistance". It has been so named because the main feature of this stage is the development of specific acquired resistance to that particular damaging agent, and a decrease in the resistance to other forms of stress. For example, if an animal has become very resistant to cold because of repeated exposure, and has therefore become specifically adapted to resist cold, sudden exposure to heat would
probably prove fatal. Adaptation to one form of stress has been acquired at the expense of a decrease in the power to produce non-specific resistance to other forms of stress.

During the resistance stage most of the manifestations of the countershock phase gradually disappear. The marked hypertrophy of the adrenal cortex subsides, but it remains slightly larger than normal and the amount of lipoid in the cortex is increased. The thymus and the lymphoid tissue recover from the acute involution caused by the excessive secretion of the cortical hormones in the countershock phase. The body has become specifically adapted to resist the particular form of stress which has been imposed, and excessive amounts of the cortical hormones are no longer required.

Despite the fact that the adrenal cortex is to all appearances able to react to the application of another type of stress, for some reason it does not do so, with the result that the resistance to any other form of stress is low.

Even when the body is perfectly adapted to the prolonged stress it cannot maintain this state of adaptation indefinitely. The power of adaptation finally wears out, the specific resistance which has been acquired by repeated exposure fails, the manifestations of the alarm reaction reappear, and death ensues. Once more the hormones are completely dis-
charged from the cortex, which hypertrophies markedly, and is completely depleted of lipoid, the thymus and the lymphoid tissues involute, ulceration of the gut may reappear, and all the biochemical abnormalities of the shock phase recur. These are the main characteristics of the exhaustion stage.

To recapitulate, the sequence of events following exposure to severe chronic stress is as follows:-

Sudden and severe stress produces shock, because the endocrine system is unable to cope with it at first, and is temporarily knocked out. In the countershock phase the endocrine system rapidly recovers, and not only reverses the manifestations of the shock phase but overcompensates for them. If the stress continues the body begins to become adapted to it. In this resistance stage the endocrine system ceases to be hyperactive, and no longer responds promptly and efficiently as it did at first to any new form of stress which may be imposed. The body may be said to have become specifically adapted as a whole to resist one form of stress only, so that resistance to other forms of stress is correspondingly low. Finally, after a varying period of time, this stage of specific adaptation breaks down, with the production of the exhaustion stage, when the endocrine system makes a vain attempt to retrieve the situation, which fails with the reproduction of the manifestations of shock.

The actual trigger which sets all this cycle of changes going has not yet been completely elucidated.
The adrenal medulla plays one part, and increased demand for cortical hormones another, but that is almost certainly only part of the story except in mild stress. It has been suggested that the liberation of toxic metabolites like histamine may be the main cause. Whatever the exact mechanism may be, it is clear that in response to stress the anterior pituitary stimulates the adrenal cortex to produce very large quantities of cortical hormones, which are mainly responsible for the phenomena associated with the countershock phase.

Subsequent sudden exposure to the same damaging agent some time after complete recovery has taken place causes both specific and non-specific resistance to fall to a lower level than the specific resistance against the particular agent begins to be acquired and reaches a high level.

Previous exposure to any particular agent, there
Specific and non-specific resistance in the adaptation syndrome.

The changes in the type of resistance offered to the particular stress which is causing the adaptation syndrome to occur are of such importance that more detailed discussion is necessary, even at the expense of some repetition.

If the animal has not been previously exposed to the particular damaging agent used to produce the adaptation syndrome it obviously cannot possess any specific resistance to that agent. After initial depression in the shock phase the non-specific resistance, which is mainly produced by the secretion of excessive amounts of cortical hormones, rises to a high level in the countershock phase. In the stage of resistance, however, the power to produce non-specific resistance falls to a low level as the specific resistance against this particular agent begins to be acquired and reaches a high level.

Subsequent sudden exposure to the same damaging agent some time after complete recovery has taken place causes both specific acquired resistance and non-specific resistance, after initial depression in the shock phase, to rise to a high level in the countershock phase, the previously acquired specific resistance always rising to a higher level than the non-specific resistance. In the resistance phase the non-specific resistance again falls as the specific resistance rises.

Previous exposure to any particular agent, there-
fore, causes the animal to become specifically adapted to resist that agent, but it is not until the countershock phase that any such acquired specific resistance rises to a high level.

Production of the alarm reaction for the second time by the same agent, or by any other agent, therefore, causes a marked rise in both specific and non-specific resistance in the countershock phase. In this phase the animal is not only markedly resistant to the agent to which it was formerly exposed, but also to any other agent as well. The alarm reaction cannot, therefore, be elicited twice in quick succession.

During this countershock phase, therefore, not only is the non-specific resistance produced by the endocrine system able to cope with any other damaging agent, but the acquired specific resistance of the animal against all the types of stress to which it has been exposed in the past rises even higher.

For example, animals which have been sensitized to a foreign protein to the extent that a further injection would produce anaphylactic shock, do not develop anaphylaxis from an injection of that protein when in the countershock phase of an alarm reaction produced by any agent whatever, including anaphylactic shock produced by that protein. (Karady et al. 1938, Gottschall et al. 1944).

The rise in the specific acquired as well as the non-specific resistance in the countershock phase would seem to have some relationship to the anamnestic response.
As ACTH has not been found to produce the anamnestic response in man, it would seem likely that some other part of the adaptive mechanisms must be responsible for this phenomenon.

In the resistance stage the experiments of Selye leave no doubt that the cortex returns to its normal size, or is slightly enlarged, that it contains more lipoid than normally, and that the thymus and the lymphoid tissues are not involuted. In chronic disease in man there is no doubt that the cortex is not enlarged to any extent. It is apparent that hypersecretion of the sugar hormones is not a feature of this stage.

Selye found that the amount of the specific stress applied daily could be increased considerably above that which would have killed the animal before it had become specifically adapted to the stress. Despite the fact that the stress was being applied every day the appearance of the cortex was as described above, so that it is obvious that the pituitary adrenal system could not be playing any major part in resisting the stress, and apparently had ceased to respond to this particular stimulus.

When specific adaptation breaks down in the exhaustion stage the endocrine system once more responds, but it is a despairing effort, and both specific and non-specific resistance fail.

Despite the increased amounts of lipoid in the cortex, the response to other forms of stress is poor in the resistance stage, so that the specific resis-
tance seems to have been acquired at the expense of a decreased power to produce non-specific resistance by hypertrophy and hypersecretion of the adrenal cortex.

It would appear that the task of specific resistance is handled by mechanisms outside the adrenal cortex, and that the response of the endocrine system to the specific stress imposed, even in doses exceeding considerably those which brought about a marked alarm reaction or death in the first place, is inhibited, and the response to other forms of stress by the endocrine system is also inhibited to some extent.

This concept is strongly supported by an observation of Selye (1937). He found that while adrenalectomy in the rat resulted in marked sensitivity to the toxic effects of morphine, as in the patient with Addison's disease, on the other hand the pre-treatment of the animal with morphine for some time before the removal of the adrenals resulted in the resistance of the animal to morphine being markedly greater than that of an adrenalectomised animal which had not been thus adapted to morphine. It should be mentioned that morphine has been found to be a strong alarming stimulus in the rat.
Endocrine Relationships in the Adaptation Syndrome.

The stimulus of severe stress causes a great increase in the secretion of ACTH by the anterior lobe of the pituitary. Selye (1937, 1946a) has reported that the basophil cells may sometimes be greatly increased in number, and that the eosinophils may show degenerative changes. D'Angelo et al. (1948) have reported similar changes in the guineapig in starvation, which is also a form of stress.

These observations may explain the inhibition of the gonadotrophic, lactogenic, and growth hormones which results from stress, an effect which Selye has called the hormonal shift. It would appear that the production of ACTH has taken priority over sex and growth, which are functions without defensive value. The depression of both male and female sexual functions which is commonly found in disease, and which was frequently observed during long periods of starvation during the recent war, would seem likely, apart from any psycho- genic factor which was undoubtedly present in prisoners, to be a manifestation of the adaptation syndrome.

Retardation of growth is a commonplace observation in children during a severe illness, and is unlikely to be purely of nutritional origin or due to metabolic dysfunction. Though this disturbance is not so obvious in the adult, it seems very reasonable to suggest that the appearance of transverse lines on the nails and the slowing of nail and hair growth during an illness is connected with the hormonal shift.
The hormonal shift has its counterpart in the adrenal cortex. During the shock and countershock phases of the alarm reaction the predominant demand is for the sugar and the electrolyte controlling hormones. Following severe trauma or burns in man, Forbes et al. (1947) have found that, after an initial rise, the 17 ketosteroid excretion in the urine falls to a low level until recovery. Several workers, particularly Venning and Browne, have shown that the urinary corticoids, which give an indication of the amount of the sugar hormones being secreted, rise to very high levels and fall to normal on recovery. In a case observed by Talbot et al. (1947) the high corticoid excretion after severe burns was observed to fall again within a few days, and a fatal issue rapidly followed.

The hormonal shift has been thought to be evidence that there are three adrenocorticotrophic hormones, each controlling one function. ACTH has, however, now been shown to be a homogeneous substance, which in large doses can stimulate all the functions of the cortex under normal conditions in man. It therefore seems reasonable to postulate that some form of competition for ACTH may take place in stress, or that some other hormonal inter-relationship is responsible for the "clearing-out"of the cortical androgens.

The thyroid may tend to involute during the acute stages of the syndrome, but this is followed by hyperplasia. Selye has suggested that an exaggeration of
continuation of this response may be responsible for the production of some cases of thyrotoxicosis.

According to Selye (1937, 1946a) the islets of Langerhans show signs of extreme activity. This would suggest that extra insulin is secreted in order to enable the tissues to utilise the extra sugar circulating in the blood and to balance the anti-insulin effects of the sugar hormones. The glandular tissue of the pancreas is also affected, but the reason for this is not clear. Selye points out that an exaggeration of these changes may be the cause of the acute pancreatitis which may follow severe burns, and of those cases of diabetes which occasionally ensue upon acute stress.

The probable endocrine relationships in the alarm reaction have been illustrated in fig. 7.
Probable endocrine inter-relationships in the Alarm Reaction.

Non-specific damage

- sympathetic
  - adrenal medulla
    - initial adrenaline discharge
      - initial rise in blood sugar and other adrenaline effects
    - Greatly increased need for and utilisation of sugar hormones
      - ? direct action
    - ?direct action

ANTERIOR PITUITARY

- Thyrotrophic hormone at first decreased later increased
  - Thyroid involution then hyperplasia
    - increased secretion thyroxine
      - synergism
    - involution thymus and lymphoid tissue

- Maximal secretion of ACTH
  - hypertrophy fasciculata hypersecretion sugar hormones
    - emergency stimulatory effect
  - hypertrophy glomerulosa and hypersecretion electrolyte-controlling hormones
    - ? main stimulus low sodium high potassium in shock phase

- decreased secretion of sex and growth hormones
  - cessation of lactation, menstruation, growth, etc.

Combined action of adrenal hormones, thyroxine, and insulin, produce reversal of shock phase and the high non-specific resistance of the countershock phase
The Adrenal Cortex in the Adaptation Syndrome.

In the last few years the changes in the adrenal cortex which occur in response to stress or ACTH have been closely studied from several angles, mainly in the rat. The alterations in the ascorbic acid content of the cortex in response to various forms of stress and ACTH have been investigated by Sayers & Sayers (1945) (1946) (1947) (1948) and Long (1947). The cytochemical appearances of the various zones of the cortex in response to stress, and to ACTH, have been reported by Bergner & Deane (1948) and by Deane & Shaw (1947). The adrenal cholesterol has also been found to indicate the cortical response to stimulation, but does not respond so quickly as the ascorbic acid. (Long 1947).

The findings of these authors and many others, and the changes described by Selye (1946) fit so closely that the best way to deal with the subject is to summarise this work as follows:-

Extremely acute stress produces haemorrhages in the medulla and cortex if there is time for this to occur before death. This is strictly analogous to acute adrenal failure in man, which is now recognised to occur in a variety of extremely acute conditions (Selye 1946).

Extreme acute stress of not quite such severity, or a more resistant animal, causes cytological changes characteristic of acute adrenaline discharge in the medulla, plus total disappearance of all the lipoid droplets in the cells of the cortex within the course
of a few hours. Cholesterol and ascorbic acid also disappear from all zones of the cortex. Death may occur at this point, or severe shock set in. These changes are characteristic of the shock phase.

Should the animal survive the shock phase, the lipoid droplets, cholesterol, and ascorbic acid, begin to reappear. The lipoid droplets are much more finely divided than normal, exhibit various cytochemical signs indicative of intense activity, and the cells, and the cortex as a whole, rapidly enlarge. These changes are characteristic of the countershock phase.

In the resistance stage the gross hypertrophy of the countershock phase subsides, and the cortex is not much larger than normal. The cells are loaded with lipoids which are not so finely divided as in the countershock phase, and the cells, and the cortex, are not so large.

Long continued stress may finally exhaust the powers of adaptation. Though the cells of the adrenal cortex hypertrophy greatly, as in the countershock phase, the lipoid droplets, cholesterol, and ascorbic acid gradually disappear, leaving a hypertrophied empty cell. These changes are found in the exhaustion phase, which is characterised by a recurrence of most of the manifestations of the shock phase.

Bergner & Deane (1948) have shown that when similar changes are produced by the administration of ACTH in the rat they are limited to the zona fasciculata,
and do not affect the glomerulosa. On the other hand, the application of severe stress to the intact animal clearly affects both these zones in the initial phases of the syndrome. This may be explained by the evidence that the blood sodium concentration is probably the main factor affecting the secretion of electrolyte controlling hormones, so that if electrolyte balance is disturbed the glomerulosa also undergoes the same cycle of changes. This explains how ACTH alone does not affect the zona glomerulosa in the rat, while stress has frequently been shown to do so. The drawings illustrating a paper by Darrow (1944) on the effects of low atmospheric pressure on the rat's adrenal cortex show particularly clearly that the glomerulosa is also affected.

Bergner and Deane found that prolonged administration of ACTH caused progressive hypertrophy of the cells of the fasciculata, which were loaded with finely divided lipoids showing cytochemical signs of hypersecretion, as in the countershock phase. After twelve days' treatment the lipoids began to disappear, and it was thought that the resistance and the beginning of the exhaustion stage had been produced. It must be pointed out, however, that they also noted that the cortex was hypertrophied and the thymus atrophied. This is certainly not typical of the resistance stage in the intact animal, for Selye and others have repeatedly pointed out that during the resistance stage
the cortex is not much bigger than normal and marked thymic atrophy is not a feature. It is evident that it is unsafe to draw conclusions from the use of a single hormone, and that it should be borne in mind that the adaptation syndrome is a reaction of the body as a whole to stress in which many other factors play a part as well as ACTH.

It must be emphasised that the changes described above do not necessarily occur, depending on the severity of the stress and the ability of the animal to cope with it. For example, in mild stress such as fasting or pregnancy the only change is some degree of hypertrophy and an increase in the number of fine lipid droplets in the cells.

Deane and Greep (1946) showed that the removal of the anterior pituitary results in the reverse of the above changes in the rat. The cells of the fasciculata become smaller, the lipid droplets larger in size and fewer in number, and the zone shrinks. The lipoids gradually disappear, leaving empty cells resembling those found in the exhaustion stage except in that they are smaller than normal. It is notable that the zona glomerulosa was not affected by these changes.
Clinical Applications of the Adaptation Syndrome.

The adaptation syndrome has been, of necessity, elucidated by experiments on animals, but it is now becoming increasingly clear that the same sequence of events occurs in man under any sort of stress. It is, therefore, of some importance to review the data which has been obtained in man, and to discuss its possible implications.

It is worthy of further emphasis that the biochemical and other changes which have been found to be characteristic of the shock phase in the experimental animal are strikingly similar to those which are found in severe shock in man, and also to those of an Addisonian or a thyrotoxic crisis. The unimpressive results which have been obtained by the use of cortical extracts in shock have prevented the acceptance of this concept, but as the daily output of the cortical hormones in stress in man has been estimated by Vogt (1943) and by Sayers (1948) to be equal to about one and a half litres of commercial cortical extract, the failure of this form of therapy is not surprising. It is to be hoped that when sufficient quantities of compound E and other hormones become available that they may be found of use in the treatment of shock.

There can be no doubt that in the reaction of the human body to any form of stress the functional efficiency of the adrenal cortices and their ability to produce the large amounts of hormones which may be required is of very great importance indeed. It is not
necessary to turn to the results of animal experiments to support this statement, as it is now well recognised that the patient with Addison's disease has very poor resistance to infections, drugs, operations, and all other forms of stress. The ineffectiveness of DOCA therapy under conditions of stress, and the lifesaving effects of whole cortical extract, serve to emphasise the essential role which the sugar hormones play in the production of resistance to stress. It is also clear, however, that some non-specific adaptation can take place in the absence of the adrenal cortex, so that though it is a very major one, the cortex is not the only factor involved.

Selye found that the protein intake preceding exposure to stress is of great importance, as fasting, which is in itself a form of stress, markedly increases the susceptibility of animals to shock (1946a). The pituitary-adrenal response to stress is increased by the feeding of a high protein diet (Moya et al. 1948), and Henriques et al. (1948) have shown that this is due to the essential amino-acid content of the diet. Sarason (1943b) has shown that high protein diets increase the lipoid content of the cortex, and Moya et al. (1948) have found that though high protein diets produced no effect on adrenal function under normal conditions, the difference became apparent when the animals were exposed to stress.

These observations may have wide application to
medicine in general, and explain to some extent the importance of nutrition in relation to resistance to disease. It seems probable that while a low protein intake may cause no apparent disability in health, the ability to produce a good general resistance to disease or trauma may be impaired. The relationship of malnutrition to the incidence of tuberculosis, rheumatism, and other diseases is well recognised, and would not seem to be wholly accounted for by other environmental factors such as more frequent infections, overcrowding, housing, heredity, and so on. At the same time it is obvious that it would be difficult to prove this point, or, indeed, to disprove it. The recent report by Keers (1948) that the course of tuberculosis in ex-Service patients has been definitely adversely affected by reversion to civilian rations since the end of the war would seem of more than passing interest in this connection.

Reifenstein and Talbot (1946), and Talbot et al. (1947) have reported that the administration of a high protein diet to both normal persons and those with Cushing's syndrome resulted in a definite rise in the corticoid excretion, and that a low protein diet had the opposite effect. It seems probable that this effect of a high protein intake may be, in some measure, the explanation of the beneficial effects of such diets in chronic disease, quite apart from the other more obvious benefits which might arise.
Hypoglycaemia has been found to occur in some cases of severe diphtheria, and while intravenous glucose had a beneficial effect in some, others were apparently unable to utilise this extra sugar as the blood sugar remained high until a few units of insulin were also given (Vere Hodge 1949). This observation would suggest that temporary failure of both the adrenal cortex and the islets of Langerhans may occur in severe stress.

The clear-cut anti-insulin effect of the sugar hormones is very likely to be the cause of the increased requirements for insulin in diabetic patients during stress, such as infections, pregnancy, operations, and so on. As glycosuria is not a common feature of stress in the normal individual it seems abundantly clear that the secretion of insulin must keep pace accurately with the increase in the secretion of the sugar hormones, not only to preserve the hormonal balance, but also to ensure that the extra sugar mobilised is utilised by the body. There is no doubt that the unfortunate individual with diabetes who subsequently develops Addison's disease as well has a very much decreased insulin requirement, and is very sensitive to insulin. Balfour and Sprague (1949) have recently demonstrated the remarkable effects of a relatively minute dose of compound E on such a patient who had been deprived of insulin and food for 24 hours. The ketosis produced was a particularly striking feature, and would emphasise the part played by the
This view of the role of the pituitary adrenal system in the causation of diabetic coma has been amply justified by the report of McArthur et al (1949) that in diabetic acidosis the corticoid excretion increases in proportion to the degree of acidosis.
unopposed action of the sugar hormones in the causation of ketosis and coma. It seems entirely probable that diabetic coma brings about an alarm reaction, so that a vicious circle of increasing output of the sugar hormones, increasing ketosis and coma, and a further increase in the sugar hormones, and so on, may be formed. This concept is strongly supported by the well known fact that though the theoretical requirements of a case of diabetic coma are small, in practice coma is most markedly insulin-resistant, and becomes more so the longer the patient is in coma - a feature well recognised to be brought about by excess of the sugar hormones. (See note on page opposite).

In pregnancy it is a well-substantiated fact that the adrenal cortex undergoes hyperplasia and hyper-secretes. Some authors have suggested that hyperemesis gravidarum may be associated with a state of relative cortical insufficiency, and some encouraging results have been reported from the use of cortical extracts in this condition. It is probable, however, that whether such treatment rests on a sound theoretical basis or not, any such reports based on the use of cortical extracts should be treated with due reserve, especially in view of the extraordinary number of so-called remedies for hyperemesis.

Venning (1946b) has shown that the corticoid excretion is, as one would expect, markedly increased in pregnancy. The beneficial effect of pregnancy on rheumatoid arthritis is undoubtedly due to the increase
in the amount of sugar hormones secreted, but this is not the only possible clinical application. For example, if one considers the elasticity of the normal female skin it seems odd that striae gravidarum should appear even in the presence of marked abdominal enlargement. In Cushing's syndrome we again have these two factors of excess of sugar hormones and rapid abdominal enlargement with striae. As it has now been found that the sugar hormones have an inhibitory effect on wound healing and on collagen tissue in general it seems most probable that the increased secretion of these hormones in pregnancy is in part a cause of the appearance of striae.

The divergent opinions regarding the effects of pregnancy on tuberculosis (Rich 1944) may be reconciled by taking into account a possible beneficial effect of the increase in the secretion of the sugar hormones on the disease by raising the non-specific resistance, and the risk of the action of these hormones on collagen resulting in the breakdown of lesions and re-activating them, or spreading the disease by releasing a flood of bacilli into the circulation.

Tobian (1948, 1949) has found that while oedema in pregnancy is associated with an excessive increase in the corticoid excretion, the presence or absence of toxaemia of pregnancy was not associated with this increase, nor was there an abnormal increase in hyper-
tensive patients. This finding is somewhat difficult to interpret.

The occasional occurrence of acute gastric ulcers as a result of severe stress has been suggested by Selye to be possibly analogous to those found in the experimental animal in the shock or exhaustion stages of the adaptation syndrome, and it may be of significance that he found that the administration of glucose prevented the occurrence of these ulcers.

Status thymo-lymphaticus is thought by many authors (Goldzeifer 1944, Selye 1946a, etc.), to be associated with adrenal hypofunction or dysfunction, and the low resistance to infection, anaphylactic shock, anaesthesia, and other forms of stress which are thought to be associated with this condition would appear to support this contention. From the well established fact that hypersecretion of the sugar hormones as a result of stress results in involution of the thymus and lymphoid tissue, it is apparent that a postmortem finding of thymic and lymphoid hyperplasia in a case in which sufficient time had elapsed before death for such involution to have occurred should suggest strongly that the adrenal response to stress had been deficient.

Sarason (1943a) has reported on the appearances of the adrenal cortex as found at postmortem in a large series of cases and a wide variety of pathological conditions. Perusal of this paper leaves no doubt that, when the clinical data are also taken into account, the state of the adrenal cortex corresponds very closely
indeed to what one might expect from the appearances of the cortex which have been found in the adaptation syndrome in the experimental animal. It is worthy of emphasis that the state of the adrenal cortex after death can only be a guide, and a rough one at that, to the state of affairs existing in the adrenal cortex immediately preceding death.

The advent of quantitative methods of estimation of the urinary corticoids has provided a means of finding out how the cortex behaves in man under stress in respect of the secretion of the sugar hormones.

A series of investigations have been carried out by Venning and Browne and their co-workers in relation to the corticoid, 17 ketosteroid, and nitrogen excretion in previously healthy subjects following acute damage such as burns, trauma, and operations (Venning, Hoffman and Browne (1944), Venning, Schenker and Browne (1944), Venning (1945)). They have also investigated these responses in debilitated persons with chronic diseases and carcinomata, and contrasted them with previously healthy subjects, (Venning (1946a), Browne, Schenker, and Venning (1946), Browne (1945a) ). When these rather scattered observations are viewed as a whole, as has been done below, they are of outstanding interest.

Any form of acute damage in the previously healthy person, particularly severe burns, results in a very marked increase in the amount of both corticoids and nitrogen excreted in the urine. It is thought that the corticoids represent a spill-over of the greatly increased amount of circulating hormones in stress. As
recovery takes place the corticoid and the nitrogen excretion slowly decrease to normal levels.

It seems entirely reasonable to suppose that these observations, which are well substantiated and regarding which there is no disagreement, were carried out during what corresponds to the countershock phase in man.

The marked loss of nitrogen which takes place during this period, which is usually referred to as the Katabolic phase, is a phenomenon for which there is as yet no satisfactory explanation. Cuthbertson et al. (1939, 1941, 1942) had previously investigated it, and Browne and Venning have confirmed that during this phase administered protein, both intravenously and orally, is not retained and is excreted as nitrogen in the urine. In this phase the patient is not only in marked negative nitrogen balance, but does not retain that which is given to him. Cuthbertson (1941, 1942) found that crude growth promoting extracts of the anterior pituitary would prevent this loss of nitrogen after trauma in the rat, and Bennet, Applegarth, and Li (1946) have found that the pure growth hormone can actually cause retention of nitrogen after fractures in the rat.

Why this marked loss of nitrogen should occur is a vexed question. It has not been found to bear a close relationship to the elevation of corticoid excretion, and it may be of some significance that Conn et al. (1949) in producing temporary diabetes in man by means
of very large doses of ACTH, concluded that increased nitrogen excretion was not related to the glycosuria, but had something to do with the relative proportions of the sugar and the androgenic hormones of the cortex which were produced as a result of the administration of the ACTH. From the studies of Selye on the adaptation syndrome it would appear that the hormonal shift, with suppression of the growth hormone, may be one other factor involved. Noble and Toby (1947) found that the nitrogen loss was similar in normal and in adrenalectomised rats following trauma, and Ingle and Oberle (1946) showed that adrenalectomy did not impair the ability of the fasting rat to utilise protein when maintained on salt alone.

Andree and Browne (1946) have investigated the remarkable consumption of ascorbic acid which takes place as a result of acute damage in man. They found that the ascorbic acid content of blood and leucocytes, fell to low levels, and it disappeared from the urine. Only after six days of the administration of 500-700 gmms. of ascorbic acid was saturation achieved, despite the fact that the subjects were not deficient of this vitamin before operation. The findings regarding the utilisation of thiamine, riboflavine, and nicotinamide also suggested that increased amounts were used in stress, but the findings were not so clear-cut. Lund et al. (1947) have also investigated this problem, confirmed these findings, and suggested that in severe
injuries, especially burns, 1-2 Gms. of ascorbic acid, 10-20 mgms. of thiamine and riboflavin, 150-250 mgms. of nicotinic acid, should be given daily, plus a high protein and carbohydrate intake, yeast, liver extract, and vitamins A and D. This would seem a policy of perfection!

The reason for the extraordinary amounts of ascorbic acid which are apparently used up in stress is still to be sought. It would seem of some significance that Stewart et al. (1941) found that large doses had an ameliorating influence in shock in the experimental animal, and De Pasqualani (1946) demonstrated a most striking protective effect of a 200 mgms of ascorbic acid on haemorrhagic shock in the guinea pig. The recent report of Dugal and Therien (1949) that the administration of large doses of sodium ascorbate had the effect of preventing the occurrence of cortical hypertrophy in the rat and the guinea pig as a result of exposure to cold, is also of interest. Noble and Toby (1947) noted that the administration of ascorbic acid brought about a marked diminution of the nitrogen excretion in the intact rat following trauma, and observation which would seem of more than passing interest. The effect of ascorbic acid on the nitrogen excretion following trauma in the adrenalectomised animal was, unfortunately, not ascertained.

It seems likely that some of this ascorbic acid is used in the manufacture of cortical hormones, and
some in wound healing, especially as Reid (1947) has noted that the utilisation of the vitamin during healing of experimental wounds in the guineapig is roughly parallel to the maximum activity of the fibroblasts. As such large amounts cannot be accounted for in these ways, it would appear that the role of ascorbic acid in stress is only beginning to be elucidated.

Browne and Venning also followed some patients who developed complications of some duration following operation. It was found that, even though the patient was still ill and becoming debilitated, the increased urinary corticoids decreased to levels which were within the normal range, and the negative nitrogen balance became gradually positive even on a low protein intake. Even when obviously debilitated these patients held on to the administered nitrogen tenaciously, even when fever was present.

In this instance it would appear that the observations were carried on from the countershock to the resistance stages, and the data suggests that the countershock phase does not last longer than about two to three weeks.

When they investigated the response of debilitated subjects with chronic infections or incurable carcinomata to operations or other forms of trauma it was found that the increase in the corticoids which resulted from stress was much less than in the previously healthy person, was rather transitory, and was sometimes absent.
The rise in nitrogen excretion and negative balance which follows stress in the previously healthy person was usually absent, and if present was slight. Before operation corticoid excretion was found to be, as a rule, normal or slightly above normal, but not below normal. A rise in the corticoid excretion could take place without a rise in the nitrogen excretion, but the reverse has not been observed except in a case of haematemesis, in which case the absorbed nitrogen from the blood in the gut could account for it.

Unlike the previously healthy patients, these debilitated individuals could be maintained in positive nitrogen balance with ease. Browne (1945b) confirmed the previous finding of Cuthbertson (1939) that rats which had been maintained on a low protein diet for some time failed to show a rise in the nitrogen excretion following trauma.

Though it does not appear to have been fully realised, it seems clear that these observations were carried out during the resistance stage of the adaptation syndrome in man, and in consequence assume exceptional importance and interest. It appears that man responds to chronic stress in the same manner as the experimental animal, and that when the body has become specifically adapted to resist one form of stress, or has become debilitated, it does not respond normally to another form of stress, such as an operation.

Venning and Browne have pointed out that the fact that the chronically ill patient holds on to his
remaining protein tenaciously, even after trauma, may be regarded as a protective response, since the conservation of the remaining body protein is obviously vital to the continued existence of the patient.

They also investigated the response of such severely debilitated patients to their terminal illness, and found that they responded by a marked rise in the excretion of both corticoids and nitrogen, just as in the previously healthy person. This loss of nitrogen could be regarded as being due to the final failure of the mechanism which has been preventing the loss of nitrogen in the debilitated patient, and amounts to a final dissolution of the body protein. Similarly, it would appear that the influence which has been holding the response of the pituitary and/or adrenal cortex in check has also vanished, and that it has undergone hypertrophy and hypersecretion as it would in the previously healthy person.

It is evident that these observations were carried out during what corresponds to the exhaustion stage of the adaptation syndrome in man, and represents the failure of adaptation and a final despairing call on the endocrine system to save the situation.

Though these scattered observations on the response of man to stress have not been carried out on any large scale, it seems to the author that they provide a composite and somewhat blurred, but definite, picture of the three stages of the adaptation syndrome in man which fits those which have been made in the experimental
animal very closely.

It is clear that any change in the body which only occurs during acute stress and is not specific to the nature of the stress is likely to be a manifestation of the countershock phase of the adaptation syndrome. On these grounds it is therefore possible to suggest that certain other findings characteristic of acute stress are part of the adaptation syndrome.

The "C reactive protein" which appears in acute states of all kinds and has been described by Lofstrom (1943, 1944) and isolated by McCarty (1947) would appear, in consequence of its complete non-specificity, to have something to do with the countershock phase.

A rise in the alpha globulins has also been reported to be found in a variety of acute conditions (Stern and Reiner 1946). It may be, of course, that this is due to the "C reactive protein" which has been said by Lofstrom to be associated with the alpha or beta globulins. It is also remarkable that the majority of chronic diseases, particularly those of the collagen group, are associated with a rise in the gamma globulins.

The significance of these changes is, of course, not clear, but their time relationships and non-specificity would suggest that they may have some connection with the adaptation syndrome.

Wilkinson et al (1949) have reported that following operation there is retention of salt and water, and that it appears to coincide with the protein katabolism. It has already been pointed out that the secretion of
the electrolyte-controlling hormones in man may be stimulated by the anterior pituitary under conditions of severe stress. This observation would appear to support this reasoning, and more than ever to corroborate the correctness of the view that the secretion of the electrolyte-controlling hormones is not ordinarily affected by the pituitary.

The above considerations are, perhaps, sufficient to demonstrate how widely the processes of adaptation must affect the whole of medicine and surgery, and how the functional efficiency of the pituitary-adrenal system is of vital importance in relation to the resistance of the body to stress. Though we cannot take out the adrenals every day to see how they are getting on, their functional efficiency is clearly reflected in the general condition of the patient.
AN INTERPRETATION OF THE SIGNIFICANCE OF THE ADAPTATION SYNDROME.

Though a vast amount of miscellaneous data concerning the phenomena which occur during the general adaptation syndrome has accumulated during the past decade, no attempt appears to have been made to answer the very pertinent question of why this most remarkable sequence of bodily reactions should ensue upon prolonged stress, or enquired into the true significance of the adaptation syndrome in relation to disease.

It is felt that there is enough information available at the present time to justify the presentation of a hypothesis which suffices to provide a simple explanation of the reasons for the occurrence of the various phases of the adaptation syndrome and for the sequence in which they occur. In order to express this concept adequately it is necessary to deal with the subject in a rather general and elementary manner at first, as it is only from a broad viewpoint that the full significance of these reactions to stress becomes apparent.

The infinite number of non-specific stimuli which may bring about the "Alarm Reaction" have the common feature of being forms of somatic stress which the body is not specifically adapted to resist, and which are of such severity as to bring about a state of generalised bodily upset, or "Alarm".
Some of these forms of somatic stress, such as burns or trauma, are clearly forms of stress to which the body cannot be expected to be specifically adapted, while others, such as infectious disease, are forms of stress to which the body may or may not be specifically adapted or immune, or to which specific adaptation may have proved inadequate.

In order to provide a further safeguard of the survival of the individual, and therefore of the species, it is essential that a mechanism must exist whereby the body is endowed with the ability to undergo rapid adaptation to any form of stress which is so severe as to constitute a threat to its continued existence. This non-specific resistance must be capable of being rapidly mobilised, maintaining the internal environment of the body fluids within those limits compatible with survival, mobilising any previously acquired specific resistance, and raising the non-specific resistance of the body to a high level.

The first such non-specific defence mechanism clearly consists of the sympathetic nervous system and the adrenal medulla, and, though capable of producing almost instantaneous non-specific adaptation, can only act for a very short space of time at maximal activation. This mechanism must hand over the task to another non-specific defence mechanism which can deal with the stress on a more long-term
basis. It has been made abundantly clear that this hand-over is accomplished by the action of adrenaline in causing the secretion of ACTH and the discharge of the cortical hormones, and in this connection the emergency function of this link between the two mechanisms is very obvious.

In very severe stress the shock phase ensues, because the adrenal cortex and the anterior pituitary require time to become adapted to supplying the huge amounts of the cortical hormones which are required. If recovery from the initial shock takes place the amount of the hormones secreted is such that the manifestations of shock are not only corrected, but overcorrected, and are replaced by the phenomena of the countershock phase.

In the countershock phase there can be no possible doubt that the degree of hypertrophy and hypersecretion of the adrenal cortex is so marked that it is completely unreasonable to expect any organ of the body to maintain this level of activity for more than a short time. Furthermore, were this process to continue, there is no doubt that in the course of time the well-known manifestations of hypercorticism would appear, with all its pathological effects, and that complete breakdown of cortical function might eventually ensue. Thus, if the hypersecretion of the hormones were to continue as a disease became chronic, the patient would
finally suffer from Cushing's Syndrome as well as the primary disease.

On common-sense grounds alone it is clearly justifiable to regard the countershock phase as a reaction to stress which can only be of a temporary nature, and cannot persist for long. Furthermore, if the marked loss of protein which is characteristic of the countershock phase were to continue there is no doubt that it would result in such rapid wasting that the end could not be long delayed.

The countershock phase of the adaptation syndrome, in which the anterior pituitary and the adrenal cortex play the leading part, must therefore constitute an emergency response to stress which is unnecessarily wasteful of the bodily resources, of a short-term nature only, and which has the function of filling the gap until such time as the body can become specifically adapted to resist the particular form of stress imposed or until recovery can take place.

There seems little doubt that the body can neither possess nor acquire specific resistance against severe trauma except perhaps to a limited extent as far as the type of trauma is concerned. After severe trauma the issue is decided one way or the other within a fairly short time, so that in this instance it is highly probable that the non-specific adaptive mechanisms of the countershock
phase serve to prevent death, if possible, until such time as recovery can take place.

In relation to adverse physical circumstances, it is clear that the function of the non-specific adaptive reactions is to ensure survival until specific adaptation can take place and render the hyper-secretion of the cortical hormones unnecessary. For example, part of the adaptive mechanism against severe cold is to raise the metabolic rate, and against anoxia to increase the oxygen-carrying capacity of the blood, and once these adjustments have been satisfactorily carried out, the non-specific mechanisms can retire.

It is of interest at this point to consider the role of the non-specific adaptive mechanisms in relation to infectious disease.

It has been previously pointed out that the development of a disease as a result of infection with a pathogenic micro-organism is really a manifestation of failure to become specifically adapted to resist that organism and to prevent the occurrence of the disease which it causes. Many factors determine the outcome, however, of which some of the most important are the virulence and dose of the organism, the speed with which it can produce the disease, the susceptibility of the host, the speed with which an adequate degree of immunity can be acquired, and whether there is any specific acquired immunity or not. For example, some diseases are so rapid in their onset that there is no time for immunity to be
acquired and, in the absence of any acquired immunity, immune bodies must be developed during the disease. In others, like typhoid, the disease develops slowly, but immunity is acquired more slowly still, while in yet others the chances may be about even, and only a minority fail to become immune. These crude examples serve to emphasise the importance of speed in specific adaptation, as it is apparent that in all cases it is really a race between the defence and the invaders.

In a disease in which the onset is so sudden that there has been no time for immunity to develop it is clear that it is the non-specific defence mechanism of the pituitary-adrenal system which ensures survival until recovery, or the acquisition of a sufficient degree of specific immunity, renders the hypersecretion of the sugar hormones and all the other adjustments of the countershock phase unnecessary. The same considerations apply in a disease in which, though the onset was slow, the acquisition of immunity was slower.

It is therefore the case that when specific adaptation has been successful there is no disease, no alarm, no activation of the pituitary-adrenal system, and indeed the subject is often unaware of having had an infection at all. If the disease develops, it is clear that the degree of specific adaptation which has been acquired, though manifestly inadequate, must nevertheless tend to make the attack a slight one, with the assistance of the non-specific mechanisms.
It must be clearly pointed out here that the above discussion of disease as a manifestation of failure of specific adaptation refers only to those diseases which are caused by the direct action of the organisms and of their toxins. The role of hypersensitivity in the production of disease is discussed at a later stage, but it may be mentioned here that the evidence indicates that the damage done to the body by pathogenic organisms may be due either to their direct effects, or purely to hypersensitivity to their products, or in many cases to both of these factors.

On many counts, there is every reason to believe that the pituitary-adrenal response to stress can only be a temporary emergency mechanism which cannot continue for more than a certain length of time, and whose function is to cope with forms of stress to which the body cannot be adapted to resist, or to make up for failure of specific adaptation to resist infection.

Entry into the resistance stage is marked by the replacement of non-specific by specific resistance, for the simple reason that the adrenal cortex cannot continue to hypersecrete as this method of ensuring survival is one which cannot be indefinitely prolonged without producing pathological effects per se. It therefore seems clear that if an adequate degree of specific resistance has not been acquired by the end of the countershock phase the
retiral of the non-specific mechanism will be likely to be marked by death. This clearly applies in the case of a severe disease of long duration such as typhoid fever, or in the case of a type of stress to which the body cannot acquire specific resistance. The end of the countershock phase is thus a critical period in any long illness, and the outcome depends on the degree of specific adaptation which has taken place by this time. It is remarkable from a general point of view how often it is at about the third week of an illness that complications, death, or relapses occur. This would suggest that the countershock phase may end at approximately this point.

On entry into the resistance stage it would at first sight appear that, as the extra-endocrine mechanisms of specific adaptation have taken over the task of ensuring survival on a long-term basis, there is no longer any need for the secretion of excessive amounts of the cortical hormones, which therefore ceases. This explanation is inadequate, because the degree of bodily upset which may be caused by a disease in the chronic stage is very often such as to cause a degree of bodily upset which would clearly be enough to cause stimulation of the pituitary-adrenal system if the individual was healthy.

It was made clear in the description of the adaptation syndrome that in the resistance stage, despite the fact that the cortex is not enlarged,
contains more of the precursors of the cortical hormones than normally, and is to all appearances capable of responding to stress, it does not respond to the specific stress at all, and only poorly to other forms of stress. All these considerations raise the question of whether some inhibitory influence is acting to prevent the adrenal cortex or the anterior pituitary from responding to stress. This inhibitory mechanism would appear to be one which is specific as far as the specific stress is concerned, and at the same time generalised, so as to inhibit the response to all other forms of stress as well.

There can be no doubt that the adrenal cortex must undergo hypertrophy followed by involution many times in the course of a life-time, and that this organ, and the anterior pituitary, is more affected by stress than any other. It therefore seems significant that uncontrolled hypertrophy of the adrenal cortex, as in Cushing's Syndrome, is very rare and has not been reported to bear any casual relationship to preceding stress which might have started off any such uncontrolled hypertrophy. The rarity of Cushing's Syndrome is in most abrupt contrast to the frequency of hyperthyroidism, in the causation of which stress may often play a significant role.

From the above considerations it seems highly though probable that the pituitary-adrenal system is capable of extremely rapid acceleration of its output of
hormones in an emergency, there must be an equally efficient braking mechanism to stop the process when it is no longer needed, and to inhibit the response to stimuli in the resistance stage.

In the preceding discussion of the adaptation syndrome it was pointed out that the evidence derived both from man and animals indicates that the exhaustion stage is marked by a final breakdown of specific adaptation to prolonged stress, so that the non-specific defence mechanism of the pituitary and the adrenal cortex is once more called on for a last vain attempt to ensure survival. It is particularly significant that in response to the terminal illness it was found that both corticoid excretion and the loss of nitrogen rose to high levels similar to those found in a previously healthy person following severe trauma.

These observations suggest strongly that the occurrence of failure of specific adaptation coincides with the removal of the inhibitory influence which has been holding the pituitary-adrenal system in check during the resistance stage. The fact that both the inhibition of the pituitary-adrenal system and the change in protein metabolism are simultaneously abolished is of interest, because it suggests that it is possible that these mechanisms may be identical, and perhaps of the nature of an endocrine adjustment.

Certain other data also indicates that the response of the adrenal cortex to stress, adrenaliné,
or ACTH, may not be so straightforward as would appear at first sight.

It is firmly established that temporary stress, a single injection of ACTH, or a single injection of adrenaline, all cause depletion of the ascorbic acid and the lipoids of the adrenal cortex, with discharge of the cortical hormones. Continuation of the stress, or of ACTH or adrenaline injections, have a completely different effect. All the observations which have been made regarding the action of ACTH on the adrenal cortex agree in that, after the initial depletion of the cortex, the subsequent doses produce not only hypertrophy of the gland, but also an increase in the amount of lipoid stored in it, similar to that seen in the resistance stage. It was previously pointed out that the effects of a single hormone on the cortex are not strictly comparable with those of stress on the intact animal, and that in the latter the cortex is not markedly enlarged in the resistance stage. Despite this objection these observations are still of interest in that the lipoid content of the cortex increased.

Vogt (1945) found that the administration of adrenaline thrice daily for eight days to rats produced an enlarged gland loaded with lipoid, and that this did not occur in the absence of the pituitary. This result bears a remarkable similarity to the effects of prolonged injection of ACTH.
The development of refractoriness to the pituitary hormones is common, and ACTH has proved no exception. (Anderson et al. (1947) abolished renal hypertension in the rat by removing the hypophysis. The administration of pure ACTH was effective in re-establishing the hypertension at first, but in about three weeks it became totally ineffective. Chase (1949) has conclusively demonstrated the formation of an antihormone to pure ACTH in the mouse. Recently, Altschule et al. (1949) found that the fall in the eosinophil count which follows the administration of electro-shock therapy or the injection of ACTH in man became progressively less with repetition, and that the response returned after about ten days. As it is now recognised that the percentage drop in the eosinophil count from preinjection values is a fair index of the liberation of sugar hormones, this result suggests clearly that both ACTH and the stress of electro-shock had become progressively less effective in causing the liberation of the sugar hormones from the cortex.

The well-known phenomenon of the development of a refractory state to adrenaline in the treatment of asthma raises the question of whether the effect of adrenaline in asthma may not be mediated to some extent by the adrenal cortex, and that this refractory state might be due to the development of a refractory state of the adrenal cortex.
All these observations suggest strongly that the response of the adrenal cortex to stimulation by the anterior pituitary decreases progressively. Instead of causing the discharge of the cortical hormones, as it did in the first place, the continued action of ACTH seems to promote the storage of large amounts of the lipoid precursors of these hormones, and has less and less power to cause the conversion of these lipoids into hormones.

So far it appears to have been tacitly assumed that the andrenocorticotrophic hormone promotes both the conversion of the cortical lipoids into hormones, and the laying down of large stores of these same lipoids. It does not seem justifiable, in the light of the evidence reviewed above, to assume that both these effects are due to the action of ACTH alone.

The observation that the stress of electro-shock has a diminishing power to cause the liberation of the sugar hormones does not indicate whether the response of the pituitary or the adrenal has decreased. On the other hand, the steadily diminishing effect of ACTH on the eosinophil count in man would seem unlikely to be due to the formation of antihormones, as there was little time for this to take place. Though this possibility cannot be ruled out, the observations of the effect of repeated injections of adrenaline would indicate that the nature of the response of the cortex to stimulation has changed.

The observations on the effects of ACTH injec-
tions in the animal also support this concept, as in
this case also it is probable that antihormones could
not have been formed so quickly. It is also of
interest to recall that Pincus et al. (1949) found
that the cortex was refractory to stimulation with
ACTH in schizophrenia.

The trend of the evidence therefore seems to
favour the cortex as the site of action of the inhibi-
itory influence which is operative during the resist-
ance stage.

The development of a refractory state of the
adrenal cortex as a result of repeated stimulation
may be regarded as a protective mechanism which pre-
vents the occurrence of uncontrolled hypertrophy of
the gland as a result of prolonged stress. It would
seem possible that this process might also go too far,
and result in a level of cortical function so low as
to allow the occurrence of hypersensitivity reactions
and the appearance of such diseases as rheumatoid
arthritis. There is, however, evidence that this is
not the case in rheumatoid arthritis, and it is an
undoubted fact that there are no clinical signs of
cortical hypofunction in any of the diseases in which
the sugar hormones have been found to have such
dramatic therapeutic effects.

It is of interest to attempt to deduce the manner
in which the inhibition of the cortical response to
stress may arise. The above discussion has shown
that the available evidence is against any marked
inhibition of the secretion of ACTH, and that the inhibitory influence is most likely to be exerted on the cortex. The fact that the cortex is loaded with lipoid in the resistance stage is rather against destruction or inactivation of the ACTH in the blood or the tissues before it can reach the cortex, and is supported by the data of Browne and Venning who showed that, in the debilitated individual, the level of cortical secretion was at about normal levels.

It has been pointed out that there is no proof that ACTH is responsible both for converting the lipoids into hormones, and at the same time promoting their manufacture and storage. If it is so that some other influence is responsible for controlling the rate at which the lipoid precursors of the hormones are formed in the gland this influence would be in opposition to ACTH, and might be that protective influence which prevents uncontrolled depletion, and also uncontrolled hypertrophy, of the gland. This influence may be that which is responsible for the inhibition of the cortical response in the resistance stage.

The recent evidence which has already been reviewed in relation to the possibility of the production of antihormones by the hypothalmus at once springs to mind as a possible origin of this inhibitory influence. It is remarkable that the experiments of Heinbecker and Keller indicated that it was
possible for these antihormones to act on the target glands rather than on the pituitary, though some influence on the latter was also probable.

The most simple explanation is that the cortex may become adapted to repeated stimulation, and cease to respond to all but maximal stimuli. This seems unlikely because the level of cortical secretion in the chronically ill patient has been shown to be normal. It would appear that the inhibitory influence is perhaps also a regulatory one, in that, while preventing excessive secretion it still allows a normal level of secretion to take place.

It would seem of no little importance to find out the nature of this non-specific inhibitor of the cortical response, as if it was possible to go a step further and find a way of controlling it we would have a means of controlling the pituitary-adrenal system which would not involve the complications which detract from the therapeutic value of ACTH and compound E.

These considerations, however, are all affected by the paucity of evidence as to whether or not the reciprocal relationship between the secretion of ACTH and the concentration of the sugar hormones in the blood still holds true in severe stress. There is no evidence against some influence, possibly of the nature of a hypothalamic secretion, actively causing the anterior pituitary to secrete great quantities of ACTH in conditions of severe stress,
so that the relationship between the adrenal cortex and the anterior pituitary returns to approximately normal in the resistance stage, thus rendering the postulate of an inhibitory influence to a large extent unnecessary.
General Review

In a series of investigations, which have been summarised by him in his reviews (1946a), (1948b), Selye and his collaborators found that the administration of large doses of DOCA, or of crude lyophilised anterior pituitary extracts, resulted in the production of gross pathological lesions in the rat, provided that excess salt was supplied in the drinking water. The lesions thus produced bore a remarkable pathological resemblance to those found in human nephrosclerosis, periarteritis nodosa, rheumatic carditis, and sometimes rheumatoid arthritis or acute nephritis. These lesions did not occur with either agent if the salt intake was restricted, or if ammonium chloride was given along with the excess salt. A low protein diet prevented both the gross hypertrophy of the adrenal cortex which was produced by the crude lyophilised pituitary extract (LAP) and also the development of the lesions, while having no such effect on the action of DOCA in producing lesions. The removal of one kidney was found to sensitise the animals to the action of either agent.

These results suggested that overproduction of the electrolyte-controlling hormones like DOCA during the adaptation syndrome produced by prolonged stress might also result in the production of lesions. Selye and Beland (1943) therefore subjected rats "sensitised" by the removal of one kidney and the administration of excess salt to prolonged stress in the form of cold, severe daily exertion, or formalin.
injections. It was found that, while all those animals who received excess salt and were exposed to cold developed nephrosclerosis, such lesions were only found in a small number of those subjected to severe exercise or formalin injections, and none in the controls. It is noteworthy that only renal lesions were produced, the other lesions which are produced by LAP or DOCA being absent. Cold seemed to be a particularly potent form of stress, and no lesions occurred in the absence of a high salt intake. Selye has pointed out in his review (1946a) that, though there is some doubt regarding the intimate mechanism by which the lesions are produced, all his observations are most compatible with the view that excessive production of the cortical hormones to produce increased resistance to stress during the adaptation syndrome may go too far, the resulting endogenous hormone overdosage becoming deleterious to the animal and causing the development of the lesions. He has suggested that an excessive response of the pituitary-adrenal system to prolonged stress, with the production of excessive amounts of the electrolyte-controlling hormones, may be the cause of hypertension, periarteritis nodosa, rheumatic fever, rheumatoid arthritis, and many other diseases, and has proposed that these diseases should be called the "diseases of adaptation".

The implications of this theory are of great
great interest, and it is therefore pertinent to attempt to elucidate the manner in which these lesions may have been produced in the experimental animal.

In order to obviate much description a great deal of the work which has been carried out on this problem has been summarised in Table III, from which it seems, at first sight, quite clear that the lesions can either be produced directly by means of DOCA or indirectly via the adrenal cortex by means of LAP. However, the effects of these agents on the endocrine system have been presented diagrammatically in Figs. 8 and 9, which at once show that, though the results of the administration of these agents is the same, their effects are so remarkably different as to demand a much closer analysis than has been previously made.
### Table III.

**The Effects of Crude Pituitary Extracts**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Lesions promoted by:</th>
<th>Lesions prevented or retarded by:</th>
<th>Lesions produced are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCA</td>
<td>excess Na, unilateral nephrectomy,</td>
<td>prevented by low Na, acid chlorides not prevented by low protein</td>
<td>nephrosclerosis, periarteritis nodosa, myocarditis with aschoff nodes, occasionally arthritis or choreiform movements.</td>
</tr>
<tr>
<td>Crude pituitary extracts</td>
<td>excess Na, unilateral nephrectomy, high protein, ? thyroxine</td>
<td>prevented by low Na, acid chlorides, adrenalectomy, low protein. retarded by thyroidectomy.</td>
<td>as above.</td>
</tr>
<tr>
<td>Prolonged stress. (cold)</td>
<td>excess Na, high protein, unilateral nephrectomy.</td>
<td>prevented by low Na, acid chlorides, low protein.</td>
<td>nephrosclerosis only</td>
</tr>
<tr>
<td>DOCA plus cold</td>
<td>excess Na, plus thyroidectomy and/or adrenalectomy or DOCA and cold alone.</td>
<td>low Na, ? NH₄Cl.</td>
<td>lesions as for DOCA above in severe form, but main feature polyarthritis.</td>
</tr>
</tbody>
</table>

This table has been compiled from Selye (1946a), the papers referred to in that review, and a further review (Selye 1948b).
Fig. 8
The Effects of Crude Pituitary Extracts.

- Pituitary extract
  - ACTH
    - zona fasciculata
      - hypertrophy of zone and hypersecretion of the sugar hormones
        - finally breakdown of the cortex and deficiency of the sugar hormones
          - may also influence splanchnomegaly
            - thyroid
              - excess thyroxine
                - indirect stimulatory effect
      - splanchnomegaly
        - antagonistic effect on target tissues
          - result is relative lack of the sugar hormones
            - promotes production of lesions
              - periarteritis nodosa of the cortical vessels
Fig. 9
The effects of DOCA plus excess salt in the intact animal.

DOCA plus excess salt

renal tubule

direct diuretic effect, plus osmotic diuresis from excess salt

increased reabsorption NaCl decreased reabsorption K

plasma and interstitial fluid

Na rises K falls

renal tubule

polyuria

polydipsia and thirst

relative lack of chlorides, rise alkali reserve

IN LARGE DOSES SUBSTITUTION OF DOCA FOR ALL CORTICAL HORMONES

deficiency of sugar hormones

suppression ACTH production

suppression pituitary

involution of fasciculata according to dose

decreased resistance to stress

excessive production antidiuretic hormone

antidiuretic effect nullified by DOCA and salt

involution glomerulosa

involution of sex glands in large dosage

posterior pituitary

increase volume
The Effects of Crude Lyophilised Anterior Pituitary Extracts.

It has already been pointed out that there is conclusive evidence that the secretion of the electrolyte-controlling hormones is not under pituitary control in the rat, so that excessive production of hormones like DOCA is very unlikely to have been produced by LAP. It seems significant that Selye (1946a), (1944a), found that neither LAP nor stress produced the changes in the blood electrolytes which are produced by DOCA.

The crude lyophilised extract used by Selye contained a mixture of pituitary hormones, and was reported (Selye, 1944a) to produce widespread effects on the organs as well as pathological lesions. Small doses caused marked enlargement of the liver, spleen, heart, thyroid, ovary, and adrenal cortex. Larger doses over a longer period, given to animals sensitised to its action by a diet rich in protein and salt, and in many cases further sensitised by the removal of one kidney, produced not only the lesions, but also even more marked enlargement of the above organs with the exception of the thyroid, which was not markedly enlarged, and the ovary, which was markedly involuted. This splanchnomegaly was apparently a simple hypertrophy akin to that found in acromegaly. Selye found that removal of the thyroid had an inhibitory effect on the production of the lesions, and also reported
that the crude LAP contained thyrotrophic hormone, so it is difficult to estimate how much of the adrenotrophic effect of the extracts was mediated by the thyroid. Hay (1946) found that this extract had definitely less adrenotrophic effect in the absence of the thyroid. Selye also found that thyroid feeding accelerated the development of the lesions. The relationship of the thyroid to the pituitary-adrenal system has already been discussed, and it was made clear that excessive thyroid activity would eventually produce exhaustion of the zona fasciculata.

It can therefore be said with justification that the use of this crude extract is tantamount to throwing a spanner into the endocrine works, and that the results are correspondingly difficult to evaluate. However, the prevention of both lesions and cortical hyper trophy by protein restriction, the prevention of the lesions alone by salt restriction, and the prevention of the lesions by adrenalectomy, indicates that, despite the changes in the other organs, the adrenal cortex is the organ directly or indirectly responsible for the production of the lesions.

While it is apparent that the adrenal cortex is concerned in the production of the lesions, it is now quite definite that, as the experimental animal was the rat, such measures will only produce hypersecretion of the electrolyte-controlling hormones if there is a deficiency of sodium. But here the exact opposite was the case, and moreover, lack of salt,
which certainly produces hypersecretion of the hormones of the zona glomerulosa which control electrolyte balance, prevents the production of lesions by DOCA, LAP and stress. The significance of this peculiar fact is discussed later.

The cytochemical appearances of the cortex in animals which these pathological lesions were produced by means of LAP are not detailed by Selye, but he does note that the use of this crude extract frequently produced marked periarteritis nodosa of the cortex, that patches of necrosis and haemorrhage were a common finding, and that in some animals the cortex was completely necrotic. The grossly pathological state of the cortex is well illustrated in some of the microphotographs which illustrate Selye's papers on this subject (1946a), (1944a).

That gross hypertrophy is commonly followed by degenerative change is a fundamental principle of pathology. In the face of such degenerative changes in the cortex it is most difficult to understand how hypersecretion of the hormones of the cortex could proceed under these circumstances, and a degree of cortical failure seems a much more likely possibility.

Owing to the lack of control of the pituitary over the secretion of electrolyte-controlling hormones in the rat, and the fact that excess salt was given, it is highly probable that the zona glomerulosa did not share in the hypertrophy and
eventual degeneration of the zona fasciculata. This is shown quite clearly in a microphotograph illustrating Selye’s review (1946a) where, while the fasciculata is necrotic and contains no lipoid, the glomerulosa still contains lipoid and is apparently intact. This suggests that the end-result of the effects of LAP on the cortex is failure of the cortex as far as the production of sugar hormones are concerned, but that the secretion of the electrolyte-controlling hormones does not fail until later. Furthermore, as excessive amounts of salt were given it is clearly possible that this salt could have offset any failure of the zona glomerulosa for some time, and thus maintained life. There is no indication of the stage of the experiment at which the secretion of the sugar hormones may have failed, but it is quite possible that in their absence life could be maintained for a considerable time during which the lesions could have developed. It is frequently reported that in these experiments the mortality rate among the animals was high, and that they often succumbed to infections such as pneumonia. This might be regarded as evidence of lack of the sugar hormones.

The fact that restriction of the protein intake prevents the development of both the lesions and the gross hypertrophy of the adrenal cortex may be due to inability of the cortex to respond to the stimulus because of lack of certain essential amino acids.
As gross cortical hypertrophy is prevented by protein restriction whether due to LAP or to stress, and as during LAP administration it cannot be said that there is lack of ACTH, it is probable that the effect of protein restriction is exerted on the cortex itself. Thus it seems most likely in the light of the foregoing discussion that the prevention of a gross degree of hypertrophy also prevents the onset of both the degenerative changes in the adrenal cortex and the production of the pathological lesions.

Though the above considerations are also applicable, recent work by Selye (1949a) in which the effects of LAP were examined more closely have introduced another factor. It was found that, though the administration of LAP produced the same degree of cortical hypertrophy as did the administration of purified ACTH, the LAP treated animals had enlarged lymph nodes and thymus, while those treated with ACTH displayed involution of these structures. The injection of India ink demonstrated that phagocytosis was increased in the lymph nodes of the ACTH treated animals and decreased in those which had received LAP.

It is firmly established that the sugar hormones cause involution of the thymus and lymphoid tissue, while the growth hormone produces enlargement of the thymus and other organs. The apparent antagonism between these hormones has already been referred to and has been illustrated in Table I.
As the cortex was equally hypertrophied as a result of the administration of LAP or ACTH it is probable that large amounts of sugar hormones were being produced in both instances, though after prolonged administration of LAP the breakdown of the cortex would have the opposite effect. It is therefore probable that the growth hormone, some other pituitary hormone contained in this crude extract, or the secretion of a target gland controlled by one of these hormones, has acted peripherally to block, or to oppose the action of the sugar hormones. As the thymus itself is still an enigma, the possibility of an unknown hormone from this gland cannot be ruled out.

In this investigation Selye found that the injection of formalin near a joint resulted in acute inflammation followed by a chronic arthritis. It was found that while LAP or DOCA aggravated the arthritis, compound E or ACTH had a marked inhibitory effect both on the acute and on the chronic inflammation. An alarm reaction, produced by various methods, was also found to inhibit the inflammatory reaction to formalin injection.

Though it is not easy to interpret the effects of the use of LAP, the evidence indicates that the other hormones in the extract oppose the action of the sugar hormones, and that gradual failure of the adrenal cortex will follow its administration over a period. The secretion of the life-maintaining hormones of the zona glomerulosa may not fail until after the secretion of the sugar hormones has become
deficient, and even if this zone failed the administration of excess salt would have the effect of prolonging life for a time.

This recent work also suggests that it is possible for this relative lack of the sugar hormones to promote the production of the lesions, and that the gross pathological changes in the cortex may be to some extent the result of periarteritis nodosa of the cortical vasculature, and not wholly due to over-stimulation.

Selye (1949b) also found that the anaphylactoid oedema produced in the rat by egg-white, to which they are naturally sensitive, is inhibited by the alarm reaction, ACTH or compound E, and aggravated by LAP or DOCA. The antagonism is once again notable.
A Critical Analysis of the Effects of DOCA.

It has already been pointed out that there is considerable doubt whether DOCA is normally secreted by the adrenal cortex in any significant amount, and that all that can be said at the present time is that there are an unknown number of hormones secreted by the zona glomerulosa which control electrolyte balance. DOCA happens to be the only one which is readily available and can be synthesised. In consequence, it must always be borne in mind that the effects of excess of this hormone on the body are not necessarily those which would be produced by the secretion of excessive amounts of the natural electrolyte-controlling hormones by the zona glomerulosa.

The following discussion attempts to take into account all the effects of this hormone on the body, and in this respect differs considerably from the usual treatment of the subject in the literature, in which there does not appear to have been much attempt made to understand the effects of this hormone apart from simply attributing them to overdosage. It will be shown that DOCA produces such widespread effects on the endocrine system that it is totally unjustifiable to assume that any effect of this hormone on the body is a direct one.

Effects on Electrolyte Balance.

There is complete agreement in the literature regarding the biochemical effects of DOCA. Both in
man and in animals it produces retention of sodium chloride and excretion of potassium, with the result that the sodium content of the plasma, interstitial fluid and tissue cells rises, and the potassium falls. There is also a relative lack of chlorides and a rise in the CO₂ combining power of the blood resembling closely that found in certain cases of Cushing's syndrome, and as a result of prolonged administration of large doses of ACTH. Ferrebee et al. (1941) and others have shown that the loss of potassium can produce a state resembling periodic paralysis, and Follis et al. (1942) found that simple potassium deficiency produced small patches of necrosis in the myocardium. Similar lesions were reported in a case of Addison's disease by Goodof and MacBryde (1944). Durlacher et al. (1942) confirmed that potassium deficiency produced myocardial lesions, and also work hypertrophy of the renal tubules, but no other lesions and no hypertension.

The effects of DOCA on the balance of water and electrolytes has already been discussed, and it was concluded the the biochemical changes referred to above probably caused increased secretion of the antidiuretic hormone in accordance with the sodium intake, and that it is possible that the excessive amounts of antidiuretic hormone may be responsible for the relative lack of chlorides.

Effects on the Endocrine Glands.

Deane et al. (1948) showed clearly that restric-
tion of the sodium intake prevented the involution of the zona glomerulosa which has been observed to result from the administration of DOCA, and Selye and many others have shown repeatedly that the same measure prevents the development of the lesions. When the salt intake is restricted there must be excess of both endogenous electrolyte-controlling hormones and of exogenous DOCA, yet no lesions result. The production of the lesions cannot therefore be due to any direct action of DOCA.

These observations leave no doubt that the administration of DOCA and salt has the effect of substituting one hormone of doubtful physiological significance for an unknown number of electrolyte-controlling hormones by suppressing their production in the zona glomerulosa.

Though the administration of potassium chloride corrects the deficiency of potassium in the blood and the tissues caused by DOCA, Selye has found that this measure has no effect on the development of the lesions. The effects of combined sodium and potassium deficiency on the zona glomerulosa as observed by Deane et al. (1948) indicated that, except when toxic amounts were injected, the concentration of potassium in the plasma had little influence over the activity of the zone as compared with sodium, and that excess of potassium will not prevent the involution of the zone caused by DOCA.

Selye and Stone (1945), Selye, Hall & Rowley (1945), and others have established that while any
salt of sodium will potentiate the pathogenic action of DOCA, any acid chloride, such as ammonium chloride, will prevent its action even in the presence of excess salt. Ammonium chloride not only promotes the excretion of sodium, but also corrects the low blood chlorides and the alkalosis produced by DOCA.

Freidman et al. (1948) found that the hypertension produced by the nephrosclerotic action of DOCA was potentiated not only by sodium, but also by excess phosphate, so that the most marked effects were produced by giving sodium phosphate.

Selye has repeatedly noted that DOCA causes adrenal atrophy, and Sarason (1943b), Carnes et al. (1941) and Greep and Deane (1947a) have shown clearly that DOCA produces involution of the zona fasciculata as well as the glomerulosa. Sayers and Sayers (1947) found that it had a slight inhibitory effect on the secretion of ACTH by the pituitary. Large doses, such as were used by Selye, therefore, must cause atrophy of the fasciculata in addition to atrophy of the glomerulosa by depressing the production of ACTH. The end-result of excessive dosage thus amounts to physiological adrenalectomy, with the substitution of DOCA for all the hormones of the adrenal cortex. Selye & Dosne (1942) and Selye (1946a) noted that pre-treatment with DOCA lowered the resistance of the animal to stress. It is quite clear that the replacement of all the
hormones of the cortex by DOCA, or, in smaller doses, depression of cortical function, would have this effect.

Selye (1941) also found that large doses of DOCA caused atrophy of the testes, and Carnes et al. (1941) found that in one group of what appeared to be very susceptible animals the pituitaries and testes were markedly atrophied. They also found some slight effect on the male accessory sex organs, which may have been due to the suppression of production of the androgenic hormones of the adrenal cortex.

Selye noted that as a result of chronic stress, LAP, or DOCA, a few animals developed arthritis, and sometimes a syndrome resembling chorea, and that these manifestations seemed to develop if the animals were exposed to cold during the experiment. He therefore gave large doses of DOCA to animals which had been adrenalectomised or thyroidectomised, and exposed a further group of intact animals treated with DOCA to cold. (Selye et al. 1944). A high incidence of arthritis was observed in all three groups, in addition to myocardial, renal and vascular lesions. The pathological changes in the adrenalectomised group were observed to be more severe, and many animals died of pneumonia. This experiment was repeated by Harrison (1946), who found that he could produce no lesions at all by means of DOCA and cold alone, and that renal and
cardiac lesions could only be produced if the animals were given a pneumococcal infection. He failed to produce arthritis or periarteritis in any animal. Harrison therefore concluded that the high incidence of infection in Selye's animals was the cause of the arthritis. It is noteworthy that Harrison did not remove the adrenals or the thyroid in any of his animals, so that it is possible that the persistence of some adrenal function prevented the development of the gross vascular and joint lesions. Levin (1945) also failed to produce arthritis, and he also did not remove the adrenals or the thyroid.

Summers (1948) failed to produce any lesions or hypertension in dogs by the administration of truly heroic doses of DOCA and salt. 50 to 100 mgms were given in one day on occasion, and a total of 2000 mgms was given in a month. Bechgaard and Bergstrand (1949) have criticised the work of Selye on pathological grounds, pointing out that the lesions produced in the kidney by DOCA are mainly tubular, unlike human nephrosclerosis, where they are predominantly vascular. They also failed to produce more than slight tubular lesions by means of DOCA and salt. Luft and Sjogren (1949) in a careful observation of a number of cases of Addison's disease, have advanced evidence that DOCA improves the renal function of those patients with no organic renal disease, and that only those cases who have renal damage react to DOCA by the development of
hypertension or oedema.

Knowlton et al. (1946) failed to produce more than slight degenerative changes in the renal tubules, and involution of the zona glomerulosa, by means of DOCA and salt. When the kidney was already damaged by the administration of nephrotoxic sera, itself capable of producing renal hypertension, the administration of DOCA and salt caused very rapid development of nephrosclerosis and hypertension but no other lesions. They also found that a low salt intake prevented the lesions and the involution of the zona glomerulosa.

Perusal of the literature therefore reveals disagreement regarding the ability of DOCA and salt to produce lesions, and the papers of Selye also show that gross lesions are by no means an invariable result. Furthermore, the dosage of DOCA used by Selye was clearly well out of the physiological range. For example, Selye and Hall (1944) administered totals of 1530 and 2450 mgms of DOCA to two puppies within about two months, with the production of some paralysis, atrophy of the adrenal cortex, comparatively slight lesions in the renal tubules, and some cardiac enlargement. Selye and Hall (1943a) gave comparably huge amounts of DOCA to two puppies and one monkey, but the renal damage produced was not a striking feature, and the pups were stated to be quite well except for some muscular paralysis, which was probably due to potassium deficiency. Up to 20 mgms of DOCA
per day was given to these animals, and in the experiments with rats the usual dose appears to have been in the region of 5 mgms.

Selye et al. (1949) reported that, though salt restriction prevented the production of lesions, the adrenals and the pituitary were similarly decreased in size whether salt was given or not. From the foregoing review it is clear that such a result is to be expected, as there is no reason to suppose that the restriction of the salt intake has any effect on the pituitary inhibition and the involution of the fasciculata caused by DOCA, and as the zona glomerulosa occupies a comparatively small part of the cortex the gland would still appear to be smaller than normal even when this zone was hypertrophied.

The antagonism which has been recently demonstrated by Selye (1949a) between DOCA and LAP on one hand and ACTH and compound E on the other in respect of the production of formalin arthritis has already been referred to in the preceding discussion of the effects of LAP. This recent work confirms the deductions presented above that the production of the sugar hormones is suppressed by DOCA, and is clearly also connected with the recent observations of Taubenhaus and Amromin (1949) that DOCA promotes the formation of granulation tissue, and that of Ragan et al. (1949) that compound E and ACTH have the
opposite effect. It would appear that the suppression of the production of the sugar hormones will promote the growth of connective tissue, possibly to some extent by removing the inhibitory effect of these hormones on the action of the growth hormone on connective tissue.

The evidence that DOCA overdosage plus the administration of excess sodium chloride results in the replacement of all the hormones of the cortex by DOCA is therefore very strong. It is also evident that salt restriction has the effect of preventing the suppression of the endogenous electrolyte-controlling hormones, but does not affect the deficiency of the sugar hormones which is produced by the suppression of the production of ACTH by the anterior pituitary. Nevertheless, it is very well-established that the restriction of salt prevents the action of DOCA in producing the lesions. There is also good evidence that DOCA reduces the resistance of the animal to stress, and it is highly probable that this effect, and the infections which were repeatedly reported by Selye to be very common in these animals, is due to the suppression of the production of the sugar hormones.

The evidence seems to suggest, in spite of the clear evidence that the sugar hormones and ACTH can inhibit the production of the lesions and have a similar effect on the human analogues of these
experimental diseases, that sodium or the electrolyte-controlling hormones must play an important part in the production of the lesions as well as the sugar hormones. This point is discussed more fully later.
The Production of Lesions by means of Chronic Stress.

A most careful search of the literature has failed to uncover more than one paper regarding the production of lesions by means of chronic stress, (Selye & Beland 1943). This paper has already been referred to, and, in brief, the results were that the exposure of unilaterally nephrectomised rats receiving a high salt intake to cold resulted in the production of nephrosclerosis and hypertension. It is specifically stated that no lesions were observed in the vessels, the joints, or the myocardium, such as were regularly produced by DOCA or APE. Adrenal enlargement was noted, but no details of the histological appearances were given.

There is therefore a remarkable paucity of data regarding this method of producing experimental adaptation disease, and the experiment does not appear to have been repeated. Selye has, however, repeatedly stated that periarteritis nodosa and myocardial lesions can be produced by this method, and in his review (1946a) refers to the above paper as authority for the statement that periarteritis nodosa can be produced in the rat by means of prolonged stress. It can only be presumed that this was an oversight, and that confirmatory experiments have remained unpublished, or have been published in a journal which is not available to the author. As this statement has been repeated on so many
occasions, it would appear that there must be a sound foundation for it.

The "Endocrine Kidney".

Selye and Stone (1946) have devised an operation by which the renal blood flow to the rat's kidney is reduced to such an extent that filtration of urine ceases. Under these conditions the kidney undergoes a remarkable transformation into a massive epithelial organ, resembling a hypernephroma histologically, which Selye has called the endocrine kidney. As a result of this measure the animals develop vascular and myocardial lesions similar to those produced by LAP or DOCA and salt. Selye and Stone (1948) have found that alterations in the diet or the sodium intake have no influence over the development of the lesions.

This remarkable and delicate experiment is only mentioned here for the sake of completeness, as the manner in which the lesions are produced is not at all clear, nor is its significance in relation to adaptive dysfunction.
A DISCUSSION OF THE PATHOGENESIS OF EXPERIMENTAL "ADAPTATION DISEASE".

Though there appears to be no independent confirmation by other investigators, there is no doubt that Selye and his group of workers have consistently produced experimental adaptation diseases by means of crude LAP. On the other hand, though there are a number of reports confirming the ability of DOCA to cause renal and cardiac lesions with hypertension, others have found that DOCA does not produce lesions in the healthy kidney, and all others who have attempted to produce periarteritis nodosa or arthritis have failed. The evidence indicating that prolonged stress plus excess salt will produce lesions is far from convincing.

The ease with which hypertension can be produced in the rat is now well-known, and suggests that caution should be exercised in attributing the development of hypertension to any particular procedure. The speedy production of pathological changes in this animal may be advantageous as far as time and the dosage of hormone is concerned, but some other factor which could produce lesions per se could easily be overlooked. It is perhaps of significance that albino rats were very often used in Selye's experiments, therefore it is possible that the strain of rat used may have been very susceptible to the action of these hormones.

It is notable that high protein diets alone
have been reported by Blatherwick and Medlar (1937) to be capable of producing nephrosclerosis in the rat, and Smadel and Farr (1939) reported that a high protein diet markedly aggravated the nephritis produced by nephrotoxic sera in the rat. Hartroft and Best (1949) reported that less than one week of choline deficiency in early life in the rat produced renal hypertension. It would therefore appear unsafe to draw any far-reaching conclusions regarding nephrosclerosis from the experiments of Selye.

On the other hand there is no doubt that a high protein diet alone will not cause the gross vascular and other lesions which were produced by Selye's experiments in the rat.

It is a most remarkable circumstance that at the same time as Selye was carrying out this series of experiments A.R. Rich was also conducting investigations which demonstrated a clear relationship between the development of anaphylactic hypersensitivity to foreign proteins, or drugs such as the sulphonamides which are capable of combining with the body proteins to form antigens, and the production of periarteritis nodosa both in man and in animals. He also produced cardiac and renal lesions by the induction of hypersensitivity to foreign proteins, which bore a remarkable resemblance to those found in rheumatic heart disease and renal disease in man. (Rich and Gregory 1943, 1944).

These results have been repeatedly confirmed by
other workers, and indeed it would seem that it is much easier to produce these lesions by means of injections of foreign proteins than by Selye's methods. The results of these investigations were summarised by Rich in 1947, and the evidence which he has produced in favour of hypersensitivity being the cause of the development of the lesions is very convincing indeed.

The fact that both Rich and Selye produced similar lesions by such widely divergent methods at once suggests that Selye may have unwittingly produced a state of hypersensitivity, or that failure of the adrenal cortex may have been the common factor in both instances. It is singular that neither Rich nor Selye has discussed this point.

While it is clearly possible that the crude pituitary extract used by Selye could have acted as an antigen, the prevention of both hypertrophy of the cortex and the lesions by a low protein intake, and the prevention of the lesions by adrenalectomy, clearly implicates the adrenal cortex. It would seem most unlikely that DOCA could combine with the body proteins to form an antigen. In short, the evidence which has been reviewed implicating the adrenal cortex in Selye's experiments is so strong as to raise the question of whether the development of hypersensitivity may not also be connected with adrenal cortical dysfunction.

Since the above concept was originally formed
it has been greatly strengthened by the incontrovertible evidence which has been obtained of the ability of compound E or ACTH to bring about a dramatic reversal of all the manifestations of the human counterparts of these experimental adaptation diseases, and the recent demonstration of the antagonism between DOCA, LAP and the sugar hormones.

In spite of these recent developments, however, the evidence which has been put forward by Rich and others in favour of anaphylactic hypersensitivity to bacterial or other proteins being the probable cause of the group of diseases in which fibrinoid degeneration of collagen is a common feature is still very convincing indeed. As will be seen later, there is very good reason to believe that the action of the sugar hormones on these diseases is completely non-specific, and it is not necessarily the case that the direct cause of these diseases is lack of the sugar hormones.

In the light of these considerations and the preceding full discussion of Selye's experiments, it seems most probable that the experimental "adaptation diseases" were produced indirectly by lack of the sugar hormones of the cortex resulting from both DOCA and LAP. In the case of LAP the matter is further complicated by opposition to the sugar hormones by the effects of the other pituitary hormones present in the extract. With LAP it is
probable that life could be maintained by the zona glomerulosa or the excess salt for a time sufficient for the lesions to develop, and with DOCA this hormone could take the place of the hormones of the glomerulosa, with the same result.

Thus, the deficiency of the sugar hormones produced by these various experimental procedures may have been responsible, not only for the high incidence of infection repeatedly noted in Selye's experiments, but may also have allowed the manifestations of hypersensitivity to the products of the infecting bacteria or to the proteins in the crude LAP to appear in the heart, kidney, vessels and joints. It is also possible that the deficiency of these hormones may have resulted in the uncovering of a latent state of hypersensitivity which was an inherited characteristic of the animal, or had been produced by some previous inter-current infection.

In this way it is possible to reconcile the results of both Selye and Rich, and to introduce a common factor of absolute or relative deficiency of the sugar hormones. There is no data regarding the state of the adrenal cortex in animals in which the lesions have been induced by injections of foreign proteins, but it would seem probable that the pathological appearances of the gland would not provide much further information.
If this hypothesis is correct, and it certainly seems to fit the facts, it remains to be explained how lack of the sugar hormones can allow the manifestations of hypersensitivity to appear, particularly as the rat is well known to be very difficult to sensitise. The evidence regarding this point is dealt with separately in relation to the discussion of hypersensitivity as a manifestation of adaptive dysfunction.

This hypothesis is, however, insufficient to account for the outstanding and consistent feature of all Selye's experiments—the remarkable role of sodium. Moreover, this feature is one which is not only unanimously supported by all other investigators who have produced lesions by means of DOCA, but also receives impressive support from the results of drastic restriction of the sodium intake in hypertension and renal disease. It also prevents the production of lesions by means of LAP, in which instance there can be no question of suppression of the zone by the rise in the blood sodium which is caused by DOCA. There is, however, no doubt that the administration of excessive amounts of salt must also have the effect of suppressing the production of hormones in the zona glomerulosa, though not to the same extent as DOCA, and might have the effect of producing a degree of salt and water retention.
As the data is not very clear it is obviously not profitable to pursue the subject of the role of sodium in the production of lesions by means of LAP any further, but in respect of the effects of DOCA, much more data is available. From the preceding analysis of the effects of this hormone it became clear that, though suppression of the production of the sugar hormones plays one part in the production of the lesions, the disturbance of the balance of water and electrolytes must play another equally important part. It was also made clear that, as endogenous or exogenous sugar hormones antagonise the action of DOCA and salt, both factors must be present before lesions will occur.

The role of sodium may be clarified by attempting to answer several questions.

Firstly, does the deficiency of the natural electrolyte-controlling hormones which is produced by DOCA and excess salt promote the production of the lesions? As the hypersecretion of the electrolyte-controlling hormones found in Cushing's Syndrome, and as a result of the administration of large amounts of ACTH, produces the same effects on the electrolytes and water as DOCA, and as the hypersecretion of these hormones is most likely to be at least partly the cause of the hypertension and vascular lesions in Cushing's Syndrome, it would seem that this possibility is very unlikely indeed. For the same reasons it is also very unlikely that the great
excess of the endogenous electrolyte-controlling hormones which is present when DOCA is given in the face of extreme salt restriction has the effect of opposing the action of DOCA in producing lesions.

Secondly, does the increase in the secretion of the antidiuretic hormone which results from the administration of DOCA and salt play any part in the production of the lesions? There is no evidence that excess of this hormone can play any part in the production of lesions, though in the presence of an adequate salt intake it is possible that the retention of water produced by it will bring about retention of salt as well.

Thirdly, does the alkalosis and low chlorides and potassium play any part in the production of lesions? The administration of potassium has been found to have no influence over the lesions, and it has been found that, in hypertensive man, the administration of DOCA while on a low salt intake abolishes the pressor effect of DOCA but does not affect these changes in the electrolytes. It would therefore seem unlikely that these changes play any part in the production of the lesions.

Fourthly, in the presence of rigid sodium restriction, even though a great excess of both exogenous DOCA and endogenous electrolyte-controlling hormones is present, retention of salt and water cannot occur, because there is no sodium to retain. It is then the retention of sodium chloride and
water which is the factor which promotes the production of the lesions?

With the possible exception of factors which have not been elucidated, there is, unlike the first three possibilities mentioned above, no bar to the suggestion that salt and water retention is the factor which, in conjunction with relative or absolute lack of the sugar hormones, is acting to promote the production of pathological lesions as a result of the administration of large doses of DOCA and salt.

The evidence, both positive and negative, in favour of this factor of retention being one of importance, not only in the promotion of the production of lesions in the experimental animal, but also in man, cannot be discussed at this juncture because it would be completely out of place.

For the present, therefore, it is sufficient to state that there is some reason to suspect that the retention of excessive amounts of interstitial fluid, and perhaps also the increase in the intra-cellular sodium which is a feature of overdosage with DOCA and salt, may have the effect of increasing vascular irritability so that the occurrence of antigen-antibody reactions is promoted, and at the same time may increase the susceptibility of the arterioles to degenerative change, as in hypertension. It is thought that these effects of retention may be due to overhydration of collagen.
The suppression of the product of the sugar hormones would not only remove any inhibitory influence which they possess on the occurrence of hypersensitivity, but at the same time render the animal liable to infections to which sensitivity may be acquired, or uncover a latent state of hypersensitivity.
HYPERSENSITIVITY AS A MANIFESTATION OF ADAPTIVE DYSFUNCTION.

As a result of the critical analysis of the manner in which the experimental "diseases of adaptation" were produced by the various methods used by Selye, it has been concluded that three main factors are concerned in their pathogenesis — lack of the sugar hormones, hypersensitivity, and retention of salt and water. This conclusion would suggest that the production of these lesions by the induction of hypersensitivity to foreign proteins in the experimental animal, and the occurrence of similar lesions in man, may not be purely due to hypersensitivity, but may also involve the participation of the other two non-specific factors of relative lack of the sugar hormones and salt and water retention. It has been suggested that overhydration of collagen tissue and perhaps of vascular structures as well may, in some way, predispose the occurrence of degenerative change. The fact that compound E or the sugar hormones liberated by the administration of ACTH has been found to have a dramatic effect on the lesions of the collagen group of diseases and on other hypersensitive states signifies that the lack of these hormones is very likely to play a part in the production of such pathological changes by being secreted in amounts which are insufficient to stop the occurrence of the hypersensitivity reaction and the production of the lesions. The deficiency is
therefore likely to be relative, and not absolute.

The work of Rich and others has resulted in the elucidation of the profound differences which exist between the anaphylactic and pollen types of hypersensitivity and the tuberculin or tissue type. To enter into a full discussion of these differences here would be mere plagiarism, but the main points are worth emphasising.

It has been established that the tuberculin type of hypersensitivity is localised in the tissue cells, so that contact with the specific antigen results in the death of the cell, but until hypersensitivity has been acquired the antigen cannot harm the cell in any way. In anaphylactic hypersensitivity, on the other hand, the tissue cell is not sensitised, so that the antigen can be added to cells derived from the sensitised body in tissue culture without any effect on them whatever. In the anaphylactically sensitised body the only cells which are sensitised are involuntary muscle and the vascular endothelium, particularly of the capillaries, but also of the larger vessels. In the Arthus type of anaphylactic hypersensitivity, which Rich regards as an exaggerated form of anaphylactic hypersensitivity, the local necrosis which follows the injection of the antigen is due to the ischaemia resulting from the contraction of the smooth muscle in the vessel walls. The fibrinoid degeneration of collagen which is a leading feature of anaphylactic hypersensitivity would seem most likely to be a secondary change.
as a result of the vascular damage.

The anaphylactic type of hypersensitivity is associated with the presence of antibody in the blood, and may be passively transferred, but as the tuberculin type is an inherent property of the cells it can only be transferred by cellular exudates or suspensions, and not by serum. While the two forms of hypersensitivity differ markedly in these and in many other ways, both forms of hypersensitivity may be present at the same time, especially to the multiple antigens contained in bacteria. For example, tuberculin type hypersensitivity may be present to the protein portion of the pneumococcus, while at the same time anaphylactic hypersensitivity may develop to the carbohydrate portion of the organism, which probably combines with body proteins to form an antigen.

In a discussion of the manner in which it is possible that hypersensitivity may play a part in the causation of disease, however, it is apparent that to limit any such discussion to the manifestations of anaphylactic hypersensitivity or to the collagen group of diseases is a grave error, and that the subject must first of all be approached from a general point of view, or not at all.

For many years the concept that the hypersensitive state is an essential mechanism of defence in acquired resistance to tuberculosis and to other infections has been accepted without much question. This view has recently been attacked by Rich and others from
many angles and on what seem to be very adequate grounds; not only in relation to tuberculosis, but also in relation to many other infections as well. Impressive evidence has been obtained in relation to the tubercle bacillus and other bacilli, particularly the pneumococcus, that acquired immunity and hypersensitivity are independent of each other, that the immunity mechanisms can operate unimpaired in the complete absence of hypersensitivity with very little inflammation and in the complete absence of the local tissue destruction which is characteristic of hypersensitivity, and that hypersensitivity has no protective value in the absence of immunity. The evidence to this effect has been marshalled by Rich in his book on the Pathogenesis of Tuberculosis (1944) and in his Harvey Lecture (1947) in a manner which the writer cannot hope to emulate.

If the views of Rich are correct, and they are well supported by the observed facts and the investigations which have been referred to by him, it follows that the occurrence of hypersensitivity is probably never of any use as a defence mechanism, produces tissue damage out of all proportion to any protective influence it might possess, and may often be the cause of disease per se. Indeed, that the hypersensitive state can cause disease has been obvious for a very long time, but it would now appear probable that hypersensitivity is always a defect, and may more often be the cause of disease than has
been thought. If this is so, then the occurrence of hypersensitivity reactions must be a manifestation of adaptive dysfunction.

From his studies on serum sickness and vaccination, Von Pirquet, in 1911, suggested that the incubation period of many of the common infectious diseases might represent the interval between infection and the acquisition of hypersensitivity. It is illuminating to quote the following from his paper on the subject:

"The incongruity between the generally accepted theories with regard to the incubation time of the infectious diseases and the phenomena which I observed in serum disease first led me to question these theories taught 'ex cathedra'. I had been taught that the incubation time was dependent on the development of the micro-organism, and that only after its toxins had reached a certain point of evolution within the human body was it powerful enough to elicit the symptoms of a general reaction. I should have supposed that in a body which, by previous infection, had acquired some resistance against a disease, the organisms would grow more slowly, and reach that limit later; therefore a second attack, if it developed at all, might be expected to develop after longer incubation time than the first. But I had seen that the symptoms of serum disease
appeared more than a week after the first injection of horse serum in man, while after a second injection these symptoms appeared immediately. This was entirely contrary to every rule with which I had been familiar. It appeared to me, therefore, that the whole question should be approached from an entirely new point of view."

The theory that the appearance of the disease signified a profound change in the body of the host which might be termed an altered reactivity to the products of the organisms of the nature of the development of hypersensitivity, is clearly applicable to most of the common infectious diseases except those where the disease is produced directly by the rapid multiplication of the organisms and the elaboration of their primarily toxic products. In this way one might distinguish between what might be termed direct and indirect diseases, though even in direct diseases hypersensitivity may play a part in the production of sequelae. For example, Von Pirquet pointed out that in scarlatina, while the disease is produced directly by the streptococci and their powerful exotoxin, it is in the convalescent period, especially in the third week, that nephritis and rheumatic fever tend to occur. Such sequelae may well be of the nature of hypersensitivity reactions.

As the evidence which has been marshalled by
Rich and many others is now heavily in favour of the development of hypersensitivity reactions of any kind being always deleterious to the body, it follows that the occurrence of these reactions and the lesions which they may cause are likewise manifestations of dysfunction of specific adaptation, that is, of the immunity mechanisms. At the same time, it becomes apparent that Von Pirquet's theory that many diseases may really be manifestations of hypersensitivity demands the most earnest reconsideration.

It has already been pointed out that, in those diseases which are produced by the direct action of the bacilli or their toxins, the endocrine system provides the emergency mechanism which ensures survival until such time as an adequate degree of specific immunity can be acquired or recovery take place. (Ref. Page 193).

On the other hand, if we consider those diseases in which the incubation period may represent the time required to acquire hypersensitivity, and in which there is little or no bodily disturbance until the disease more or less suddenly becomes manifest, it seems quite obvious that, during this incubation period, there can be no reaction of any consequence on the part of the endocrine system. In other words, there has been no alarm, therefore no stimulus and no great increase in the output of the sugar hormones. At the same time, even in an individual who is completely susceptible to the infec-
tion in question, there is no doubt that some antibodies are being formed, so that some degree of specific adaptation against the specific infection is proceeding. Whether immunity can reach a sufficient degree of development before the point at which a hypersensitivity reaction, in the form of the disease, becomes manifest, is the factor on which the question of whether the individual develops the disease or not depends. In this way the situation is very similar to that in a disease not caused by hypersensitivity and in which the incubation period is long. If, by reason of previous exposure, passive or active immunisation, a low dose, low virulence, high natural resistance, and probably many other factors, the infection is eradicated before the incubation period is up, then, as the antigen is no longer present, an antigen-antibody reaction cannot occur, and therefore neither can the disease. The tissues are still sensitised however, and remain so for a varying period, but as specific adaptation has been successful no reaction can take place.

If the sequence of events in a case which does develop the disease is considered, it would appear that it may be as follows. During the incubation period, just as in the case which did not develop the disease, hypersensitivity and some degree of immunity are both acquired. In this case, however, due to factors in the host or in the organism the reverse of those mentioned above, the infection cannot be eradicated before the incubation time of the hypersensitive
state is finished. Therefore, the antigen is still present in the body, and the antigen-antibody reaction which causes the disease can take place, with the result that the disease becomes manifest.

It is very notable that neither in the case which did, nor in the case which did not, develop the disease was any severe bodily upset, apart from mild prodromata, produced during incubation, and that there is therefore no reason whatever to suppose that the pituitary-adrenal system was activated to any extent, if at all. In the case which developed the disease, however, there is no doubt that, for reasons in the host or in the organism, specific adaptation has failed in its object of preventing the disease.

It is obvious that many of the diseases which may be due to hypersensitivity reactions, such as smallpox, are diseases to which the human body is to all intents and purposes 100% susceptible, so that without specific immunisation the body is never able to overcome the infection before the hypersensitivity reaction occurs. At the other end of the scale of susceptibility are those diseases which may also be caused by hypersensitivity, but in which there is no doubt that it is only a very small minority who develop the disease. For example, if it is accepted that rheumatic fever and acute nephritis are caused by hypersensitivity to the products of the haemolytic...
streptococcus, these manifestations of hypersensitivity clearly fall into the latter category when it is considered that it is only a very small minority indeed who develop these diseases as a sequel to a streptococcal infection.

It would therefore seem justifiable to suggest that those hypersensitivity diseases which only occasionally develop as a result of some specific infection are those in which a combination of factors which predispose to the occurrence of the hypersensitivity reaction, or which tend to bring about a poor cortical response, may be sufficient to tip the balance and to promote the occurrence of the disease. On the other hand, the considerations which follow are also applicable.

There can be no possible doubt that in the presence of large amounts of the sugar hormones of the cortex, whether endogenous or exogenous in origin, the lesions of the collagen group of diseases and other hypersensitive states undergo rapid reversal. It has been made clear elsewhere that the amount of these hormones which is required to produce this effect is so great that it is only in severe stress that such amounts are produced by the adrenal cortex.

Even if it is considered that such large quantities of the sugar hormones may be necessary because they have to reverse changes which have taken some time to produce, it is still obvious that, had the pituitary-adrenal system produced an adequate
quantity of these hormones when the hypersensitivity reaction took place in the first instance the reaction would have been inhibited and the disease would have been slight.

It was previously pointed out that in the resistance stage of the adaptation syndrome the task of specific resistance is apparently handled by influences outside the endocrine system, that during this stage the response of the pituitary-adrenal system to the specific stress is completely inhibited, and that the response to other forms of stress is also partly inhibited. The reasons for the postulate of a very efficient "brake" to prevent the occurrence of uncontrolled cortical hypertrophy have also been detailed.

It seems clear that on the occurrence of the antigen-antibody reaction in any disease caused by hypersensitivity the cortical response has not been sufficient to inhibit the reaction. At the present time there is no data regarding the excretion of corticoids in rheumatic fever or allied states, nor in infectious disease, but it is clear that, even if the results of such investigations show the corticoid excretion to be increased, the fact that the reaction is still proceeding is evidence that the amount of the sugar hormones which is being secreted is inadequate to stop the process, so that there is a relative deficiency.
There can be no doubt that the person who is suffering from a severe attack of rheumatic fever, for example, is definitely ill, and that the degree of bodily upset which is present would appear to be of such intensity that a great increase in the secretion of the sugar hormones is to be expected, yet does not occur.

In the causation of any disease which is caused by hypersensitivity it has been argued that there is reason to suppose that the occurrence of the reaction is a manifestation of failure of specific adaptation, and that during the incubation period the non-specific adaptive mechanism of the pituitary-adrenal system has not been activated. In disease of this type it is therefore evident that specific adaptation has preceded any need for the production of any degree of non-specific adaptation by the pituitary-adrenal mechanism, and that the need for the production of non-specific resistance has been brought about by the failure of specific adaptation to accomplish its object without causing any bodily upset.

It is therefore possible that the appearance of a disease which is caused by a hypersensitivity reaction is not only a manifestation of failure to become specifically adapted to resist that disease, but also that the imperfect and inadequate degree of immunity which has been developed may be responsible for inhibiting the response of the pituitary-adrenal system to the general bodily upset which marks the
onset and the course of the disease. In effect, the patient is in the resistance stage at the beginning of the disease, and the half-baked specific adaptation has not only failed, but has also brought about a poor response on the part of the endocrine non-specific adaptive mechanism which could, by means of a maximal or near-maximal response, cut the disease short and hold the fort until such time as the specific adaptive mechanisms could deal with the problem by themselves.

From a general point of view there are a remarkable number of the common infectious and other diseases which might fall into this category. For example, it is notable how often a relative lymphocytosis and enlargement of the lymph glands and/or the spleen is a feature, and as we now know that excess of the sugar hormones brings about involution of the glands this might suggest, even admitting that the disease process itself may be causing an increase in these structures and in the lymphocytes, that there certainly is not a gross excess of these hormones being secreted during these illnesses, as there should be if the pituitary-adrenal response is adequate.

Support for this concept is also provided by the observation of Randolph (1947) that in certain allergic disorders the introduction of the allergen and the production of an attack is marked by a
transitory fall in the eosinophil count, followed by a prolonged rise in the eosinophils and a fall in the neutrophil count. Such a finding, in view of the well-established observation that the secretion of the sugar hormones brings about a marked drop in the eosinophil count, would suggest that if specific adaptation to any foreign protein is inadequate the cortical response to the antigen-antibody reaction is also poor, occurs after the reaction has taken place, is transitory, and tends to be followed by a prolonged depression of pituitary-adrenal function. The possibility that an attack causes a marked outpouring of eosinophils into the blood must also be taken into account however, and may vitiate this argument.

If the suggestion above is anywhere near the truth, it would follow that if specific adaptation to any one foreign protein is defective the pituitary-adrenal response to an allergic attack produced by that protein is also defective, while the individual might be perfectly normal in all other respects and react normally to any other form of stress. It would seem to raise the question of whether it may not be the case that imperfect specific adaptation against any particular protein may also cause imperfect non-specific adaptation to the effects of a hypersensitivity reaction to that one protein, while being normal in all other respects.

The implication that non-specific adaptation by
the pituitary-adrenal mechanism may be specifically deficient in respect of any antigen to which specific adaptation is defective receives some support from the observation of Selye that the pituitary-adrenal system does not respond at all to the specific stress imposed when the animal is in the resistance stage of the adaptation syndrome, and that at the same time the response to other forms of stress is slight. Selye's observation that the adrenalectomised rat is very sensitive to the toxic action of morphine, but that, if the animal is pre-treated with morphine for some time before removal of the adrenals, such an animal is much more resistant to morphine than one which has not been pre-treated, clearly indicates that specific adaptation is carried out by forces outside the endocrine system which do not depend on the cortical hormones for their action.

On the other hand, it is also possible that the antigen-antibody reaction itself produces some substance which has the property of inhibiting the pituitary-adrenal response to the generalised bodily upset, or that an antigen-antibody reaction of the type seen in serum sickness and rheumatic fever does not constitute a powerful enough stimulus to pituitary-adrenal secretion. In this way the awkward question of specific failure of the pituitary-adrenal response would not arise, but the reason for the failure of the pituitary-adrenal response being specifically inhibited in the resistance stage still
remains to be explained, possibly by specific adaptation, in the form of immune bodies, dealing with an infection directly, so that there is no stimulus to pituitary-adrenal hypersecretion.

It is conceivable that anaphylactic hypersensitivity could exert a direct inhibitory effect on the secretion of the cortical hormones by causing spasm of the smooth muscle with which the adrenal veins are provided. These muscle bundles have been referred to elsewhere (Page 358), and would appear capable of regulating the discharge of blood from gland, and therefore the amount of the cortical and medullary hormones which are poured into the circulation. Spasm of these muscles therefore might have the effect of shutting off, or at least diminishing, the supply of the very hormones which would inhibit the antigen-antibody reaction, and might also have an adverse effect on the secretions of the gland, the blood supply of which is very lavish. If the adrenal vein was closed the various venous anastomoses which exist between the superficial venous plexus of the adrenal and the other abdominal veins obviously cannot carry as much blood as the adrenal itself.

Though this argument has the virtue of simplicity, it is undoubtedly true that the concentration of the cortical hormones in the adrenal vein is the highest in the body, so that any such effect of anaphylactic hypersensitivity would be prevented. The suggestion outlined above would therefore seem
unlikely except perhaps in acute anaphylactic states. It is apparent that this point could only be determined by the direct experimental approach.

Quite apart from the ways in which it is conceivable that the pituitary-adrenal response to a disease which is caused by a hypersensitivity reaction may be inhibited, it seems obvious that as there is no generalised illness until a disease has become manifest the pituitary adrenal non-specific mechanism cannot be called on before the onset of a disease. It is only because the specific adaptive immunity mechanisms have failed to prevent the occurrence of the disease that the non-specific adaptive mechanisms are called on at all. In consequence of this sequence of events the best that can be hoped for is that the pituitary-adrenal response will be adequate and prompt, so that the attack of the disease is aborted or is slight.

The above considerations also apply to diseases which are not caused by hypersensitivity, and in which the incubation period may truly represent the multiplication period, as it is once more apparent that the non-specific adaptive mechanisms are not activated until they are brought into action by the generalised bodily alarm which is caused by the onset of the disease. In this type as well it is clear that any circumstance which tends to decrease the capacity of the pituitary-adrenal system to
respond to the disease will adversely affect the patient's chances of survival, and that the occurrence of the disease as a sequel to infection signifies that specific adaptation has failed.

This discussion would not be complete without some consideration of other diseases in which hypersensitivity of the tuberculin or tissue type plays a significant role.

Rich, Chesney, and Turner (1933) made an investigation of the role of tissue hypersensitivity in syphilis, and demonstrated that acquired resistance in this disease is not dependent on hypersensitive inflammation, that hypersensitivity does not develop concomitantly with acquired resistance, and that the inoculation of a very large dose of virulent spirochaetes into a rabbit which had been immunised against the disease produced neither a hypersensitive inflammatory response nor a lesion, as it did in the controls.

The close similarity between syphilis and tuberculosis from the pathological and many other aspects makes it interesting to regard this disease from the point of view of adaptive dysfunction.

There can be no doubt that the manifestations of syphilis are only very rarely so severe as to produce any marked bodily upset and the activation of the non-specific adaptive mechanism of the pituitary-adrenal system. Though man is probably 100% susceptible to the disease, the degree of specific resistance which is acquired against the disease is also high, though
not such as to eradicate it from the body, with the result that a sort of symbiosis results. The process is slow, and may go on for many years unknown to the sufferer until the more serious sequelae of the insidious pathological processes become manifest. There is therefore no reason to call on the non-specific emergency adaptive mechanism for assistance.

On the other hand it has been found that various non-specific stimuli, such as malaria and fever therapy, and pregnancy, have an inhibitory or a helpful effect on the lesions even when in an advanced stage. That such measures bring about a greatly increased secretion of the sugar hormones there can be no possible doubt, and it follows that the beneficial effect of these non-specific stimuli is very likely, just as in rheumatoid arthritis, to be due to the effect of the sugar hormones on the fibrotic and degenerative lesions of the vessels and other structures.

Syphilis would therefore appear to be an example of a disease in which is so stealthy in its attack on the body that it fails to awaken the non-specific adaptive mechanisms. It is also a disease in which the clinical features and the data secured by Rich et al. mentioned above suggest most strongly that the lesions are the result of tissue type hypersensitivity to the organism or its products, and not due to the direct attack of the organism on the tissues. It has been suggested that the three stages of the disease represent the acquisition of
hypersensitivity by the different sets of tissues involved.

The immunity to a second attack of syphilis in the already infected individual is evidence that the disease produces a fairly high degree of specific immunity, and it is notable that most of the cases in which a reinfection has been recorded were in the early stages of the disease. The fact that the Wasserman reaction only becomes positive after the primary lesion has appeared would also indicate that, though specific immunity is acquired against this organism, it is only slowly acquired, and that the disease becomes manifest before specific adaptation can reach a level high enough to overcome the infection. Though specific adaptation to resist syphilis is acquired, the degree of adaptation is only partly successful because it is unable to completely eradicate the infection, and therefore the antigen, from the body, even though there may be no manifestations of the disease for many years at a time. It has been said that in syphilis there is an adaptation, a partial tolerance of host to organism or organism to host, which is particularly unfortunate because it prevents the violent reaction which alone can lead to self-cure.

It is well known that the resistance of the syphilitic patient to other diseases is low. This would suggest that specific adaptation to resist syphilis may adversely affect the capacity of the
individual to produce non-specific adaptation to other forms of stress, as in the adaptation syndrome, and that the high degree of specific adaptation to the infection may inhibit the pituitary-adrenal response to the disease. There is, however, little to support this theory as this effect may easily be accounted for by general illhealth and other such factors.

There is now overwhelming evidence that a primary tuberculous infection must very often produce no illness, or only a slight upset which passed unrecognised for what it really was. It would appear that tuberculosis is, like syphilis, stealthy and insidious in its onset, so that unless the primary attack is a severe one there is no reason whatever to suppose that the pituitary-adrenal system participates in the reaction to the disease. In the majority of cases, therefore, the attack is dealt with by the specific adaptive mechanisms alone, which in this case also involves the isolation of the lesion by fibrous tissue, which may later become calcified. The body becomes relatively immune to the bacilli, but at the same time sensitised to the products of their death or destruction, and virulent bacilli may persist for many years in the walled-off lesions.

Though a degree of specific resistance is acquired as a result of a primary infection, there is no doubt that the degree of this resistance is not great, while hypersensitivity is a constant and marked
feature. In other words, the power of the body to become specifically adapted to resist tuberculosis is notably less than the degree of hypersensitivity which is simultaneously acquired, and which remains as a characteristic of the body for many years and may be speedily reactivated by a subsequent infection if it has disappeared or diminished in the interval. It would therefore appear probable that the absence of hypersecretion of the sugar hormones in the primary infection may be a happy circumstance, as if these hormones were present in excess they would prevent the sealing off of the primary lesion and permit the dissemination of the infection in a body which, though resistant, is at the same time highly sensitised.

It is well recognised that a variety of non-specific stresses may reactivate a latent or smouldering tuberculous lesion. It would appear that this effect of stress may not be wholly due to lowering of specific acquired resistance against tuberculosis, but also to the effect of the excess of sugar hormones on fibrosed lesions which they may break down and reactivate, or even on an old primary lesion which still contains virulent bacilli which had been hitherto securely walled off. The relationship of pregnancy to tuberculosis has already been dealt with from this point of view (Page 178), and it was concluded that the divergence of opinion regarding the influence of pregnancy on the disease
may be due to the interaction of the two factors of breakdown of the lesions and the increase in the non-specific resistance and decrease in the hypersensitivity caused by the increase in the amount of sugar hormones secreted.

Despite the above considerations, it is also clear that the general measures employed in the treatment of tuberculosis are at the same time capable not only of building up the general resistance, and perhaps the specific resistance as well, but are also measures which may tend to increase the amount of the sugar hormones which are being secreted. For example, it has been found that a high protein diet causes an appreciable increase in the corticoid excretion.

It would appear likely that while a marked increase in the amount of the circulating sugar hormones may be deleterious and result in an exacerbation of the disease by breaking down the fibrosis round the lesion, a slight increase in an active case of tuberculosis may have a beneficial effect by decreasing the sensitivity of the tissues to the products of the tubercle bacillus. That an increased output of the sugar hormones results in a decrease in hypersensitivity as judged by the tuberculin reaction may be inferred from the observation that the reaction has been found to be depressed during acute infections, pregnancy, and in the terminal stages of the disease. In the latter
it would seem probable that the depression of the reaction is due to the great outpouring of the cortical hormones in the exhaustion stage of the adaptation syndrome.

It has often been suggested that adrenal function, in the absence of actual destruction of the adrenals by tuberculosis, is poor in chronic tuberculosis, and Kolmer et al. (1948) and Thorn (1940) have reported that tuberculous patients tend to excrete sodium and chloride even when the blood levels of these elements are low. Whether this defect also involves the secretion of the sugar hormones, and whether it is due to a direct effect of the disease on the adrenals or not, is not clear. Many investigators have suggested that the asthenia and low blood pressure of the tuberculous patient may be connected with a degree of adrenal insufficiency, but positive evidence except in respect of electrolytes is lacking. Some sort of vicious circle mechanism would seem not improbable, quite apart from any theoretical possibility of inhibition of the pituitary-adrenal response to the disease because the chronic tuberculous patient must certainly be in a condition corresponding to the resistance stage of the adaptation syndrome.

There are reports in the literature regarding the effect of the administration of oestrogens, of thyroid extract, and of antihistamine drugs on the experimental disease, but though all these agents
brought about some amelioration of the disease the significance of these experiments in relation to human tuberculosis is not clear, except perhaps with regard to the clinical observation that a degree of hyperthyroidism tends to protect against tuberculosis.

The well-known tendency of the diabetic to develop tuberculosis, in view of the lack of opposition to the adrenal cortex which is present, is of some interest. The matter has been discussed by Rich, and it would appear to be complicated by evidence suggesting that the liability of the diabetic to any infection is associated with defective antibody response and lack of phagocytic activity of the leucocytes. It would appear that, in addition to these defects in the specific resistance, it is possible that, if the diabetes is poorly controlled, the periodic excess of sugar hormones may prevent the healing of the lesions.

In tuberculosis it would appear likely that, as a result of the relatively poor capacity of the body to become specifically adapted to resist the disease and the concomitant acquisition of a degree of hypersensitivity which is such as to bring about very considerable tissue destruction, the role of the sugar hormones may be detrimental in excess but beneficial in normal quantity. Whether the sugar hormones can actually produce a degree of non-specific resistance to the tubercle bacillus is not
known with any certainty, but the results of Pottenger (1937), in which he showed that injections of cortical extract had a marked inhibitory influence on the development of tuberculosis in the guinea pig as compared with the controls, would suggest that this might be the case. It is, however, notable that this experiment involved a primary infection, not a secondary one, so that even if the sugar hormones can help to overcome a primary attack they may have a deleterious effect on a secondary one.

It has previously been suggested that the damage done by pathogenic bacteria may be due purely to hypersensitivity, purely to direct action, and perhaps most commonly to an element of both. It has also been pointed out that, though there is no direct evidence in support of the assumption, the general impression derived from the clinical features of many diseases is that the period at about the third week is critical, and may mark the transition from the countershock to the resistance stage.

At the same time serum sickness commonly ensues in the second or third week after the injection, though wide variation may occur. It is therefore probably true that anaphylactic hypersensitivity to the products of the bacteria which are causing a disease has been acquired before the end of the countershock stage, and that the removal of the inhibitory influence of an excess of the sugar
hormones at the end of this phase may also unmask a state of hypersensitivity. If this postulate is correct, it follows that we must suspect that the non-suppurative arthritis which may follow many illnesses, especially streptococcal or meningococcal infections, as being of the nature of hypersensitivity reactions.

It is also notable that serum injections may very rarely result in involvement of the central nervous system, and that there are many reports of various peripheral nerve palsies resulting from serum. That these palsies could not have been confused with the sequelae of the disease for which the serum was given is shown by the fact that most of the cases have been reported following the administration of prophylactic doses of anti-tetanic serum, (Kojis 1942). These observations would suggest that it is not impossible that the occurrence of post-diphtheritic paralyses in the third week may also be due to hypersensitivity, though such a postulate is perhaps unjustifiably speculative.
The Causation of Anaphylactic Hypersensitivity.

Though the subject is one which the writer is not qualified to discuss, it nevertheless seems pertinent to enquire into the question of what the defect in specific adaptation may be which leads to the occurrence of serum sickness and probably of the collagen group of diseases.

In serum sickness the investigations of Von Pirquet and of those who followed him indicated that the presence of both specific precipitins and the antigen in the body after the expiry of the incubation period was commonly, but not invariably, associated with the onset of the illness. It would appear that if the antigen has not disappeared by the time the smooth muscle and vascular endothelium have become sensitised a reaction occurs, and that if the antigen has disappeared serum sickness does not follow, though these tissues are still sensitised and may react violently to a second injection of the antigen after the expiry of the incubation period.

The injection of a dose of antigen short of the shocking dose after these tissues have become sensitised results in the temporary disappearance of the precipitins, and a short period in which the tissues are desensitised. It is now clear that, if the injection has been such as to produce "alarm", the refractory period is due to the hypersecretion of the sugar hormones. This cannot be the case,
however, with a series of injections of gradually increasing quantities of the antigen. After the refractory period in which the antibody in the tissues appears to have been neutralised, and the precipitins tend to disappear, the production of precipitins is stimulated, and the titre rises to higher levels than before. As a result of a course of injections of gradually increasing doses of the antigen the precipitin titre becomes much higher than before, yet desensitisation has been accomplished. It would seem as if the stimulation of the production of precipitins by a course of injections had completed specific adaptation to the injection of the antigen.

There is so far no agreement in the literature regarding the role of the precipitins in the production of anaphylaxis. That this is so is amply borne out by the most comprehensive review of serum sickness by Kojis (1942), and it is apparent that there is little to be gained by recounting the claims and counterclaims, and the plethora of theories which have been advanced regarding the mechanism involved. While some have stated that the presence of precipitins is an invariable accompaniment of serum sickness, others have denied this, so that there is no clear proof that the appearance of precipitins is related to the onset of serum sickness.

The finding of Mainwaring et al. (1927), that the transfusion of blood from a dog which had been
found to be immune to anaphylactic shock after repeated injections into a sensitised dog resulted in the latter becoming refractory to anaphylaxis after twenty-four hours, while the precipitin titre was found to be about the same in both, would suggest that the precipitin and the anaphylactic bodies are not only dissimilar, but unrelated. This experiment does not seem to have been either confirmed or denied.

The latest and apparently the most thorough investigation of the mechanism of serum sickness, (Karelitz 1942, Karelitz and Stempien 1942, Karelitz and Glorig 1943), showed that the sensitising antibody was thermo-stable and non-precipitatable, and might be of the nature of a reagin, as in pollen type hypersensitivity. It was found that in the convalescent sera of some cases of serum sickness there was no precipitin, but that passive transfer of the sensitivity could still be carried out. They concluded that the sensitising antibodies to horse serum seem not to be dependent on the presence of antihorse precipitin in the convalescent sera.

These observations seem strikingly similar to those of Loveless (1940, 1943) in the pollen type of hypersensitivity, which Rich has pointed out possesses many more features in common with the anaphylactic type of hypersensitivity than otherwise. Loveless produced evidence, as a result of a series of investigations, that two antibodies are concerned in the pollen type of hypersensitivity; the reagin,
which is the sensitising antibody; and the precipitin, which acts as a blocking antibody by combining with the antigen before it can reach the sensitised tissue. A course of increasing doses of the antigen caused a marked rise in the precipitin titre which was accompanied by a decrease in sensitivity to the antigen. In this instance as well it would seem that the stimulation of the production of the precipitins had the effect of completing specific adaptation. It is also of interest that Lowell (1944) demonstrated that insulin hypersensitivity was associated with two antibodies, one of which neutralised the insulin and was specific for the proteins of the pig from which it was derived, and the other which was a skin sensitising antibody.

Recently Kabat and Benacerraf (1949), in the latest of a series of studies of anaphylaxis by means of accurate quantitative micro-methods, have shown that the non-precipitable or "univalent" antibodies which are formed in the rabbit in response to pure egg albumin as an antigen are equally effective, on a weight for weight basis, as the heterogeneous mixture of precipitable and non-precipitable antibodies in the original serum in respect of the power to transfer passive anaphylaxis. This investigation would therefore suggest that the non-precipitable or "univalent" antibody is the sensitising antibody, and that the precipitable antibodies are not concerned in anaphylactic sensitisation. The appear-
ance of both precipitable and non-precipitable anti-
bodies to egg albumin as a pure antigen had already
been reported by Heidelberger and Kendall (1935),
Heidelberger et al. (1940), and other workers.

It has long been known that the route of
administration of the antigen has marked influence
over antibody production. Further evidence on this
point has recently been obtained by Heidelberger (1947)
and Treffers et al. (1947), as they have demonstrated
that the intravenous injection of antigen results in
the production of precipitins, while the subcutaneous
injection gives rise to a "univalent" antibody which
was only precipitable by special methods.

This work may be of some practical importance,
because it is remarkable that subacute bacterial
endocarditis and other septicaemic states are not
commonly associated with acute rheumatism or other
states which may be due to hypersensitivity.

It would seem possible that streptococcal
pharyngitis may act like a subcutaneous injection,
and call forth the univalent or sensitising anti-
bodies, and not the precipitins, with the result that
the tissues become sensitised. Perhaps it is the
case that this type of infection does not provide
sufficient of a stimulus to antibody production. It
is perhaps pertinent to note that Swift and Derick
(1929) found that subcutaneous injection of non-
haemolytic streptococci produced a high degree of
hypersensitivity, while intravenous injection produced immunity but very little hypersensitivity.

It should be mentioned, however, that the question of valence of antibodies, and indeed the whole subject of the causation of anaphylaxis, is in a highly controversial and fluid state.

Further evidence which may have some application to the problem of univalent antibodies and sensitisation has recently been provided by Weiner and his co-workers in relation to "univalent\(^{R_{h}}\) antibodies, and there seems to be no bar to the suggestion that this work may be of general immunological significance.

Very briefly, it has been found by Weiner (1946), and by others, that Rh antibodies can be detected in the serum of some patients by means of agglutination tests carried out in saline media, while in others the presence of antibodies can only be detected in plasma or serum media. Weiner has therefore postulated two varieties of antibody, the bivalent or agglutinating antibodies, which can agglutinate the cells by themselves, and the univalent, or blocking, antibodies. Thus, when serum containing univalent antibodies is mixed with Rh positive cells in saline media these antibodies "coat" the cells, but no agglutination occurs unless plasma or serum is added. Weiner et al. (1947) have demonstrated that the substance in the plasma which is responsible for completing the second phase of this reaction is a colloidal aggregate of the plasma proteins, which
has been termed "conglutinin". It was found that altering the proportions of serum albumin and globulin in the mixture of proteins which was used altered its conglutinating power, and that the proportions found in the plasma were about the most efficient. Weiner and Sonn-Gordon (1946) have also shown that, as the univalent antibodies can pass the placenta and the bivalent apparently can not, there is reason to believe that the former are smaller than the latter.

Though there is absolutely no evidence that such may be the case, it does seem at least possible that, if this phenomenon is of general significance, the increase in the gamma globulin and the decrease in the albumin which is found in all the diseases of collagen may be in some way connected with the role of the plasma proteins in conglutination, and therefore in the occurrence of hypersensitivity reactions.

Though the evidence is controversial, there would nevertheless appear to be reason to suspect that sensitisation may be due to univalent antibodies, and that the precipitins are of the nature of blocking antibodies, whose function is to combine with the foreign antigen before it reaches the tissues. Thus the antibodies which arise following the injection of a foreign protein may be of two sorts, good and bad, and the relationships between the two may be of great importance in determining whether the manifestations of hypersensitivity occur or not. The defect
in specific adaptation which may occur in serum sickness and other hypersensitive states may thus be due to poor production of the precipitins. Thus, if by the time hypersensitivity has developed the precipitins have not succeeded in removing all the antigen from the blood, the result will be that a reaction will occur. Subsequent desensitisation by means of increasing doses of the antigen may therefore act as a stimulus to precipitin production, completing the process of specific adaptation.

It may be mentioned in passing that there can be no possible doubt that man was never meant to be injected with horse or any other kind of serum. Hence, serum injection is therefore a procedure to which the body cannot be expected to undergo specific adaptation with ease, so that it is no surprise to find that untoward effects may occur.

Though this hypothesis may apply to the anaphylactic type of hypersensitivity, it is apparently not applicable to the Arthus type, which Rich regards as an exaggerated form of the anaphylactic type of hypersensitivity. Cannon and Marshall (1941), and other investigators, have demonstrated that there is strict parallelism between the precipitin titre and the development of Arthus type hypersensitivity. Very recently, Benacerraf and Kabat (1950) have found, in contra-distinction to their previous investigation of anaphylaxis, that the univalent
antibody to egg albumin was far less effective on a weight for weight basis in passively transferring the Arthus type of hypersensitivity than was the mixture of all the antibodies in the original serum. They therefore suggested that a fundamental difference must exist between the two types of hypersensitivity, and that in the Arthus type the precipitins play a significant part.

If it is so that the precipitins may be beneficial in anaphylactic hypersensitivity and harmful in the Arthus type of hypersensitivity, this would seem a matter of some importance. In animals the lesions have generally been produced by the use of large doses of foreign protein, either given on one or several occasions, so that the type of hypersensitivity is probably of the Arthus type. The result has usually been the production of several of the experimental analogues of the diseases of collagen at the same time. On the other hand, the evidence seems to indicate that serum sickness in man is a manifestation of the anaphylactic type, and the many similarities between it and acute rheumatism would suggest that the latter is also caused by this type of hypersensitivity. In periarteritis nodosa and allied states, however, it would seem possible that the more intense lesions are more likely to be accounted for by the Arthus type of hypersensitivity. There is, unfortunately, no evidence indicating the truth or falsity of this assumption.
In conclusion, it must be mentioned that this section has been included mainly from a sense of completeness; that the author's lack of familiarity with the subject clearly renders it unjustifiable to include it at all, and that the speculation which has been indulged in may well rest on faulty premises.
THE ROLE OF RETENTION IN
ANAPHYLACTIC HYPERSENSITIVITY AND HYPERTENSION.

This discussion follows from the critical analysis of DOCA and salt in the experimental animal and the attempt to elucidate the remarkable part which sodium appears to play in these experiments. It was concluded that both the factors of lack of the sugar hormones of the cortex and the retention of an undue amount of interstitial fluid was necessary before the lesions could be produced.

It is helpful first of all to consider the negative evidence in support of this hypothesis, and henceforward to make full use of clinical as well as experimental data.

If it were the case that lack of the sugar hormones is sufficient to allow the manifestations of hypersensitivity to any antigen to which the body happens to be sensitive to make their appearance, it would be expected that the patient with Addison's disease, or Simmond's disease, would suffer from all manner of those diseases which may be caused by hypersensitivity. There is no doubt that this is not the case, though one might expect it to be so from the recent demonstrations of the dramatic effects of the sugar hormones in rheumatic disease, asthma, and so on.

While it is simple to account for this remarkable discrepancy on the grounds that complete absence of all the cortical secretions in Addison's
disease may depress the reactions of the tissues to such an extent that hypersensitivity does not develop, it is also the case that many cases have an insidious onset which may last for a time ample for the production of lesions. Furthermore, it would be expected that any state associated with a degree of adrenal hypofunction would be associated with hypersensitivity.

The use of DOCA and salt over prolonged periods in the treatment of Addison's disease would appear likely to supply the conditions necessary for the production of lesions, but it is only occasionally that some arthritis has been noted, and Luft and Sjögren (1949) have reported that only those with renal damage are liable to develop hypertension. It is, however, notable that Selye gave 5 mgms. of DOCA daily to the rat, a dose which would suffice for the treatment of a severe case of Addison's disease in man. In the treatment of adrenal insufficiency it is also the case that it is good policy to give a dosage of DOCA which tends to err on the safe side, and that if salt and water retention occurs the condition is not allowed to persist for any length of time. It is also known that the amorphous fraction is much more powerful than DOCA, and that though the latter may have similar actions, it is not the natural hormone.

It would appear likely that the loss of salt and water in the untreated case of insidious Addison's disease, and the tendency for replacement therapy to
both

err on the safe side, result in a tendency to lose
salt rather than to retain it, so that the appearance
of lesions as a result of hypersensitivity is inhi-
bited. Though lack of the sugar hormones is present,
the retention factor is not, so no lesions result.

According to the views presented here it would
seem that the manifestations of hypersensitivity
might appear in the hypophysectomised animal or in
man with pituitary insufficiency, as it has been
pointed out that the absence of the pituitary implies
lack of the sugar hormones with persistence of the
secretion of the electrolyte-controlling hormones.
However, in Simmond's disease, though the control
over the electrolytes is not lost, it is impaired,
so that the tendency is to lose salt rather than to
retain it. In the hypophysectomised animal there
is no reason for the zona glomerulosa to hypersecrete,
so that there is no tendency to retention. In both
instances the retention factor is absent, though the
sugar hormones are lacking, so no lesions result.

There is therefore little doubt that lack of
the sugar hormones does not produce disease per se,
even in the presence of infection, to which persons
with adrenal and/or pituitary insufficiency are
peculiarly liable. There is therefore good reason
for the belief that the absence of retention, and
indeed the tendency to loss of sodium and water, is
the main reason for the absence of hypersensitive
states in these conditions.
Though this negative evidence is rather circum-
stantial in character, it nevertheless suffices to
provide an explanation for the paradox that while
there is no clinical or other evidence suggesting
adrenal insufficiency in any of these diseases in
which the administration of compound E or ACTH has
been found to have such a dramatic therapeutic
effect, frank adrenal or pituitary insufficiency is
not associated with the manifestations of these
diseases.

The positive evidence is to be sought in rather
widely differing fields, encroaches to some extent on
the discussion of other subjects, and is also mainly
concerned with observations which have been made in
man.

Kern, in 1940, published a most thought-
provoking discussion of the role of salt and water
retention in allergy. Briefly, he pointed out
that allergic attacks tend to occur as a result of
any circumstance which brings about retention of
salt and water, and argues that this factor is a
non-specific one which favours the development of
hypersensitivity reactions. He suggested that there
may be two factors in the production of an attack,
one being the non-specific one of salt and water
retention, and the other the hypersensitivity itself.
If the hypersensitive state is such that contact with
the antigen alone is just insufficient to induce an
attack, then the addition of the non-specific factor
of retention will cause an attack, while the abolition of that retention will tip the scales the other way and prevent an attack. If, on the other hand, the hypersensitivity is highly developed, the presence or absence of the retention factor cannot either prevent or appreciably aggravate an attack.

He reviewed the evidence which has been obtained by previous workers, and pointed out that though salt restriction, the administration of potassium salts, or of ammonium chloride, have been found to be of assistance in some cases their failure in others is probably due to the removal of the retention factor being unable to have any influence on a highly developed state of hypersensitivity. In this way he has reconciled the divergent and contradictory results and opinions concerning the value of such measures in the treatment of hypersensitive states.

It must be pointed out here, however, that there can be no doubt that really drastic sodium restriction, such as is now practised in the treatment of hypertension, has certainly not been tried in the treatment of hypersensitive states. It is therefore possible that the retention factor may play a greater causative role than is thought.

Fibrinoid degeneration of collagen is the common denominator of that group of diseases in which we now possess evidence that excess of the sugar hormones will cause dramatic reversal of the
manifestations of the disease. There is also good evidence that anaphylactic hypersensitivity is most likely to be the direct cause of the fibrinoid degeneration. It is notable that though we are in possession of much data regarding the relationships between the intra-cellular and extra-cellular fluids and the exchanges which take place between them, there does not appear to have been any investigation regarding possible differences in behaviour between collagen tissue and the other tissues of the body in this respect.

Kern has emphasised that it is common experience in allergy clinics that a large number of patients report a sharp exacerbation of symptoms on a day when a severe storm is approaching, and that he has repeatedly noted a correlation of the incidence of such exacerbations with the fall in barometric pressure. He further points out that this increase in the incidence of attacks occurs irrespective of differences in the allergens to which the patients happen to be sensitive.

He has drawn attention to the experiments of Smith (1928), who showed that the exposure of dogs to reduced barometric pressures well within the range of human experience produced definite retention of water and marked restlessness.

It is a most commonplace observation that old scars of any sort, whether they be caused by trauma,
rheumatism, or anything else, tend to make their presence felt during or just before bad weather. It is also a commonplace observation that during a storm one tends to be irritable and out of sorts. This latter observation would appear to be correlated with the well recognised tendency for epileptic fits, attacks of asthma and other allied allergic phenomena, and marked mental irritability to occur as a result of the premenstrual retention of salt and water. It is also well established that an epileptic fit can be provoked by the administration of pituitrin. Kern quotes a case in which the presence of intracranial scar tissue was associated with epileptic attacks which commenced with the menarche and recurred just before every period. It was found that there was increased secretion of the antidiuretic hormone just before the period, and deep X-ray therapy to suppress posterior pituitary function resulted in the abolition of the attacks.

According to these considerations it would be expected that exposure to high altitudes might also precipitate the production of fits or allergic phenomena. As no such effects appear to have been noted as a result of the sudden changes experienced in aviation, it would seem probable that the sudden and temporary nature of such changes may be insufficient to bring about retention, or that the increase in the output of the sugar hormones which takes place under stress acts to prevent such an occur-
There is, however, one report in the literature (Baker 1944) in which it is reported that a few weeks after arrival in Mexico City, which stands at an altitude of 7000 feet, the incidence of allergic phenomena is remarkably high. It is, however, difficult to attribute this report to retention, as a few weeks after arrival it is likely that the individual might be passing into the resistance stage of the adaptation syndrome which must be called out by the strain of becoming adapted to such an altitude. It is therefore possible that a factor of a relative deficiency of the sugar hormones is also involved. It may be mentioned in passing that the symptoms of mountain sickness have been attributed by some authorities to relative cortical insufficiency.

Returning to the subject of retention, it appears to be the case, without going into the matter very deeply, that the retention of excessive amounts of salt and water is not only associated with a lowering of the threshold sensitivity to any antigen to which the individual happens to be sensitive, but also with an increase in the excitability of the central nervous system. It is well recognised that the manifestations of hypertensive encephalopathy in man and of water intoxication in the experimental animal are associated with cerebral oedema, so that it is not surprising that lesser degrees of cerebral
oedema should result in an increase in excitability.

Goldzieher, in his work on the endocrine glands, (1939) has paid considerable attention to the factor of retention in relation to hypersensitivity, and has come to conclusions which are remarkably similar to those of Kern. He points out that states of retention of salt and water are characterised by a peculiar sensitivity to various irritations, that the cause may be endocrine or nervous, and that allergic states may be divided into two groups — the genuine case who is very sensitive to the antigen, and the case which reacts to antigens because of the increased irritability resulting from the retention of salt and water.

The question of retention of nervous origin is also of interest in relation to the demonstration by Rydin and Verney (1938), O'Connor and Verney, (1942) and others, that emotion can cause an increase in the output of the antidiuretic hormones, and to those extraordinary cases of extreme retention of emotional origin which are occasionally seen. It would seem possible that the undoubted relationship of emotion to the onset of an allergic attack in those cases in which there is a pronounced psychosomatic element may be related to excessive secretion of the antidiuretic hormone and the
retention of salt and water, with the result that the state of hypersensitivity becomes accentuated and an attack results.

The above considerations raise the question of whether collagen tissue is particularly sensitive to changes in the balance of water and electrolytes. For example, it would seem possible that the aching of wounds may be due to swelling of the scar tissue and resultant pressure on nerve endings, and leads to the suspicion that retention may have the effect of causing overhydration of collagen.

Though this suggestion would seem to be sheer speculation, evidence which may support this concept has been provided by the series of investigations of the role of the lymphatics and connective tissue fibres in relation to the formation and absorption of tissue fluid which have been carried out by McMaster.

In 1939 McMaster and Parsons injected vital dyes into the lymphatics of the connective tissues of the ear of the mouse and observed the diffusion of the dye from them under high magnification. The dye could be seen escaping from the lymphatics as bristly lines of colour extending from them along the connective tissue fibres. These lines of colour could be bent and twisted by pressure with a micro-probe, and sprung back to their original positions when the pressure was removed as if the dye were
fixed upon or between the fibres. In contrast, these projections of dye were absent in oedematous tissue, and the escaping dye took the form of a diffusely coloured cloud freely movable in the oedema fluid when pressed upon by the micro-probe.

They pointed out that all previous workers who had used methods of micro-injection had been impressed by the resistance of connective tissue to the introduction of fluid, and that it seemed as if the cells and the connective tissue fibres were embedded in a homogeneous ground substance. They found that the dye, which at first appeared as hair-like projections between or on the connective tissue fibres as described briefly above, later spread and coloured the neighbouring tissues blue. Pressure over these diffused blue areas failed to squeeze away the colour as it would have done had it been dissolved in free fluid, but resembled the paling in colour observed as a result of pressure on a coloured block of agar.

For these and other reasons they concluded that the interstitial fluid does not exist in tissue spaces as is popularly supposed except in the presence of frank oedema. They therefore suggested that the connective tissue fibres may act as a pathway for the transport of the tissue fluids, and point out that these connective tissue fibres form a network of millions of fibres connecting capillaries,
lymphatics, and other tissues. They suggested that the state of the tissue fluid might be "analogous to the film of water caught between two pieces of glass, to all purposes captured, unable to move freely this way and that, but still chemically capable of behaving as fluid, — to diffuse into cells, to transport ions, to permit the exchange of solutes through it. The captured films of water, if they exist, must be so thin that they are practically part of the connective tissue, not interstitial pools of fluid. This concept of fluid captured by capillary forces would explain the fact that fluid does not normally seep through the tissues and collect in the dependent portions of the limbs."

The question as to whether vital dyes and tissue fluids also escape from the blood capillaries along the fibres of connective tissue with which they are surrounded does not appear to have been settled. According to Chambers and Zweifach (1947) the bulk of fluid interchange occurs between rather than through the endothelial cells, and capillary permeability depends on the state of the inter-endothelial cement. They also draw attention to the potential importance of the pericapillary sheath of connective tissue in pathological conditions, and to the report that it may be hyalinised in hypertensive states.

Further work by McMaster (1941, 1946, 1947)
has produced no evidence against this concept of the function of the connective tissue fibres in the transport of fluid, and the existence of a homogeneous matrix in which they are embedded. It has also been shown that the lymphatics, though very permeable, are devoid of actual fenestrations, like the capillaries, and that the dilatation of the lymphatics which was observed in the presence of oedema is most probably caused by the stretching of the connective tissue framework caused by the oedema pulling out the walls of the lymphatics.

This work would therefore suggest that it is possible that the fibres of connective tissue may have an active function in the transport of fluid in addition to providing support to the vessels and other structures. There is, however, no indication of whether this function is carried out by the connective tissue fibres alone, and likewise there is no positive evidence that filtration and reabsorption of the tissue fluid does not at the same time occur through the walls of the capillaries and the lymphatics, as is ordinarily thought.

It is well established that the volume of the interstitial fluid fluctuates widely, that the interstitial compartment serves as a reservoir to accommodate excess of fluid pending excretion and that many litres of excess interstitial fluid may be present before oedema is clinically detectable. As the evidence reviewed above indicates that it is likely
that no tissue spaces exist except when frank oedema is present, it follows that excess interstitial fluid is likely to be stored in the homogeneous matrix in which the connective tissue fibres are embedded and possibly in the connective tissue fibres themselves. It would seem that the matrix and the connective tissue may be like a sponge, and act as the labile reservoir of the interstitial fluid, unless there is such an excess that it cannot be thus accommodated and oedema fluid makes its appearance.

Just as it appears to the the case that retention, presumably by rendering endothelium and smooth muscle more irritable, predisposes to the occurrence of hypersensitivity, so it would also seem possible that collagen may be rendered more susceptible to degenerative change as a result of over-hydration. It is also possible that the tendency to an increase in the intra-cellular sodium which takes place as a result of the action of excess of electrolyte-controlling hormones may play some part.

The above theory is, of course, frankly speculative and rests on rather scanty and circumstantial evidence, and it is not justifiable to go further than to indicate that, in the presence of a relative deficiency of the sugar hormones, the retention factor may operate in this way. It is also realised that it is subject to many obvious objections, of which perhaps the most obvious is the fact that frank clinical oedema does not act in this manner. It is
not intended to do more than indicate that the presence of an excess of interstitial fluid may conceivably act in this way. The evidence has been derived mainly from the observations of the subcutaneous connective tissue, and provides no explanation of the capricious distribution of the lesions of the various diseases in which fibrinoid degeneration of collagen is the common feature, and of which anaphylactic hypersensitivity may be the cause.

The matter is therefore better left at this point, but with emphasis laid on the positive and negative evidence which was previously recounted in favour of retention being one of the factors which predispose to the occurrence of hypersensitivity. One further possibility regarding which there is no data is the question of the effect of the electrolyte-controlling hormones on the permeability of connective tissue.

As a result of the discussion of the causation of hypertension in man, (Page374), it has been concluded that there are good grounds for the belief that, in many cases of hypertension of both renal and essential types, the tendency to retain undue amounts of salt and water is most probably due to a degree of hypersecretion of the electrolyte-controlling and the antidiuretic hormones, and that the beneficial effects of sodium restriction in the
treatment of the condition is mainly due to the abolition of this abnormality. The experimental evidence is also concordant with this theory. The abolition of the apparent imbalance between the sugar and the electrolyte-controlling hormones by the administration of sugar hormones or the stimulation of their production by means of non-specific stimuli has been found to have a hypotensive effect, which may be due partly to a possible beneficial effect on the vascular lesions, and partly to the correction of the imbalance between the two groups of hormones, the antagonism between which in respect of salt and water has previously been referred to.

In hypertension it seems to be generally agreed that the arteriolar lesions are more likely to be an effect than the cause of the hypertension, being the result of the undue strain imposed upon the vessels by the pressure, and perhaps representing an acceleration of the normal degenerative changes resulting from the processes of ageing. In essential hypertension the lesion takes the form of hyaline degeneration of the subintimal tissues and, in the muscular arteries, of the reduplication of the internal elastic lamina and replacement of the muscle by elastic and fibrous tissue. In the malignant form of hypertension cellular hyperplasia of the arteriole, which may be followed by collagenous change, is seen if the process is fairly slow, but if the disease is
very rapid in its attack actual necrosis of the arterioles may be found.

It would appear as if the vessels were unable to remain adapted to the strain, and that a vicious circle mechanism may be set up in the later stages of the disease. If it is the case that overhydration of collagen predisposes to the occurrence of degenerative changes, it therefore follows that the salt and water retention which is to be found in many cases of hypertension may promote the occurrence of the degenerative changes in the arterioles.

As there is some reason to suspect that retention increases the irritability of the vessels, it is also possible that their sensitivity to constrictor influences is increased.

Some of the results which have been obtained by the use of drastic sodium restriction, as judged by the regression of apparently irreversible retinal changes, seem so good as to be difficult to account for on the grounds of lowering of the blood pressure alone. Some support for this concept has very recently been provided by the demonstration by Sapirstein et al. (1950) that giving rats hypertonic saline as drinking water will produce hypertension after four weeks.

This theory is again a highly speculative one, but it does seem to offer at least a tentative explanation of the manner in which the retention of an undue amount of interstitial fluid and overhydra-
tion of collagen or other tissues may contribute to the causation of hypertension. In common with the suggestion that overhydration of collagen may predispose to fibrinoid degeneration as a result of anaphylactic hypersensitivity this theory would suggest that collagen may act in a manner somewhat different from other tissues in respect of water and electrolytes, and it would appear that the first step to be taken in investigation of this point is to find out if this is the case or not.
The Thyroid and Hypersensitivity.

At the time of writing Long and Miles (1950) have just published an account of an investigation which appears, at first sight, to provide strong presumptive evidence that thyroxine can cause a marked increase in sensitivity to tuberculin in the sensitised guinea pig, and that, as would be expected, compound E, or the sugar hormones liberated by ACTH peptide, has the opposite effect. As this investigation has implications which are, in some ways, contrary to the interpretation of adrenal-pituitary relationships which has been expressed in this thesis, it is felt that some comment, and a much closer analysis of this work, is very necessary.

It has already been pointed out in this thesis that Deane and Greep (1947) have carried out a careful cytochemical investigation of the effects of thyroidectomy, thiouracil, and thyroid feeding in the adrenal cortex of the rat. They have shown most clearly that, while thyroid feeding initially produces hypertrophy and signs of hypersecretion in the zona fasciculata, more prolonged administration results in signs of exhaustion, cell degeneration, and the accumulation of large fatty droplets in many cells. It has previously been stressed that many authorities have commented on the various points of similarity between Addison's disease and hyperthyroidism, and that this is supported by the evidence of Talbot et al. (1947) and Daughaday et al. (1948) that the corticoid excretion in hyperthyroidism may be increased, normal, or
markedly decreased in this disorder. All this evidence, of which Long and Miles are apparently unaware, suggests most strongly that excess of thyroxine causes an initial rise in the output of the sugar hormones, but that this effect is followed by exhaustion, with the result that the level of secretion of the sugar hormones becomes lower than normal. Thus, mild hyperthyroidism may be associated with hypersecretion of the sugar hormones, but severe hyperthyroidism with hyposecretion.

Though the work of Long and Miles is not strictly comparable with that of Deane and Greep in view of the fact that the former used the guinea pig and sodium thyroxine, while the latter used the rat and thyroid powder, it would seem very probable that the effects on cortical function were similar. Long and Miles state that the degree of hyperthyroidism induced was not severe, but they also note that two animals died during the experiment with haemorrhages in the adrenal cortex. The illustration in their paper showing the adrenals stained for cholesterol is also of doubtful significance in view of the large fatty droplets observed by Deane and Greep, and therefore would not seem to provide a true indication of cortical function.

It is therefore probable that the marked increase in sensitivity to tuberculin which was noted as a result of the administration of thyroxine by Long and Miles was not a direct effect of the thyroxine, but due to a decline in cortical function as a result
of prolonged dosage, despite the grossly enlarged glands which were present.

Closer analysis of this paper also brings out several other points of interest. In one group of animals tuberculin sensitisation by means of bi-weekly injections was commenced when the animals had already been on thyroxine for ten days, so it is reasonable to assume that by this time any initial increase in the cortical secretions from the thyroxine had been replaced by a decline. In half the controls receiving tuberculin alone thyroxine administration was commenced on the twenty-eighth day, and the hypersensitivity was rapidly aggravated. An initial decrease just before the rise in hypersensitivity would be expected in this group, as a result of the initial stimulation, but was not observed, though it is possible that this did occur in the interval between tuberculin injections. No details are supplied, but it can be inferred from the comments that reactions to repeated injection of tuberculin occurred, so it is entirely possible that the animals were undergoing the adaptation syndrome. This may have had the effect of inhibiting the initial effect of thyroxine in increasing the rate of secretion of the cortical hormones, as they would be in the resistance stage by the twenty-eighth day.

No effect on tuberculin hypersensitivity was noted in another group of animals receiving 25 mgms. of propyl-thiouracil thrice weekly. It may be pointed out that this dosage is much less than that
used by previous investigators, and that though the thyroid was probably suppressed, the effect on the adrenals is doubtful. (Vide Deane & Greep, Endocrinology 41,252). Furthermore, no note of the effect of the propyl-thiouracil on the adrenals is given. It would be expected that an effective dose of thiouracil might increase sensitivity by suppressing adrenal function, but the effect of an increased dose was not investigated. As the dose of thiouracil used was probably ineffective, the increase in sensitivity to tuberculin which followed the administration of thyroxine to half the thiouracil treated group after the twenty-eighth day is probably accounted for in the same manner as for the controls who received thyroxine.

Half of the group of animals on thyroxine who had received tuberculin twice weekly from the 10th day had the thyroxine stopped on the 28th day, with the result that the sensitivity to subsequent tuberculin injections declined to the same levels as those controls who had received tuberculin only.

A further group of animals were infected with B.C.G., and were given thyroxine from the 35th to the 47th day after infection, at which point the tuberculin sensitivity was estimated and the thyroxine stopped. 14 days later it was found that the sensitivity had declined to less than half that of the controls. It may be suggested that the rise in sensitivity was caused by the decline in cortical function as a result of thyroxine administration.
The decrease in sensitivity 14 days after the cessation of the thyroxine may be accounted for by assuming that cortical function had recovered, and that the small amount of thyroxine still remaining in the body was now having the effect of causing the level of cortical function to rise above normal, as it was now capable of responding to the stimulus, which was not so excessive as to exhaust it.

The authors of this paper have passed no comment on the fact that, in the animals which were repeatedly injected with tuberculin after the thyroxine was stopped, the sensitivity only declined to control levels, not below, as in the B.C.G. group. Perhaps this may be accounted for by the tuberculin injected animals being in the resistance stage, so that the cortex did not respond to the mild excess of thyroxine 14 days after its cessation. As far as the data indicates, the B.C.G. infected animals were only tuberculin tested twice, and as B.C.G. is unlikely to have caused much general upset it is probable that these animals were not in the resistance stage.

A few hours after one injection of ACTH peptide, or the third daily injection of a milligramme of compound E, it was found, as would be expected, that the tuberculin hypersensitivity in the B.C.G. infected animals was markedly decreased, but 14 days later it was found that sensitivity in the ACTHP treated animals was over three times that of the controls, and in the compound E treated group nine times that in the controls. The authors suggest that hyper-
secretion by the thyroid might be responsible, yet do
not appear to have examined the thyroid to find out if hypertrophy had occurred.

This remarkable increase in sensitivity as a late effect of such temporary use of these powerful hormones does not seem reasonably accounted for by the period of suppression of the production of endogenous ACTH which must have followed their administration, as such a period surely would not have lasted for 14 days, but this is again conjecture as there is no information regarding the adrenals in those animals. However, it would seem not at all impossible that, though B.C.G. is of low virulence in the guinea pig, the effects of these powerful hormones in producing rapid breakdown of the lymph glands, or of any fibrosis which had occurred, plus the period of suppression of pituitary and adrenal function, which must have followed their administration, and during which the non-specific resistance must have been low, may have had some effect on the infection. As there is no data regarding the effects of the infection with B.C.G. on either hormone injected animals or in the controls, this question cannot be answered. Indeed, the factor of infection does not seem to have been considered at all.

The fact that the animals which received compound E for three successive days were nine times as sensitive, and those which received one dose of ACTH peptide only three times as sensitive, as the controls 14 days later, would suggest that there is some
foundation for the above surmise. The effect of compound E over three days was very probably greater than that of one dose of ACTH peptide.

So far the criticism of this paper has been purely destructive, though the inadequate data and scanty investigation has necessitated much of it being hypothetical. It is therefore just and proper to tentatively suggest how the question might be elucidated more clearly.

Unless no hormones were available, it is difficult to understand why the effects of compound E or ACTH peptide were not ascertained in the animals which were sensitised by repeated injections of tuberculin, as the possible factor of the B.C.G. infection would be ruled out. It could thus be plainly discerned whether, or not, after the acute effects and the aftermath of these hormones had passed off, any increase in hypersensitivity would occur in 14 days' time.

It would seem very desirable to determine the effect of a minimal dose of thyroxine on the development of tuberculin hypersensitivity, as it is possible that sensitivity would be decreased by low dosage, and there are contrary reports in the literature regarding the effect of hyperthyroidism on tuberculosis, both in man and in animals, (Rich 1944, Storey 1944, Izzo and Cicardo 1947). The latter authors obtained opposite results by the use of 30 microgrammes
of thyroxine twice weekly, while Long & Miles used 0.2 milligrammes of sodium thyroxine thrice weekly.

As the evidence is none too conclusive, a re-investigation of the effect of thyroidectomy on hypersensitivity would be in order, and the effects of larger doses of thiouracil would also be of interest.

It might be possible to determine whether the adrenals were exhausted or not during thyroxine treatment by the administration of ACTH and the observation of its effects on hypersensitivity. This investigation would probably have to be carried out with care, as too big a dose might mask any exhaustion except if it were absolute, which is unlikely. The dose used by Long and Miles was probably excessive, as they reported that one micro-gramme of this peptide would cause a decrease 30% decrease in the adrenal ascorbic acid in the rat, and they administered 0.6 mgm., i.e. 600 times that which would give unequivocal evidence of adrenal stimulation.

In conclusion, it is felt that the foregoing lengthy analysis is of value in that it points out many possibilities which the authors of this paper have not taken into account. This criticism is based on recent work with which they appear to be unfamiliar, and is fully justified because it demonstrates why this work should not be accepted at its face value, despite the clear-cut nature of the results. It may be a good example of the danger of
attributing the results of the administration of any powerful hormone to its direct action, as the delicate balance of the endocrine system must always be disturbed. This work cannot therefore be regarded as indicating that the thyroid affects hypsensitivety, just as this analysis cannot conclusively show that the thyroid has no such influence.
THE THERAPEUTIC USE OF THE
ADRENOCORTICOTROPHIC HORMONE AND COMPOUND E.

Hench (1949) has drawn attention to the potential reversibility of rheumatoid arthritis as an occasional result of such diverse forms of stress as pregnancy, surgical operations, anaesthesia, starvation, injections of foreign proteins or T.A.B., and so on. It is quite evident that all such agencies are non-specific stimuli capable of producing the alarm reaction, and therefore the secretion of large amounts of the hormones of the adrenal cortex.

Hench et al. (1949a) then demonstrated the dramatic effects of compound E and of ACTH in the treatment of this disease. It is now common knowledge that all the clinical manifestations of the disease disappeared with great rapidity, accompanied by equally great, and even more rapid subjective, improvement. Following this remarkable success, they (1949b) showed that these hormones also have a very favourable effect on the course of acute rheumatic fever. These original investigations have since been fully confirmed by other investigators.

The fact that ACTH has the same effect on the disease as compound E clearly signifies that the adrenal cortices of these patients were capable of being stimulated to produce amounts of the sugar hormones large enough to bring about dramatic reversal of the disease. There is therefore nothing wrong
with the cortex in rheumatoid arthritis, and indeed there is no obvious sign of cortical deficiency.

Good reasons have already been given for the belief that the dosages of ACTH which have been given both experimentally and therapeutically must be grossly in excess of the amount of the hormones normally secreted by the anterior pituitary except under conditions of severe stress. Hench found that, though the effect on the disease was similar to that of compound E, retention of salt and water, and a rise in blood pressure in one case, was produced by the hormone. It may be deduced from this that an amount of ACTH which was sufficient to stimulate the production of the electrolyte-controlling hormones as well as of the sugar hormones was being given.

The high dosage of ACTH, and the severity of the various forms of stress which have been noted to bring about remissions, would seem to suggest that the adrenal cortex is refractory to stimulation in rheumatoid arthritis, and that the disease may be partly due to an exaggeration of the resistance stage of the adaptation syndrome. That this is a complete misconception is shown by the following facts.

Hench found that about 100 mgms. of compound E daily is required to produce a remission, while Thorn et al. (1949) have reported that only 20 mgms. of this hormone daily will suffice to maintain a case of complete adrenal insufficiency. Kendall (1942)
has given good reason for the belief that there is a marked degree of synergism between the cortical hormones, so that it is possible that more compound E, as opposed to the natural secretion of the gland, would be required. At the same time it is clear that the cortex is capable of producing the equivalent of at least 100 mgms. of compound E per day when stimulated by stress or ACTH.

The important point is therefore whether the amount of the sugar hormones which must be injected or secreted in order to produce a remission is grossly in excess of the normal amounts secreted by the gland. Proof that it is grossly in excess is provided by the report of Hench et al. that compound E produced some of the features of Cushing's Syndrome as well as a remission. There is therefore no ground for the supposition that the cortex is refractory, and it is quite clear that amounts of the sugar hormones of the cortex which could only be secreted in severe stress are required to cause a dramatic remission. That is not to say that smaller amounts over a longer period might not have some effect, and indeed just this state of affairs exists in pregnancy.

Thorn et al. (1949) have reported on a small series of cases of rheumatoid arthritis in which the cortical response was estimated by the drop in the eosinophil count following the administration of 0.3 mgms. of adrenaline or 25 mgms. of ACTH. They found that nearly all cases responded normally to ACTH, while the results of adrenaline administration,
though not so clear-cut, showed that most of them also responded normally to this stimulus. Some who failed to respond to adrenaline responded to ACTH, so that they postulated a possible hypothalamic defect. If, however, the effect of adrenaline is mediated by its peripheral effects in increasing the rate of utilisation of the cortical hormones, the defective response could also be accounted for by insensitivity of the pituitary to a fall in the blood concentration of the sugar hormones. If it is the case that there is no significant degree of refractoriness of the pituitary-adrenal system in rheumatoid arthritis, it follows that this disease must not constitute stress of a degree sufficient to activate the pituitary-adrenal system.

However, as the amount of the sugar hormones which is necessary to produce a remission of rheumatoid arthritis is in the region of that which is secreted in Cushing's Syndrome there is no basis for any suggestion that deficiency of the sugar hormones is concerned in the causation of the disease. It is apparent that a relative deficiency exists, because a greatly increased output of these hormones will abolish the disease, but it is at the same time obvious that the continuation of the secretion or the administration of these amounts of the sugar hormones would result in time in exchanging rheumatoid arthritis for Cushing's Syndrome.

Even though no data have been published so far,
it is of interest to postulate what the effects of this form of therapy on the adrenal cortex and the anterior pituitary may be.

The fact that the adrenal cortex produces so many hormones, with such varied and far-reaching effects on the body, must constitute a considerable difficulty in the treatment of any disease by means of a single hormone of the cortex, since the use of that hormone in the treatment of that disease must result in a deficiency of the others. Were the adrenal cortex a gland like the thyroid, which produces only one hormone, the problem would be simple, but it is quite evident that the adrenal cortex is equivalent to many glands in one. The use of any one hormone of the cortex may perhaps involve the risk of substituting one deficiency for another.

The use of compound E in the treatment of rheumatoid arthritis or any other disease will undoubtedly have the effect of suppressing the production of ACTH by the anterior pituitary, probably with the production of Crooke's changes in the basophil cells. Atrophy of the inner zones of the cortex, with the production of deficiency of all the other sugar hormones, and of the sex hormones as well, will occur to an unknown extent, so that the final result may well be the substitution of compound E for all the hormones of the cortex with the exception of the electrolyte-controlling hormones.
Were the production of the electrolyte-controlling hormones also inhibited some demonstrable upset in the electrolytes would surely have been produced, but no conclusive changes have been found to occur. It remains to be seen if the deficiency of these hormones will produce any untoward effects. Hench et al. have already noted that the 17 ketosteroid excretion is reduced by compound E, suggesting suppression of the production of the sex hormones, and that the corticosteroid excretion exhibits an initial rise followed by a return to a lower level. The latter can be explained by assuming that in the initial stages of the treatment the corticoid excretion represented compound E plus what secretion of the sugar hormones was already present. When this initial increase disappeared the decretions of these endogenous sugar hormones had ceased owing to pituitary inhibition, and the corticoid excretion probably represented the administered compound E alone.

The salt and water retention, the rise in blood pressure which was observed in one case by Hench and Kendall, and the production of some of the features of Cushing's Syndrome, would suggest that prolonged treatment with ACTH might produce untoward effects. Ragan et al. (1949) have reported one case of disseminated lupus erythematosus treated with this hormone which was found to have adrenals three times the normal size at postmortem, and there seems little doubt that prolonged administration of large doses
would cause the features of adrenal hyperfunction to appear. At the same time the production of large amounts of the sugar hormones as a result of the stimulation of their production by the use of exogenous ACTH must have the effect of suppressing the production of any ACTH by the anterior pituitary. Koneff (1944) has already shown that ACTH will produce Crooke's changes in the basophil cells of the anterior pituitary of the rat in the presence of the adrenals. It is possible that the production of the other pituitary hormones may be affected by prolonged administration of ACTH, particularly as it has been clearly demonstrated that ACTH and the growth hormone are in many ways antagonistic to each other.

It may be significant that Severinghaus and Thompson (1939) found that anterior pituitary extracts from other species could make animals refractory to their own pituitary hormones and cause atrophy of the target glands. It remains to be seen if this will happen in man as a result of prolonged treatment with ACTH.

Conn et al. (1948) produced a temporary diabetic state in man by the use of large doses of ACTH, and made the significant observation that, after the cessation of administration of the hormone a period of relative hypopituitarism was followed by a rebound of pituitary function with the transitory reappearance of the glycosuria.
In consequence of the above considerations it is difficult to see how either form of treatment can ever be stopped once it has been started, and indeed it has already been found that the cessation of the administration of either hormone results in the prompt reappearance of all the manifestations of the disease. In rheumatic fever, however, it seems possible that the use of these hormones for a short time may suffice to tide the patient over the acute phase of the disease, though it remains to be seen whether temporary suppression of adrenocorticotrophic function will cause difficulty in stopping treatment.

From an endocrine standpoint the undoubted preponderance of females among those afflicted with rheumatoid arthritis would seem of possible significance. Davison et al. (1947) found that the 17-ketosteroid excretion in rheumatoid arthritis was slightly above normal in some cases, but the differences were not striking. On the other hand there may well be some other abnormality in the secretion of the sex hormones which is still unknown, though the fact that the disease also occurs in quite a number of men clearly indicates that any such factor cannot be a major one.

Hench (1949) pointed out that in his experience the most powerful non-specific stimulus capable of producing a remission of rheumatoid arthritis is infective hepatitis, and he has found that the cause of the remission is hepatic damage, however
brought about, and that the administration of bile salts and pigments is without effect.

It seems most remarkable that infective hepatitis should have such particularly favourable effect when other infections of considerably greater severity have not been reported to do so. The corticoid excretion in this disease has not been estimated so far. This would appear to be a most important investigation, as if the corticoids are not found to be at a high level attention should be focussed on the liver as being concerned in the pathogenesis of the disease.

The remarkable effect of liver damage may have some connection with the work of Gilder and Hoagland (1946) who, struck by the tendency to feminisation not uncommonly seen in chronic hepatic disease, estimated the excretion of oestrogens and 17 ketosteroids in a number of cases of infective hepatitis. They found that oestrogen excretion was high in the early stages of the disease, rose again in a relapse, and appeared to be roughly proportional to the severity of the case. The 17 ketosteroid excretion was low in the acute stages, rose gradually to normal on recovery, and fell again in a relapse.

It is firmly established that the oestrogens are destroyed in the liver, and that they have a stimulatory effect on the adrenal cortex, therefore it is possible that the excess of oestrogens may account, to some extent, for the beneficial effect
of the disease on rheumatoid arthritis. As oestrogens have not been reported to have a beneficial effect on the disease it would appear likely that any stimulatory action they may exert on the cortex is not of sufficient intensity to induce a remission. Also the fact that the disease is commoner in the female seems to suggest that oestrogens may not play any significant part, though it is perhaps possible that the beneficial effect of these hormones in menopausal arthritis may be explained in this way.

The possible role of salt and water retention in aggravating hypersensitive states has been discussed elsewhere in this thesis. If, as is not unlikely, rheumatoid arthritis is a manifestation of hypersensitivity, it is possible that one factor in its causation may be retention. Even though ACTH produces retention, it also causes the secretion of large amounts of the sugar hormones, the effects of which would mask any deleterious effect of retention on the disease. There is no evidence suggesting that retention may play a significant role, but it would be of interest to find out if drastic restriction of the sodium intake, such as is practised in hypertension, would have any effect on the disease. Such an experiment would be difficult to evaluate, as the effects of such a regime would be slow and difficult to dissociate from a remission. The diet would also have to be ample, as an element of starvation might also induce a remission, a fact which has
been taken advantage of by quacks for many years.

The undoubted functional element in some cases of rheumatoid arthritis may be explicable on an endocrine basis, as it is possible that mental upset can cause the adrenal cortex to become refractory to ACTH to some extent, and also perhaps bring about hypersecretion of the antidiuretic hormones and retention as well.

The recent investigation of Ragan et al. (1949) in which they found that ACTH inhibited the healing of wounds and the formation of granulation tissue, is of interest in view of the reports that DOCA increases the rate of growth of granulation and fibrous tissue and that compound E has an inhibitory effect. Weakness of the supporting tissues is a definite feature of Cushing's Syndrome. This effect on fibrous tissue is clearly of importance in relation to the manner in which ACTH or compound E produces the disappearance of the changes in the joints and the periarticular tissues.

At the same time Ragan et al. found that 50% of cases have agglutinins for group A streptococci, and 60 to 70% agglutinate sensitised sheep red cells. Both these reactions, and the titre of antistreptolysin "O", did not alter significantly even after 27 days of ACTH therapy, while all other demonstrable biochemical and clinical features regressed rapidly, only to return promptly on stopping the treatment.
They have therefore suggested that the serological changes may be of a primary nature and have something to do with the causation of the disease. All the evidence at present available tends to support this latter hypothesis.

While ACTH or compound E therapy produces a dramatic remission, the endocrine side-effects of these hormones cause a rapid return of the disease on cessation of the treatment. On the other hand non-specific stimuli may sometimes induce a remission which lasts for some time, and very rarely for good. This suggests that some sort of vicious circle mechanism may be operative in rheumatoid arthritis, and that, if this vicious circle is cut by the hypersecretion of the sugar hormones as a result of non-specific stimulus at an early stage of the disease, it may be some time before relapse occurs.

It is therefore of some interest to review the various ways in which the pituitary-adrenal system may be stimulated. Apart from accidents, operations, pregnancy and so on, there are some other methods which may be briefly dealt with. Adrenaline is unlikely to be of any use because of the development of refractoriness, and electroshock therapy is probably subject to the same and other objections. Insulin or metrazol shock is also not likely to be of general application. Vogt (1949) found that adenosine triphosphate had a direct stimulatory effect on the isolated adrenal, and Carlstrom and Lovgren (1949) have published a preliminary report.
that it is useful in the treatment of rheumatoid arthritis. Bonsnes and Dana (1946) produced, though they did not recognise it, evidence of hypersecretion of the sugar hormones by means of raising the blood sugar by intravenous glucose, and enlargement of the adrenals has been noted in the rat as a result of force feeding a carbohydrate diet. Intravenous glucose is again a short-term method of treatment, though it might be possible to depress islet function with alloxan, a procedure which would not find much favour. X-rays have been found to stimulate the adrenals in the experimental animal, and encouraging results in rheumatoid arthritis have also been reported. Unfortunately it is unlikely that a sufficient dose to produce a marked effect could be tolerated. It seems probable that the effect of Deep X-ray therapy in anklosing spondylitis is due to stimulation of the pituitary and adrenals.

In toto, all these non-specific stimuli do not seem to hold out much hope, mainly because of the temporary nature of the stimulus, but at the same time they may, on occasion, induce a lasting remission, unlike ACTH and compound E.

Following the first demonstration of the dramatic effects of compound E or ACTH in rheumatoid arthritis it has been found that equally impressive results follow the administration of these substances in a wide variety of acute and chronic diseases. The list has steadily grown with the passage of time, so
that now similar results have been reported in gout (Wolfson et al. 1949), chorea, scleroderma, Hodgkins disease, lymphosarcoma and other lymphadenopathies (McNee 1950), serum sickness and asthma (Bordley et al. 1949), (Rose et al. 1950), disseminated lupus erythematosus (Ragan et al. 1949). In myasthenia gravis Torda and Wolff (1949) have reported that ACTH will induce a temporary remission, but Hellman (1949) has reported that, while ACTH had an adverse effect, 500 mgms. of compound A produced a dramatic but temporary restoration of muscular function.

The number of totally unrelated conditions in which the injection of compound E, or the stimulation of the production of large amounts of the sugar hormones by means of ACTH, has been found to be of therapeutic value, plus the observation that the sugar hormones inhibit wound healing, the formation of granulation tissue, and fibroblastic proliferation, indicates clearly that the effects of these hormones are completely non-specific. There is no reason to suppose that there is any actual deficiency of the hormones in all these diseases, and this work only implies that an amount of the sugar hormones similar to that which is secreted in severe stress will reverse their manifestations. This work therefore does not provide us with any further indication of the true causes of these diseases, and in many of them the pathological process is an insidious one which certainly does not produce a sufficient degree
As Cranswick and Hall (1950) have just reported that this agent causes a fall in the eosinophil count, it is most unlikely that this method of treatment is devoid of endocrine complications, and should be used with due care.
of bodily upset to cause the activation of the pituitary-adrenal system.

The treatment of rheumatoid arthritis by means of a combination of DOCA and ascorbic acid, which was first introduced by Lewin and Wassen (1949) and has been the subject of a number of small reports since, is a development of great interest. It is certain that this form of treatment will also require the most careful investigation before we can be sure that no deleterious effects can result from it. LeVay and Loxton (1950) have demonstrated that the action of this agent is peripheral, but it remains to be seen if any endocrine or other side-effects will be produced in time. It is now obvious that what is needed for the treatment of the diseases of collagen which is an agent will have the same effects on the lesions as the sugar hormones, without the endocrine complications. If the compound which is formed from DOCA and ascorbic acid acts in this way it is clear that it will speedily become the method of choice. (See note on opposite page).

There now seems to be considerable doubt whether the treatment of chronic disease by means of compound E or ACTH holds out any promise of cure, though in rheumatoid arthritis short courses of this form of therapy may be of considerable benefit. It would seem that the main usefulness of compound E may be found in acute states such as surgical shock, where the cortex has discharged all its hormones and there is an acute need for them, or at the junction between
the countershock and the resistance stage in severe prolonged illness. In such circumstances the hormones may succeed in tiding the patient over a critical point in the illness, or ensuring recovery from shock.
FACTORS IN THE CAUSATION OF RHEUMATIC FEVER,
AND RELATED DISEASES

Reference to acute rheumatic fever has frequently been made at various points in this thesis, but it is felt that the importance of this disease merits closer examination of the various factors which may predispose to its occurrence, and some discussion of the possible nature of the defect in adaptation which may cause it. A full review will not be attempted, and indeed would be rather pointless in view of the fact that several most comprehensive reviews have just been published. (Waksman 1949, Swift 1949, Fischel 1949). It is therefore intended to draw attention only to what appear to be factors of significance.

At the outset, however, it seems correct to make some brief mention of those other diseases which have become associated with acute rheumatic fever on the grounds that fibrinoid degeneration of collagen is a common feature, and that the lesions are often markedly similar. Thus, while some authorities have suggested that anaphylactic hypersensitivity may be the common cause of rheumatic fever, rheumatoid arthritis, periarteritis nodosa, diffuse thromboangiitis obliterans, and scleroderma, others have refuted this concept on the grounds of lack of evidence.

In rheumatic fever, rheumatoid arthritis, periarteritis nodosa, and glomerulo-nephritis the pathological similarities would suggest a common defect in all, especially as the injection of foreign
proteins, or the use of Selye's methods, tends to produce several of these diseases. Rich and others are in favour of anaphylactic hypersensitivity as this common factor, and much of the clinical immunological evidence in relation to rheumatic fever is also in support of this concept. In respect of the more uncommon members of this group of diseases there is so little evidence that any discussion of a common cause is bound to be inconclusive and will not be entered upon. Some incidental reference will, however, be made to rheumatoid arthritis and acute nephritis when relevant to the discussion.

**Streptococcal Infection.**

The association of a streptococcal pharyngitis some two weeks or so before the onset of many cases of acute rheumatism has long suggested that this organism may play a significant part in the causation of the disease. In consequence, an enormous amount of investigation has been carried out regarding the bacteriological and immunological aspects of this relationship. These investigations have shown that the haemolytic streptococci belonging to Lancefield's Group A are almost invariably associated with rheumatic fever, but that the relationship is indirect, and all attempts to implicate any bacillus or virus as the direct cause of this disease have failed or not been confirmed. The evidence, which has recently been summarised by Swift (1949) is strongly in favour of the disease being due to hypersensitivity to the products of this group of streptococci.
There have been many attempts to demonstrate
some difference in the antibody response between
those who do, and those who do not, develop rheumatic
fever as a sequel to streptococcal infection. None
of these investigations has so far resulted in the
demonstration of any unequivocal difference, and the
matter is further complicated by the fact that the
haemolytic streptococcus is a complex antigen which
gives rise to many antibodies, the quantitative
estimation of some of which is no easy matter. Some
of the most recent attempts have been those by Roth-
bard et al. (1948), Rantz et al. (1948), and Anderson
et al. (1948). The result is that there are claims
in the literature that the antibody response is tardy,
deficient, or exaggerated in rheumatic fever. There
is, therefore, little point in further discussion,
except to suggest that the defect in specific adapt-
ation which leads to the onset of this disease is
most likely to be found in the immunological response.

Attempts to show that rheumatic patients are
more sensitive to the intra-dermal injection of
streptococcal endotoxins have succeeded in demonstra-
ting that these are many more positive reactors among
the rheumatic subjects than in the controls, but the
fact that an appreciable percentage of the controls
were also positive tends to confuse the issue. The
most recent investigation of this sort was by Humphrey
and Pagel (1949). They found that the intra-dermal
injection of heat-killed haemolytic streptococci produced local reactions in all cases of rheumatic fever and erythema nodosum tested, and in the majority of the cases of subacute bacterial endocarditis and rheumatoid arthritis, and in none of the controls. On account of the small numbers of cases these findings cannot be regarded as significant, but the main interest of this study lies in the fact that they excised the areas from ten to eighteen days after the injection, studied them from a pathological point of view, and came to the conclusion that the reaction was typical of the Arthus type of hypersensitivity.

Certain other observations suggest that rheumatic individuals, and some normal subjects, may on occasion be markedly sensitive to haemolytic streptococci. Green (1941) gave subcutaneous injections of streptococcal endotoxin to patients who had recovered from rheumatic fever, in an attempt at desensitisation and the prevention of further attacks. While some of the patients responded to the injection by a slowly developing reaction which came to resemble erythema nodosum closely, certain others suffered a short recrudescence of the disease. In some cases this was shown to follow every injection, so that any incidental relapse was ruled out as the cause. Friedman et al. (1938) found that if serum which had been obtained from patients in the acute phase of the illness was reinjected intravenously in convalescence.
escence a slight "relapse" occurred within three to eleven days in six of seven cases. This result cannot be said to have ruled out a natural relapse, but it is suggestive. Rhoads and Afremow (1943), reported that a large number of nurses who had received active immunisation against scarlatina with sterile streptococcal toxin developed joint pains as a sequel. Investigation showed that a high percentage of those who had reactions had previously had rheumatic fever, or acquired the disease some time later. Copeman (1944) carried out the only experiment of its kind when he administered blood intravenously from a case of rheumatic fever to five volunteers, of whom two developed what was thought to be mild rheumatic fever, and one fibrositis, within twenty-four hours. Blood from the two cases who developed "rheumatic fever" was administered to four others, of whom one developed fibrositis, and blood from this case produced mild "rheumatic fever" in one of four others. Pooled blood from the first five resulted in fibrositis in one of four others. Copeman contends that this remarkable experiment supports a virus as the cause of the disease. It is, however, perhaps possible to explain these results on the grounds that those who developed a mild form of rheumatic fever or fibrositis were all individuals who happened to be among those normal subjects who are sensitive to streptococci, and that the blood of
the patient with the rheumatic fever contained an antigen which, by reacting with the sensitised tissues, produced the result. The experiment may be analogous to the induction of passive serum sickness by the injection of serum sickness convalescent serum, except that the transfer was carried through four subjects, and the question of sensitisation is a matter of conjecture. (Vide Karelitz & Glovic 1943). In the absence of data speculation as to the mechanism involved in this experiment is fruitless, though interesting, and it is unfortunate that this experiment could not have been carried out under conditions where investigations of immunological phenomena could be made.

These somewhat scattered observations have been mentioned here because they seem to provide much more positive evidence of hypersensitivity to streptococci or their products than the immunological studies, and because they suggest that the manifestations of the disease may be produced in a mild form by the injection of endotoxins into subjects who are sensitive to them. The systemic reaction produced by the subcutaneous injection of tuberculin in a sensitive individual as described by Rich (1944) would seem to have many features in common with the reactions to streptococcal endotoxin, and with serum sickness, so in consequence the observation that the histological features of the lesion produced
by the injection of killed streptococci is suggestive of the Arthus type of sensitivity seems of some possible importance.

It would appear to the author that perhaps the most significant of the recent observations in rheumatic fever is of the nature of negative evidence. Loge and Kilbourne (1948) and Kilbourne and Loge (1948) have found that intensive penicillin treatment of streptococcal pharyngitis in individuals who were subject to a relapse as a result, not only prevented the relapse, but also prevented the rise in antibody titre which accompanies the relapse. There can be no possible doubt that the destruction of the streptococci by the penicillin renders the production of antibodies against them unnecessary, and indeed removes the stimulus to their production. This work, which has since been confirmed, in conjunction with the fact that penicillin has no curative effect on rheumatic fever, seems to make the causal relationship between the haemolytic streptococcus and the disease abundantly clear, and also provides powerful support for the concept that the disease is a manifestation of hypersensitivity.

Another question to which there is no satisfactory answer is why Group A streptococci in particular should be so closely associated with rheumatic fever. It would seem as if this group of bacteria have some common property which tends to cause the development of hypersensitivity. In this connection
there has been much recent speculation regarding the possible role of hyaluronidase and hyaluronic acid in the rheumatic diseases. Many papers have been published recently on this subject, again with equivocal results, and the subject is not a fruitful one for discussion.

The relationship of an increase in the gamma globulins to rheumatic fever has also been the subject of much recent work. Jager et al. (1948) and Jager and Nickerson (1948), have carried out long-term observations on subjects liable to rheumatic fever, and found that the gamma globulins often underwent cyclical rises when the case was inactive by all the usual standards, and was a more accurate denominator of activity than any other criterion. The significance of the rise in the gamma globulin in this disease, and in many others, is still to be sought, despite a vast amount of work on many diseases within the past few years. It may be of some significance that every one of what have been called the collagen group of diseases have been found to manifest a rise in the gamma globulin, especially in disseminated lupus erythematosus (Coburn and Moore, 1943).

Though the relationship between streptococcal infection and acute rheumatism seems clear, it is also a remarkable fact that the vast majority of streptococcal infections do not result in acute rheumatism or any other disease. It has been pointed out elsewhere that this fact is probably explicable on the
grounds that the borderline between perfect specific adaptation to a streptococcal infection, and imperfect specific adaptation with the production of acute rheumatism, is probably a narrow one, and that a combination of non-specific factors may determine whether an attack occurs or not. Thus it seems reasonable to suggest that acute rheumatism does not ensue unless the ground has been prepared by ascorbic acid deficiency, poor nutrition, a generally debilitated state, and probably other factors, all combining to bring about what has been termed the "pre-rheumatic state". It is apparent, however, that this hypothesis will not suffice to explain many cases which occur in persons who do not show any such signs of debility.

There is, however, some evidence that protein deficiency, both in man and in animals, has an adverse effect on antibody production (Wohl et al.1949, Cannon et al.1943, and others). In conjunction with evidence previously cited regarding the possible role of a low intake of essential amino-acids in the production of a low resistance to stress, it would seem possible that protein deficiency might play some part in the production of a defective antibody response, and also a poor pituitary-adrenal response to the infection. It is, however, impossible to go further than to suggest the possibility of this being a contributory factor.

The relationship of rheumatoid arthritis to streptococcal infection is not at all clear, and it
is common experience that the removal of septic foci is often disappointing. There has been some controversy as to whether the antistreptolysin titre is increased in this disease, and according to Perry (1940) such a finding is the exception rather than the rule both in rheumatoid arthritis and in ankylosing spondylitis. This finding would appear to be in accord with the lack of evidence of streptococcal infection as a direct aetiological factor in the causation of this disease. On the other hand, there is no doubt that, owing to the usual insidious onset of the disease as opposed to acute rheumatism, it is possible that a latent streptococcal infection could have been the original cause, but that, once the condition became established, all trace of it vanished.

Without entering into a full discussion of the matter, it is notable that acute glomerulonephritis bears substantially the same relationship to streptococcal infection, and may also be manifestation of hypersensitivity. It is difficult to account for the localisation of the lesions in the kidney and vascular endothelium, but it seems that the nature of the antigen involved may have some influence. Hawn and Janeway (1947) have found that while sensitisation of rabbits with pure serum albumin produces vascular changes like periarteritis nodosa, pure gamma globulin produces glomerulonephritis as the most prominent change. A further theory which has
been advanced is that the renal changes may be due to the action of streptococcal toxins in splitting otherwise non-antigenic renal proteins to form antigens, which in turn give rise to antibodies specifically directed against the kidney, (Kerr and Calveti, 1947). Lange (1949) claimed to have demonstrated these auto-antibodies in a large percentage of cases of nephritis. It had been claimed previously that anti-heart antibodies had been demonstrated in rheumatic carditis, but subsequent work failed to substantiate this observation.

Ascorbic Acid Deficiency.

The role of ascorbic acid in the body is still being unfolded, and it has become apparent that this vitamin is intimately concerned with many aspects of metabolism. Mitchell (1943) has reviewed much of the voluminous literature concerning its role in amino-acid metabolism, in haemopoiesis, and many other aspects of the bodily economy, and the reports that it may be of value in allergic states and in the prevention of anaphylaxis. Since then there have been several reports indicating its role in carbohydrate metabolism (Banerjee and Ghosh 1947, McKee et al. 1947, and others), its relationship to pteroylglutamic acid (Johnson and Dana 1948, Woodruff and Darby 1948), the successful use of sodium ascorbate in the treatment of allergic states (Ruskin 1947), the inhibition of passively transferred serum sickness (Karelitz and Glorig 1943), and many others, some
of which have been referred to elsewhere in this thesis.

The vast number of papers which have been published regarding the many ways in which ascorbic acid may play a part in physiological mechanisms and in disease seems singular in view of the inconclusive results which have attended its therapeutic use. Indeed the only disease in which there is unequivocal evidence of its therapeutic usefulness is scurvy. Despite this, there is no doubt that ascorbic acid is intimately concerned in non-specific adaptation, and that any increase in bodily activity, or any chronic disease, increases the requirements for the vitamin. It seems probable that most of the equivocal results which have been obtained in the therapeutic use of ascorbic acid may have been caused by the interference of other factors, so that it was not clear whether any improvement was due to the vitamin alone, and possibly because it seems to have more preventive than curative value except in scurvy.

Many studies have been made of the possible relationship between subclinical vitamin C deficiency and rheumatic fever, but all have suffered from the defect that so many other factors could also affect the incidence of the disease that no clear-cut relationship could be demonstrated, (Rinehart 1943).

The observations of Roff and Glazebrook (1939) and Glazebrook & Thomson (1942) on the relationship
between ascorbic acid deficiency and acute rheumatism do not seem subject to any such objections, and are therefore of much greater significance. These observers had the unique opportunity of observing the effects of ascorbic acid deficiency in a naval training establishment, and in a large institution, and carried out a controlled experiment. In these institutions there was no question of malnutrition, but the cooking arrangements were such that the ascorbic acid content of the food was very low. It was found that cases of lassitude and joint pains, and of low grade "pneumonitis", either cleared up on saturation with large doses of ascorbic acid, or progressed to acute rheumatism and carditis. The administration of adequate amounts of ascorbic acid to 335 boys, though having no effect on the incidence of haemolytic streptococcal infections, reduced the occurrence of pneumonitis or rheumatic fever. Among the 1100 controls there were in the same time 16 cases of acute rheumatism and 17 of pneumonitis. It would seem very probable in the light of these observations that lack of ascorbic acid renders collagen tissue more susceptible to degenerative change, and that ascorbic acid can stop the process if given soon enough. Once the damage is done, however, no amount of the vitamin can stop the process or repair the damage. Furthermore, unlike observations carried out on the civilian population, many variables were
automatically ruled out in this investigation. It is noteworthy, therefore, that many surveys have shown that the intake of ascorbic acid and the incidence of deficiency is much higher among the poorer classes, (Rinehart 1943). The observations quoted above, however, would indicate that poor nutrition, though it may play a similar role, may take second place to ascorbic acid deficiency in predisposing to the occurrence of acute rheumatism.

It is firmly established that any infection, acute or chronic, increases the rate of utilisation of ascorbic acid, and Parsons (1938) has pointed out that any cause of an increase in the rate of metabolism demands an increased supply of the vitamin. This may explain why scurvy was once thought to be caused by damp and exposure, as the extra demand for ascorbic acid might precipitate acute scurvy. It is therefore possible that the initial streptococcal infection, or exposure to cold or damp, which commonly precedes the onset of acute rheumatism may cause lowering of the ascorbic acid stores of the body to a level where collagen becomes susceptible to fibrinoid degeneration. At any rate, this is one other way in which a relative deficiency of this vitamin could play a part in the production of the right background for the production of the disease, though it is obvious that it is not a direct cause.

The experimental evidence in support of this concept is somewhat equivocal. Rinehart and Mettier (1934) produced lesions of the heart valves and the
joints closely resembling rheumatic fever, and occasionally even subcutaneous nodules, in scorbutic guinea pigs who had been given streptococcal infections of guinea pig origin. This observation was confirmed by Schultz (1936), but later McBroom et al. (1937) found that similar lesions could be produced in the guinea pig by severe scurvy alone. They considered that the diet used by Rinehart and Mettler was only capable of producing mild scurvy, and that the added factor of infection had the effect of producing severe scurvy, which was the cause of the lesions. The production of endocarditis and myocardial lesions in scorbutic guinea pigs by means of injections of streptococcal toxin alone was reported by Stimson et al. (1934).

Climate.

It is generally believed that acute, and chronic, rheumatism is much less common in temperate than in tropical climes. Waksman (1949) has quoted evidence against this view, but it is felt, on the grounds of personal experience, that this widely held concept is true, though it is not easily explained.

Edstrom et al. (1948) appear to have mimicked the removal of the patient to sunnier climes by confining patients to an air-conditioned ward with a dry atmosphere. They found considerable benefit, and that the streptococci tended to disappear from the throat. It would seem that there cannot be much
change in the environment in the throat under these conditions except in so far as the host himself is concerned. It is possible to suggest that adaptation to a warmer climate may activate the pituitary-adrenal system, and thus raise the non-specific resistance, but it is apparent that once adaptation had been accomplished this would probably no longer hold good. One possibility is that an increase in sweating might have an effect similar to that of a low sodium diet, but it does not seem convincing. As it is a clinical observation that thyrotoxicosis tends to predispose to rheumatism, it would seem possible that a lower level of thyroid secretion in a warm climate might be responsible for the low incidence of rheumatism. It is perhaps significant that some observers have suggested that tropical neurasthenia may be a state of mild adrenal insufficiency, or, in other words, a failure of adaptation to the environment, both physical and mental. If this is the case, it would appear that it is possible for the level of cortical secretion to be at a higher level in the tropics. In the absence of evidence, however, it would appear that further speculation as to the manner in which climate affects rheumatism is unlikely to be profitable.

Age.

The fact that the incidence of acute rheumatism is at its height during the years of growth may be of possible significance from an endocrine standpoint.
It may be pointed out that the growth hormone is opposed to the sugar hormone in many ways, and that the overgrowth of connective tissue in acromegaly would indicate that the growth hormone has a powerful effect on the growth of connective tissue. It is therefore possible that there may be a relative preponderance of the growth hormone in the rheumatic child, and that this endocrine imbalance may perhaps be concerned in the pathogenesis of the disease.

**Diabetes Mellitus.**

Joslin (1937) has reported that he has only seen six cases of rheumatic fever in over 6000 cases of diabetes mellitus over a period of twenty-nine years. This observation would surely seem of some significance, especially when it is added that allergic manifestations are also uncommon in this disease. Kern (1940) has suggested that the freedom from allergy may be due to dehydration, but it would seem more likely that this is due to the lack of opposition to the adrenal cortex, and to occasional hypersecretion by the cortex when the diabetes tends to get out of control. Abrahamson, (1944) has reported that a small series of cases convalescent from rheumatic fever tended to have hypoglycaemia six hours after a glucose tolerance test, and that the use of a high fat, low carbohydrate, diet prevented the occurrence of relapses. He thought that there was hyperactivity of the islets, but in the light of recent work it would seem more likely that the level of adrenal function was low. Steincrohn
(1938) had previously reported that the blood sugar curves in rheumatic children tended to be flat.

**The Causative Mechanism in Rheumatic Fever.**

The evidence in favour of hypersensitivity to the haemolytic streptococcus as the commonest indirect cause of acute rheumatism appears very strong, but the actual type of hypersensitivity concerned is not clearly defined. Thus, though the evidence indicates that the Arthus type of anaphylactic hypersensitivity may be that concerned, it is not impossible that there may also be an element of the tissue type as well.

Whatever the actual type of hypersensitivity concerned may be, and irrespective of the true nature of the defect in specific adaptation which causes it, it is evident that, as a result of an infection with the haemolytic streptococcus, certain individuals become hypersensitive. Of these hypersensitive individuals only some develop acute rheumatism, so it is essential to discuss the factors which may promote, or inhibit, the occurrence of an antigen-antibody reaction and the onset of the disease.

It is therefore reasonable to regard the hypersensitive state as the basic abnormality, so that if the antigen is present in the circulation an antigen-antibody reaction may occur if the relationship between those influences which tend to promote reaction, and those which tend to prevent it, is such as to favour its occurrence. Those influences which tend to promote the occurrence of the reaction are hard to
define, as they must involve the degree of hypersensitivity, the quantity of the antigen present, the nature and degree of the defect in the immunological response to the present or previous infection, and probably many other factors. The inhibitory influences are certainly the level of the secretion of the sugar hormones at the time, and the presence of an adequate amount of ascorbic acid, but many other general factors are probably concerned.

For example, a low protein intake may be associated with a defective immunological response, a low normal level of cortical secretion, and a defective response to stress. If the protein intake is so low as to produce these effects it is entirely probable that there is also a sub-clinical state of deficiency of ascorbic acid, and no doubt of other vitamins too. Add a high incidence of streptococcal infection, poor housing, and all the other social evils, and it is not difficult to surmise many ways in which almost any added adverse circumstance may act as the trigger which fires off the antigen-antibody reaction and produces the disease.

In the light of the observations of the role of ascorbic acid which have been briefly summarised here, it would seem possible that the cases, especially the relapses, which have been reported to follow all sorts of non-specific stress, such as anaesthesia, operations, other infections, accidents, T.A.B., injections, exposure, and others which have been quoted as occa-
sional precipitating factors, (Garrod, Batten and Thursfield 1947), may be due to depletion of the already low ascorbic acid stores as a result of these stresses touching off the reaction in a sensitised individual.

It is, of course, obvious that the stresses noted above are almost identical with those which have been noted to cause occasional remissions in rheumatoid arthritis. This point demands an explanation, and the one which is offered here is that the many debilitating factors which have already been mentioned as tending to bring about the pre-rheumatic state are at the same time those which also tend to place the individual in the resistance stage of the adaptation syndrome. That is to say that these non-specific stresses cause the prior activation of the pituitary-adrenal system, with the result that the response to non-specific stress is inhibited as in the resistance stage. As a result of this poor response to stress there may be a period when the cortical hormones are being used up at a rate in excess of that at which they can be supplied. The resultant temporary relative deficiency may allow the reaction to take place, and when the relapse occurs the cortical response to it will also be poor. Depletion of the ascorbic acid stores may also play a part in promoting the reaction.

The observations of Dugal and Therien (1949) are of possible significance in this connection, as they noted that ample doses of ascorbic acid prevented
the alarm reaction as a result of cold. One may deduce from this that ascorbic acid may, in some circumstances, perform the functions of the cortical hormones, and render hypersecretion of them by the cortex unnecessary. Conversely, if the cortex does not respond adequately, it may be the case that the ascorbic acid stores are drawn on to an excessive extent to make up for the poor cortical response.

The above considerations may perhaps explain the mechanism of causation of many of those cases of insidious onset which occur in children, but it remains to consider those in which a definite streptococcal infection seems to play the part of a prodromal illness. If the initial streptococcal infection is severe enough to cause generalised bodily upset it must involve an increase in the secretion of the cortical hormones, especially in scarlatina. In those cases where there is an asymptomatic interval between the infection and the onset of rheumatic fever it seems clear that the time between the beginning of the infection and the occurrence of the rheumatic fever most probably represents the time of incubation of the hypersensitive state. In those who have a more severe illness, such as scarlatina, the interval may represent either the incubation period as above, or the duration of the countershock phase, as the ending of this phase and the fall in the amount of sugar hormones secreted may result in the unmasking of the hypersensitive state.

Whichever of the above mechanisms is operative,
the result may be that by the time the hypersensitivity reaction occurs the individual is in the resistance stage because of the initial infection, and the response of the cortex to the bodily upset caused by the rheumatic fever is poor, and cannot cut it short. A further factor must be the effects of the initial infection in depleting the ascorbic acid stores, so that, by the time the hypersensitive state has developed, this inhibitory influence is greatly decreased.

Though there must be many other factors, including the hypothetical one of specific inhibition of the pituitary-adrenal response to an infection to which a degree of imperfect specific adaptation has been acquired (Page 249), the above considerations seem, to the author at least, to provide a rough working hypothesis as to the possible mechanism of causation of all types of rheumatic fever.
THE PATHOGENESIS OF ESSENTIAL HYPERTENSION.
The Role of Environmental Stress

In recent years many leading authorities have been inclined, on general grounds, to regard essential hypertension as one of the "stress diseases". This point of view has most recently been expressed by Ogilvie (1949), and though the evidence is almost wholly circumstantial, it is in clear accord with the concept that essential hypertension is a manifestation of adaptive dysfunction.

The recent comprehensive review by Smirk (1949), and the papers referred to by him, show that the surveys of the blood pressure which have been carried out from time to time among many races in different parts of the world are in agreement in that both the average normal pressure and the incidence of hypertension have been found to be lower among the more primitive and less civilised races, and that when these races have to live under civilised conditions their average pressure and the incidence of hypertension become greater than that of the civilised white man. This is particularly well-marked in the case of the American Negro, who has been found by many observers to have a higher normal pressure and incidence of hypertension than the American white man. This latter data would seem particularly significant, as there has undoubtedly been more opportunity and better facilities to carry out such studies in America than under more primitive conditions.

Though these primitive races certainly live in
the warmer parts of the globe and eat different food, it seems much more likely that their environment and mode of life are the main factors to which their low incidence of hypertension is attributable.

It is of interest that investigations quoted by Smirk showed that the average pressures of Chinese rose after long residence in America, and fell on their return home, and that a group of Americans were found to display a fall in pressure while in China. In this instance any influence of diet would appear to be ruled out, as both groups almost certainly adhered fairly closely to their original diets.

It is notable that, though in their native environment the incidence of hypertension among the more primitive races is low, under civilised conditions they have a greater tendency to develop hypertension than the white population. This observation appears to suggest that these races, having lived at a comparatively slow pace for countless generations, are constitutionally unsuited to stand the strain of "civilised" life. It may be that they have a tendency to adapt excessively to the civilised environment, and that a cardiovascular system genetically unsuited to civilised life is more liable to break down under the strain.

Heredity also has an influence on the liability of any individual to develop hypertension, but, from the above, it is clear that whether hypertension will
or will not develop in a person who is genetically predisposed to it may depend to a large extent on environmental factors.

Obesity, which also tends to be inherited, also has a definite relation to the incidence of hypertension. It is not purely genetic, as loss and gain in weight has been shown to be associated with a fall or a rise in the pressure even in normal man and in animals, (Smirk 1949). Though the fundamental causes of common obesity are so far unknown, there is more than a suspicion that obesity is often of endocrine origin.

From a general point of view it therefore appears to be correct to regard essential hypertension as being caused initially by prolonged overactivity of the normal pressor responses to stress over a long period of time. These excessive demands on the cardiovascular system may be said to result, in the course of time, in a more or less permanent degree of adaptation to this higher level of activity. Finally, one or more vicious circle mechanisms are set up, causing progressive raising of the pressure and permanent pathological changes.

From these observations it appears justifiable to conclude that the average normal pressure and the incidence of hypertension tend to rise in proportion to the stress or "pressure" of the environment.

It is therefore felt that an attempt to indict any single factor as the "cause" of essential hyper-
tension must be foredoomed to failure, and that the correct approach to the problem is to attempt to elucidate the manner in which these normal physiological mechanisms may become disordered, in the hope that some common feature of the disorder which is accessible to therapy may be elucidated.

The removal of the cause is always the most rational method of treatment of any disease, but in essential hypertension the removal of the stressful influence of civilised existence is obviously an unattainable ideal. Moreover, by the time they seek medical aid, the majority of cases of essential hypertension are probably suffering from the effects of the stress of the last twenty years or so. The problem of the treatment of cardiovascular changes which may have taken a lifetime to produce cannot therefore be an easy one, and in the light of present knowledge it appears unlikely that reversal of permanent changes can be hoped for. The best that can be done is to stop the advance of the process, improve the expectation of life, and relieve the symptoms of the disease.

In certain cases who have been treated by means of sympathectomy or the "rice diet" regime, the visible evidence of regression of the vascular changes as seen in the fundus oculi is so marked that the rather gloomy tone of the preceding paragraph does not appear to be wholly justified, and suggests that
the reparative powers of the body are greater than realised. Though such dramatic results are not consistently obtained, the fact that they can be obtained at all would suggest that apparently irreparable damage might be reversible to a much greater extent were the fundamental aetiology of the disease finally elucidated and specific therapy introduced. It is thought that were a sympathectomy performed in the early stage of the disease any further advance of the process would be stopped. On the other hand, few would feel justified in suggesting such a major procedure to a patient who probably feels perfectly well, especially when the result could not be guaranteed and there would always be doubt, if successful, whether the operation had really been necessary or not. It is obvious that were specific treatment of a medical nature available it would be of very great value in the early stages of the disease.

In the following discussions essential hypertension has been regarded as a result of faulty adaptation to chronic environmental stress, with particular emphasis on the endocrine aspects of the problem of its pathogenesis.
Emotional and Nervous Factors in Hypertension.

It has been suggested that those individuals who display an excessive rise of pressure in response to emotion or the cold pressor test are likely to develop essential hypertension in later life. This hypothesis appears to be a very reasonable one, provided that the presence or absence of predisposing factors such as heredity, obesity, and especially environment, are also taken into account. The effect of reassurance, rest, and freedom from worry on an established case of hypertension is clear evidence that the emotional factor is one which is by no means negligible even in the later stages of the condition, and suggests strongly that the emotional factor may play an important part in the initial stages. How prominent the emotional component may be is impossible to estimate, as it must be subject to wide individual variation, and be greatly modified by the other factors, tending to promote or retard the development of hypertension. On commonsense grounds, however, the emotional factor must undoubtedly play a part in the causation of this disease.

There have been attempts to define a psychological type which is associated with hypertension, but perhaps it is better to divide the victims of this disorder into two broad types—those who drive too fast, and those who are driven too hard.
The end-result is the same, and as this aspect of the causation of this disease is one about which we can do nothing, further discussion is pointless.

The beneficial results of sympathectomy, and the influence of emotion, would suggest that overactivity of the sympathetic centres in the hypothalamus exists in hypertension. Occasionally hypothalamic lesions have been reported which were apparently directly responsible for the development of hypertension, but the rarity of such reports would suggest that a primary hypothalamic cause is uncommon. Nevertheless, it is possible that this most mysterious part of the nervous system may play a part via its influence on the endocrine glands.

The possibility of hypothalamic control of the anterior pituitary or its target glands by means of antihormones has already been discussed. It is not impossible that, in hypertension, excessive activity of the hypothalamic centres may render the anterior pituitary hypersensitive to a fall in the concentration of the cortical hormones in the blood, or that the secretion of antihormones is inhibited, so that the adrenal cortex is rendered hypersensitive to the stimulatory action of ACTH. There is, of course, no evidence that such may be the case in hypertension, but it is notable that in schizophrenia, an affliction of mental origin, the adrenal cortex has been found to be very often refractory to ACTH, and that hypertension is a common association. It would appear
possible that the reverse could be the case in hypertension, though such a suggestion is pure speculation.

The recent studies of Wolf et al. (1948) have shown that the blood pressure of the hypertensive patient may depend to a much larger extent on emotional factors than has hitherto been realised.

They recorded the blood pressures of hypertensive patients over long periods in conjunction with the life problems with which they were confronted at the time. Their data leave no doubt that the level of the blood pressure can be profoundly influenced by situations causing restrained aggression and suppressed resentment. In one case, for example, the discharge of suppressed resentment towards another individual by the simple and direct procedure of giving him a "beating up" was found to result in a drop of the blood pressure from 185/110 to 125/85!

The introduction of unpleasant topics during examination was shown to cause a striking rise in pressure, which was accompanied by a decrease in the renal blood flow as a result of constriction of both afferent and efferent glomerular arterioles. After sympathectomy it was found that the same procedure caused constriction of the afferent vessels only, but a rise in the blood pressure still occurred. This is also of interest in relation to Wolf's finding that sympathetic "block" produced by tetraethyl ammonium chloride produced a fall in the pressure
which varied according to the degree of relaxation of the subject. Similar results were obtained in response to the cold pressor test.

It would appear from the above that both neural and humoral mechanisms may be concerned in the rise of blood pressure resulting from emotional stimuli.

Wolf et al. concluded that the hypertensive subject tended to meet the stresses of life by an attitude of restrained aggression which resulted in the needless activation of the pressor response as a type of defence mechanism and that, when this essentially emergency pattern of reaction to stress is adopted as a way of life, essential hypertension may eventually result.

In relation to the nervous and humoral components of raised blood pressure, it is of interest that Brown et al. (1948) found that the fall in the blood pressure which is produced by tetraethyl ammonium chloride is much greater and lasts much longer after sympathectomy than before sympathectomy.

Corcoran (1948), in discussing the role of the central nervous system in hypertension, points out that, contrary to expectations, spinal anaesthesia produces a similar fall in the blood pressure whether the hypertension is renal in origin or not. It would appear that the nervous system may have more influence over vascular reactivity and peripheral resistance than is realised.
The Anterior Pituitary.

There is no pathological evidence to show that this gland is concerned in the pathogenesis of essential or any other type of hypertension. A survey of the literature reveals that the whole subject of the histological appearances of the anterior lobe is an extremely controversial field. Though it has been reported that an excessive number of basophil cells is associated with hypertension, others have found that this change is also associated with aging.

Such a state of affairs is hardly surprising, as it is quite evident that we can have little hope of detecting functional deviations from the normal in such a minute scrap of tissue. The importance of this organ to the endocrine system is so disproportionate to its size that it is very probable that an abnormality which is not apparent may well be of major importance to the body.

There is, however, no doubt that hypotension is a feature of pituitary insufficiency in man, and that removal of the pituitary has a similar hypotensive effect in animals with or without hypertension.

Page and Sweet (1937) found that hypophysectomy in the dog with experimental renal hypertension reduced the pressure to normal or almost normal levels, though it did not prevent against a further rise. Leathem and Drill (1944) found that, though DOCA would restore the blood pressure in the normal rat after hypophysectomy, it was not effective in
restoring the pressure to its former levels in the hypertensive rat, and that large doses of cortical extract were only partially effective. Anderson et al. (1944) found that ACTH was fully effective in restoring the hypertension in the hypophysectomised rat, though Anderson and Page (1947) reported that this effect could not be maintained owing to the development of refractoriness to the ACTH. Page et al. (1946) also found that DOCA and cortical extract were only partially effective in restoring the pressure in the hypophysectomised hypertensive rat, and found that certain other steroids were ineffective. Ogden, Page, and Anderson (1944), found that removal of the posterior pituitary alone in the rat had no influence on established hypertension, that it did not have any effect on the production of hypertension, and that pitressin had no effect on the blood pressure in the hypertensive animal.

In conjunction with the evidence which has already been reviewed, these observations suggest strongly that the sugar hormones of the cortex as well as the electrolyte-controlling hormones are concerned in the maintenance of both normal and abnormal blood pressure.
The Adrenal Medulla.

The production of paroxysmal hypertension by tumours of the phaeochrome tissue of the adrenal medulla is by now a well recognised syndrome, but of recent years it has become clear that such tumours may also produce chronic hypertension.

It is very significant that Smithwick (1948), in reporting the results of 256 sympathectomies, mentions that five per cent of the cases were found to have a phaeochromocytoma. There can be no doubt that those cases of hypertension who are operated on represent but a small fraction of those who suffer from the disease. It is therefore somewhat disturbing to consider how many of those others may harbour a similar tumour which could be removed, with most gratifying results.

This observation of Smithwick's constitutes a powerful argument for the testing of every case of hypertension by means of one of the new adrenolytic drugs, in order to rule out any possibility that such a tumour or hyperplasia of the adrenal medulla may be the cause.

Goldzieher (1944), (1932) has demonstrated hyperplasia of the adrenal medulla in hypertension, but it is not clear how common such hyperplastic changes may be. He also points out that similar hyperplasia of the medulla can be produced in the experimental animal by means of nicotine, but there is, of course, no indication whether or not this can also occur in man.

Interest in the adrenal medulla in relation to
the causation of hypertension has recently been aroused by recent work regarding the nature of its secretions.

Briefly, there is some evidence that the sympathetic transmitter may not be adrenaline, but nor-adrenaline, which differs from adrenaline only by the absence of an N-methyl group. Apart from this question, which is controversial, the investigation of the pharmacological properties of the two substances has shown them to be markedly different.

In contrast to the action of an infusion of adrenaline in causing tachycardia, an increase in the systolic and a decrease in the diastolic pressure, and vasodilatation, an infusion of nor-adrenaline has been shown by Barcroft and Konzett (1949) and Goldenberg et al. (1948) to cause bradycardia, a rise in both systolic and diastolic pressures, and vasoconstriction. Goldenberg et al. also found that infusion of both adrenaline and nor-adrenaline resulted in blocking of the vasoconstrictor action of nor-adrenaline. Holton (1949) and Goldenberg et al. (1949) have demonstrated that phaeochromocytoma tumours of the adrenal medulla may contain an excessive proportion of nor-adrenaline, and the latter have suggested that under normal conditions it is possible that the nor-adrenaline content of the medullary secretions may vary widely under physiological conditions. They suggest that as long as
the nor-adrenaline proportion of the \( \alpha \) secretion of the medulla is not more than about 18% any effect would be masked by the adrenaline, and put forward the theory that essential hypertension may be due to the failure to convert nor-adrenaline to adrenaline.

By perfusion of the isolated adrenal gland with heparinised blood some of the factors regulating the secretion of the adrenal medulla have recently been demonstrated by Bulbring (1948). Lowering of the oxygen saturation of the blood or lowering of the blood flow increased the output of adrenaline. The increase in the secretion caused by stimulation of the splanchnic nerve was shown to depend on the amount of adrenaline already present in the blood. As the amount of adrenaline in the perfusing blood was increased, the increase in adrenaline secretion in response to splanchnic stimulation also increased, but increasing the adrenaline content of the blood over a certain limit resulted in a diminished response to stimulation of the nerve until finally no effect at all was obtained. This would appear to constitute a type of vicious circle mechanism, plus a "safety valve".

It is perhaps of interest that Green et al. (1948) have observed a somewhat similar result in man. They found that as the rate of administration of an intravenous infusion containing adrenaline was progressively increased the pressor response to the increase steadily diminished. When the infusion was stopped a tremendous fall in the pressure took place,
lasting for about fifteen minutes. When the same procedure was carried out in hypertensive patients it was found that, even in those who had been previously found to have "fixed" hypertension by means of the usual tests, the pressure immediately after the infusion was stopped fell abruptly to normal levels or below. It was found that the higher the pressure was before the infusion of adrenaline, the greater was the subsequent fall, and that this fall had a more direct relation to the diastolic pressure before the infusion than to any other factor. As the reactions of the blood pressure to changes in posture were retained during this period of hypotension, it did not appear that sympathetic block had been produced, and the patients also had very obvious symptoms of vasodilatation.

The investigators suggest that these results indicate that "fixed" hypertension cannot exist, as the vasodilator mechanisms of these hypertensive patients were apparently intact. They suggest that these results could not have been produced by a purely circulatory mechanism, as the pressures of both normal and hypertensive subjects fell to the same levels, and the vasodilatation in the hypertensive subjects was very obvious. They supposed that, on the sudden removal of the pressor effect of the infusion of adrenaline, the depressor mechanisms, which had been acutely stimulated by the adrenaline, continued to overact for a short time.
On the other hand the results of perfusion of the isolated adrenal would suggest that an excessive amount of adrenaline in the blood might have completely inhibited the production of adrenaline by the medulla, and that the lack of secretion of adrenaline was the cause of the fall in pressure. There are doubtless many ways of accounting for this drop in the diastolic pressure however, and any further speculation is unjustifiable.

Even the most recent investigations of the haemodynamic effects of sympathectomy by Wilkins et al. (1949) have failed to confirm that the beneficial effects of this operation are due to vasodilatation alone, and it is not unreasonable to suggest that, as the adrenals are simultaneously denervated by the division of the splanchnic nerves, some of the benefit derived from the operation may be due to this fact. Denervation alone had previously been shown to have a beneficial effect, which is unfortunately temporary owing to regeneration of the nerves, (Crile 1934).

When essential hypertension is regarded as a stress disease, it is clear that the adrenal medulla must play some part in its causation. Whether that part is a major or a minor one is far from clear, and there is no doubt that the whole subject of the secretions of the adrenal medulla is in a state of flux at the moment.
The Adrenal Cortex in Hypertension.

The association of adrenal insufficiency with hypotension and of Cushing's Syndrome with hypertension would suggest that a lesser degree of cortical hypersecretion might play a significant part in the causation of essential hypertension. The role of the adrenal cortex in hypertension as a whole has recently been reviewed by Sapeika (1948), but certain aspects of the problem are worth further discussion.

The pathological appearances of the cortex in hypertension have been the subject of many investigations. Sarason (1943a), Russi et al. (1945), Rinehart et al. (1941), Fisher and Hewer (1947), and Rogers and Williams (1949), to quote only the most recent papers on this subject, agree that the adrenal cortex in hypertension is commonly the site of benign adenomata or of adenomatous hyperplasia, and contains more lipoid than normal. Rinehart et al. (1941) concluded that adenomata or adenomatous hyperplasia was almost constantly associated with hypertension, and may be regarded as pathognomonic of the disease.

On the other hand, Dempsey (1942) and Bruger et al. (1944) contend that these changes are just as common in normotensive subjects.

This controversy is not surprising when it is recalled that the adrenal cortex is in a continually varying state of activity throughout life, and that in response to infection, trauma, pregnancy, and
many other influences it undergoes hyperplasia followed by involution. The post-mortem appearances of the cortex are greatly affected by the clinical state in the few hours preceding death, so that any pathological investigation which does not take into account the pre-mortem clinical state is likely to be misleading. Only in a case of very sudden death can the cortical lipoids be any guide to the state of the gland during the years preceding death.

In the light of these considerations the substantial agreement that the cortical lipoids are increased in hypertension is remarkable, and therefore would seem more likely to be of significance.

Goldzieher and Sherman (1928) reported that the adrenal vessels showed marked degenerative changes in hypertension, and that, in the hypertensive gland the bulk of injected dye went into the medulla, and only penetrated the cortex in irregular masses, large areas remaining clear. This finding does not appear to have been confirmed or denied, but would appear to suggest that the adenomata found in the cortex in hypertension may be caused by vascular changes.

The results of Victor (1945), who claimed to have produced sustained hypertension by ligation of the vessels to one adrenal gland in the dog, have occasioned widespread interest. Some investigators failed to confirm this, but Ogden et al. (1948) have succeeded in producing hypertension by this method,
though their evidence is not unequivocal. It is unfortunate that no pathological details of the effects of this procedure on the cortex have been reported, but it is of interest that Rogoff (1931) found that subtotal ligation of the adrenal vessels in the dog resulted in chronic adrenal insufficiency with degenerative changes and adenomata of the cortex. In man Snell et al. (1936) reported adrenal insufficiency following denervation of the adrenals two years before. They found that the cortices were represented by small adenomata which were loaded with lipoid despite very severe stress for some time before death. They compared the state of the glands to multiple nodular hyperplasia of the liver following subacute atrophy, and considered that the condition was brought about by interference with the blood supply of the glands as a result of the operation.

It is necessary at this point to draw attention to some most peculiar anatomical features of the adrenal gland which do not appear to have attracted much attention. (Goldzieher 1944).

The artery coming directly from the aorta is the largest, and passes into the gland to supply the medulla. The superior and inferior arteries, from the phrenic and the renal arteries respectively, form a plexus on the surface and supply the cortex. The blood from the medulla and from the cortex meets in the venous sinusoids of the zona reticularis. The veins which drain these sinuses are unique in that
they are equipped with well developed longitudinal muscle bundles, which are seen most highly developed in man, and according to Zechwer (1935) develop gradually throughout life. The sinusoids empty into the smallest veins in a manner which suggests that a sphincter-like control is possible, and they all drain into a single adrenal vein, which is itself richly endowed with longitudinal muscle bundles. A fine venous plexus on the surface also has anastomoses with the veins of the liver, the pancreas and the kidneys.

The evidence seems to indicate that these muscles are ordinarily under the control of the parasympathetic, and that adrenaline relaxes them, but there does not appear to be any proof of this. Goldzieher & Sherman (1928) showed that a most striking hypertrophy of these muscles is found in hypertension affecting both the small and the large veins. This evidence seems impressive, but does not appear to have attracted much attention, though confirmed by Allen (1929).

Structure usually reflects function, yet there is no explanation for this most peculiar arrangement. The medulla and the cortex are, as far as is known, functionally separate just as they are developmentally separate. That they should have separate blood supplies is not surprising, but why they should discharge into a single vein plentifully supplied with muscle is a mystery.
As the pathological evidence regarding the state of the adrenal cortex in hypertension or any other disease must necessarily be of a circumstantial nature it has not been dealt with in any great detail. On the whole there seems to be quite a large body of evidence that the adrenal cortex may often be the site of adenomatous hyperplasia in hypertension, but it is not an invariable association and may be found in normotensives. The functional state of the glands in life is clearly a matter for clinical and biochemical investigation.

There is more agreement that the lipoid content of the gland is increased in hypertension than there is regarding any other feature, and it is possibly of significance that Rogers and Williams (1949) noted that, in those cases of hypertension who had had acute infections or other forms of acute stress preceding death, the adenomatous areas were not depleted of lipoid. This observation would suggest that these adenomata are not functioning, or are not functioning normally, and it would appear likely that vascular changes may be responsible for their appearance. They also noted that in cases of Cushing's Syndrome the cortex, though markedly hyperplastic, was markedly depleted of lipoid, in contrast to hypertension. It is notable that no description of the pathological changes in the adrenal cortex in hypertension mentions any abnormality of the zona glomerulosa, but this negative
finding may well be of no significance from a functional point of view.

In the pathological observations which have been briefly reviewed above it has not been possible to limit the discussion to essential hypertension alone, as many of the papers quoted have not clearly differentiated between essential and other types of hypertension.

It is well established that renal hypertension cannot be produced in the adrenalectomised animal, and that adrenalectomy in the already hypertensive animal results in the abolition of the hypertension. Cortical extracts will restore the hypertension, though not to its former levels, and the presence of only a fraction of one cortex is enough to enable hypertension to be produced. (Goldblatt 1937, Collins and Wood 1938, Page 1938 and others).

In man, subtotal adrenalectomy has been advocated for the treatment of essential hypertension by De Courcy (1934), who reported encouraging results, but there does not seem to have been any long-term follow-up of these cases. It seems probable that the effects were only temporary, as in the presence of a normal or perhaps hyperactive pituitary some regeneration of the adrenals would be expected. The risks of such an operation would not appear to be negligible.

The converse of the above procedure appears to have been carried out in man by Broster and Gardiner-
Hill (1946). They grafted a gland from a case of Cushing's Syndrome due to simple adrenal hyperplasia into a case of Addison's disease. Perusal of their paper leaves no doubt that they not only cured the Addison's disease, but also gave the patient a degree of hypertension. The subsequent history of this case would be of some interest.

The effect of removal of the hypophysis on the blood pressure of normal or hypertensive animals has already been discussed, and it was pointed out that the evidence clearly indicated that the sugar as well as the electrolyte-controlling hormones of the cortex must be concerned in the maintenance of both normal and high pressure.

In relation to the well-known renin-hypertensin pressor mechanism, it is now well established that the removal of the adrenals results in a fall in the amount of hypertensinogen in the blood, and that the administration of DOCA or cortical extract restores it to normal (Collins and Hamilton 1944, Collings, Ogden and Taylor 1944, and others). It has also been found, as would be expected, that the adrenalectomised animal has a decreased pressor response to renin, (Williams et al. 1939, Houssay and Dexter 1942, and others). As quoted by Sapeika (1948), Gaudino (1944) found that compound E was much more effective than DOCA in restoring the blood by hypertensinogen to normal. This latter observation would seem to be
of some significance in relation to the effects of hypophysectomy. Finally, Haynes et al. (1949) have reported that in the hypophysectomised rat the administration of ACTH will restore the blood hypertensigen, but only in the presence of the adrenals.

The above observations would seem to provide a fairly clear link between the renin-hypertensin pressor mechanism and the adrenal cortex, particularly the sugar hormones, but the significance of this pressor mechanism in the causation of renal or any other sort of hypertension is now very much in doubt.

Quinby et al. (1945) proved by direct experiment in man that obstructing the renal artery caused an increase in the amount of renin in the renal venous blood. Dexter and Haynes (1944) found increased amounts of renin in the blood only in cases in which the pressure was rising acutely in eclampsia or severe glomerulo-nephritis. Haynes and Dexter (1945) showed that there was about the same amount of hypertensinase in the blood of normal and hypertensive individuals, so that lack of this enzyme could not be the cause. Haynes et al. (1947) showed that renin was increased only in the initial stages of experimental hypertension in the dog, and that in hypertensive patients an increase in the amount of renin in the blood was no commoner than in other non-hypertensive states. Pickering (1945, p. 363) also concluded that the renin-hypertensin mechanism was only initially involved, and that after the
first week a non-renal factor is responsible.

Corcoran (1948) has recently reviewed the evidence, pointed out that it is unsatisfactory, and that the diminishing pressor effects of repeated injections of renin, which has not yet so far been obtained in a pure form, is against the participation of this pressor system in the production of sustained hypertension. It seems more likely that this mechanism is concerned with the maintenance of a normal pressure than responsible for sustained hypertension.

On the other hand, the investigations of Shorr, Zweifach (1947) (1948) and their collaborators have introduced a further complication, the significance of which is not yet clear. Very briefly and roughly, they have produced evidence that the peripheral circulation distal to the arterioles is largely controlled by two opposing "vasotrophic principles"; Vaso-excitor material (VEM) of renal origin, and Vasodepressor material (VDM) from the liver. Apart from the role which they have shown these substances to play in shock, it has been found that renal anoxia results in the appearance of excess VEM during the period when the pressure is rising, but it is then balanced by the production of more VDM by the liver. As a result excess of both is present both in experimental hypertension in animals and in essential hypertension in man. Shorr et al. have shown that though the liver, spleen and skeletal muscle all produce VDM as a result of anoxia, it is
inactivated by the liver alone, and prolonged anoxia will irreversibly depress the ability of the liver to inactivate it. Similarly, prolonged renal anoxia results in permanent inability of the kidney to inactivate VEM so that it is then secreted continuously even when a normal blood flow is re-established.

Adrenalectomy decreases the capacity of the kidney to produce VEM, and is restored by DOCA but not by salt alone. VDM has been reported by Baez et al. (1949) to have an antidiuretic effect, and by Mokotoff et al. (1949) to be present in excess in congestive cardiac failure. It would therefore seem possible that excess of VDM may play a part in the retention of salt and water which takes place in congestive failure, in chronic hepatic disease, and perhaps in the causation of the tendency of the hypertensive patient to retain salt and water.

The evaluation of the role of these new factors in relation to hypertension and other diseases must clearly await further investigation, but it is once again notable that the adrenal cortex seems to be involved in this pressor system.

At the present time there is no doubt that the role of the kidney in hypertension is an extremely controversial subject and other considerations as well as those which have been discussed above have recently made the subject more confused than ever. As nothing is to be gained by recounting the claims and counterclaims which have been made further discussion will not be entered into.
From the clinical and pathological aspect, however, a primary role of the kidney in the causation of essential hypertension has met with serious objections except in those rare cases of unilateral renal disease in which removal of the affected organ has achieved a dramatic and lasting result. It has been pointed out by Boyd (1944) that the renal lesions in essential hypertension are often minimal, and seem more likely to be an effect than the cause. Castleman and Smithwick (1943) found that renal biopsy during sympathectomy revealed no significant degree of arteriolosclerosis in the renal vessels in over half their cases, and Master et al. (1943) as a result of a similar investigation, concluded that the renal involvement was very often inadequate to account for the hypertension, and that hypertension preceded the renal lesions in many cases. At the same time there is no reason to suppose that it is not possible that the renal vascular damage caused by the hypertension may not eventually result in the establishment of a vicious circle in the later stages of the disease. It has also been found by quantitative methods of estimation of renal function and blood flow that many hypertensive subjects are apparently normal in these respects (Smith 1943, Goldring and Chasis 1944).

The recent review of the results of nephrectomy in unilateral renal disease by Langley and
Platt (1947) has demonstrated that a good result is rare. It is notable that in one such case reported by Maitland (1949) one adrenal was noted to be enlarged and was removed in addition to the kidney. No tumour was found, but it would seem not improbable that the good result obtained was at least partly due to the removal of the adrenal as well as the kidney, so that it is not justifiable to attribute the gratifying result to nephrectomy alone. It is also notable that there are several reports in the literature of cases of gross unilateral renal disease without hypertension, so that renal involvement does not necessarily result in hypertension.

The significance of the increased quantity of lipoid in the cortex in hypertension is not easy to interpret. As previously described, the fineness of the lipoid droplets and certain other cytochemical appearances are the criteria of activity. It is obviously not possible to gain reliable information regarding this point from post-mortem material in man, and there do not appear to have been any such investigations of the appearances of the cortex reported in respect of animals in which experimental hypertension has been produced by means other than DOCA or LAP.

The functional state of the cortex in hypertension is therefore not known to any extent, but the fact that the lipoids are so uniformly reported to
be increased, despite the stresses which must have preceded death in very many cases, would suggest that in hypertension the cortex does not discharge all its hormones, or that certain of its cells have become, as a result of vascular or other changes, unable to convert lipoids into hormones.

This state of the cortex recalls that seen in the resistance stage of the adaptation syndrome, but there is no evidence that the response of the cortex to stress in hypertension is lacking, and indeed Laragh and Almy (1948) have noted, in a very small series, that the response as estimated by the fall in the eosinophil count in the hypertensive patient to operations, adrenaline, and insulin, is exaggerated as compared with the normal. This series of observations is, however, so small as to be no more than suggestive that the cortical response in respect of the sugar hormones in the hypertensive is greater than normal.

The methods of estimating the cortical end-products in the urine have steadily improved and the evidence that the amounts of these substances reflect cortical activity is very convincing, though how close the parallel may be is not clear. Bruger et al. (1944) reported that the 17 ketosteroid excretion in hypertension was low, and therefore postulated that the corticoids might be high on account of a shift of hormonal production. However,
no significant increase in the corticoids in essential hypertension has been found by Tobian (1949), though Corcoran and Page (1948) noted that the corticoid excretion in malignant hypertension was sometimes at the upper limit of normal. The significance of this latter finding is doubtful, as any bodily upset will cause a rise in the urinary corticoids.

It is now well established that infections, trauma, and the injection of bacterial pyrogens will cause a definite fall in the blood pressure in hypertension, and that the same agencies will also cause greatly increased secretion of the hormones of the adrenal cortex, particularly of the sugar group. Taylor and Page (1944) have ruled out pyrexia and leucocytosis as possible causes of this fall in pressure following the injection of pyrogens.

Corcoran and Page (1943) and Taylor, Corcoran and Page (1949) have recently reported very good results in the treatment of advanced cases of malignant hypertension by means of a course of pyrogen injections. Though tolerance was acquired after a period, the subsequent course of the disease was said to be improved. They noted (1948), without comment, that, while the pressure was markedly lowered, the values for the urinary corticoids as quoted were often higher than those observed in Cushing's Syndrome.

These results are most difficult to correlate with the concept that the adrenal cortex is hyper-
functioning in hypertension, and would seem to suggest that hypofunction or dysfunction of the cortex is a more likely possibility. It is of interest at this point to recall that Perera et al. (1949) found that, while 80 mgms of compound E daily would raise the pressure of a patient with Addison's disease to normal, in the hypertensive individual the pressure was lowered by the hormone. Pines et al. (1948) had found that cortical extract caused slight lowering of the pressure in hypertensives, and Perera and Pines (1949) found that cortical extract would block the pressor effect of DOCA in hypertensive patients.

The observation of Vogt (1945) that injections of adrenaline, when given to the rat for some days, results in a cortex which is enlarged and loaded with lipoid, would seem of interest in this connexion as it would appear possible that sympathetic overactivity in hypertension could produce a similar result. This is, however, sheer speculation.

What appears to be the most outstanding feature in respect of stress in the hypertensive patient is that while mental stress tends to raise the pressure, somatic stress tends to lower it. As somatic stress is clearly connected with hypersecretion of the sugar hormones, and it has been shown by Perera et al. (1949) that compound E lowers the pressure in the hypertensive subject, it would seem likely that this is at least part of the reason for the hypotensive
effect of somatic stress. On the other hand, mental stress involves not only activation of the psychosomatic link and stimulation of the production of more sugar hormones, but also of the sympathetic nervous system and the adrenal medulla. It is therefore possible that the difference is accounted for by the sympathetic nervous system.

As a matter of interest a most odd effect of the glycerin extract of the adrenal cortex which was noted a few years ago by Hoskins & Fierman (1937) and apparently never explained is perhaps worth mentioning. They found that the administration of amounts of this extract by the oral route which were so small as to be almost certainly without effect, regularly produced over a period of months a marked rise in both systolic and diastolic pressure in schizophrenic patients, but was almost totally without effect in normal persons. There are a small series of papers on the subject, and there is no doubt that the pressure rose to definitely hypertensive levels. Any possibility of adrenaline being responsible was ruled out, and though it is certain that some toxic product had been produced in the process of extraction, the fact that only the schizophrenic responded to it is most remarkable, and particularly interesting in view of the evidence of cortical hypofunction in schizophrenia.

Though there is much evidence suggesting that the adrenal cortex may play some part in the
causation of essential and other forms of hypertension, it is not at all clear how commonly it may play a primary role. In the absence of the adrenals hypertension cannot persist, but it is not clear whether the gland is acting as a maintenance influence or actively raising the pressure.

That the cortex may sometimes play a primary role is indicated by the report of Selye (1947) that some cases have a hypochlorelmic alkalosis similar to that caused by DOCA or ACTH, and the reports of cases in the female with features suggestive of mild Cushing's Syndrome described by Goldzieher (1944), Williams and Harrison (1939) and Schroeder et al. (1949). How common such cases may be is difficult to estimate, as it is entirely probable that many of them have been overlooked.

When essential hypertension is regarded as a result of faulty adaptation to stress it is evident that the adrenal cortex must be involved, but the evidence does not indicate whether the adaptive dysfunction takes the form of failure, disordered adaptation, or of over-adaptation to prolonged environmental stress. It is possible that as a result of prolonged stress the cortex may secrete too much or too little of certain of its hormones, or that its secretions may become abnormal in some way.

The paradoxical effect of the sugar hormones
on the blood pressure of the hypertensive would seem to be due to the antagonism between them and the electrolyte-controlling hormones which has been found by Thorn et al. (1949), and it is also possible that the action of a large dose of compound E, or of the large amounts of endogenous sugar hormones secreted in response to pyrogen therapy or other forms of stress may have some ameliorating effect on the vascular lesions, especially in malignant hypertension. At the same time it is possible that the extra amounts of sugar hormones may offset any excess of the electrolyte-controlling hormones, which certainly can produce a rise in the blood pressure if adequate sodium is given.
The Balance of Water and Electrolytes in Hypertension.

The rise in the blood pressure which results from the administration of DOCA to the human subject would suggest that a close study of the effects of this hormone might give some indication of the role of the electrolyte-controlling hormones in hypertension. A series of investigations have therefore been carried out within the last few years regarding the results of the administration of DOCA to both normal and hypertensive subjects by Perera and his co-workers. (Perera et al. 1944, Perera and Blood 1947a, 1947b, Perera 1948.)

These investigations have shown that the effects of DOCA on the body water and electrolytes, plasma volume, and cardiac output in both normotensive and hypertensive subjects are practically identical. Both groups retain salt and water for about ten days, following which the excess salt and water is excreted, but the increase in the plasma volume, serum sodium, and CO₂ combining power, and the decrease in the potassium and chlorides, persist until the DOCA is stopped.

The only significant difference which was found was that the blood pressure in the hypertensive subject rose within a few days, while in the normotensive subject it did not rise until about ten days had elapsed.

It seems reasonable, from the analysis of the effects of DOCA which has been made here, to deduce
that the initial retention of salt and water occurs during the period in which both endogenous and exogenous electrolyte-controlling hormones are acting to retain salt, and therefore water as well, in the body. The diuresis at the tenth day may represent the point at which the secretion of the endogenous electrolyte-controlling hormones became depressed and their functions supplanted by the DOCA. As the dose of DOCA employed is certainly small in comparison to that used in animal experiments, it would seem most unlikely that this amount of the hormone (5-10 mgms. daily) could produce retention by itself in the absence of the secretion of the endogenous electrolyte-controlling hormones. Evidence in support of this concept has also been provided by the report of Zierler and Lilienthal (1948) that, after the cessation of the administration of DOCA, the typical pattern of cortical hypofunction appeared, and lasted for about ten days.

While the above interpretation appears to fit the facts as far as the retention of salt and water is concerned, it clearly does not account for the earlier rise in the blood pressure in the hypertensive subjects.

Perera et al. (1944) concluded that hypertension during treatment of Addison's disease with DOCA and salt takes some months to produce, and did not appear to bear any definite relationship to the degree of retention. Oedema, increased plasma
volume, hypertension, and occasionally cardiac failure is clearly easier to produce in the Addisonian patient than in the normal person, probably owing to the absence of the sugar hormones, which oppose the action of DOCA. In the normal person it is apparent that the pressor effect of DOCA becomes manifest at about the same time as the disappearance of the initial retention of salt and water, but in the hypertensive subject the pressor effect takes place well within this period.

Perera and Blood (1947a) found that the pressor effect of DOCA in the hypertensive patient could be prevented or abolished by rigid salt restriction. It is particularly notable that rise in the CO₂ combining power and the fall in the chlorides and potassium were not abolished by the salt restriction, though the pressor response was inhibited.

Perera and Blood (1947a) also found that raising the salt intake of the hypertensive patient from four to fifteen grammes of salt daily has a slight but definite pressor effect within a few days, as judged by the resting blood pressure, with a slight gain in weight and reduction in urine output, while rigid salt restriction had the reverse effect. In neither case were there any significant changes in the electrolytes.

The above observations would suggest that, as the only significant difference between the normotensive and the hypertensive was the earlier rise in
the pressure in the latter, the hypertensive subject must be unusually sensitive to an increase in the volume of the body fluids or to an increase in the sodium of the blood or the tissues. The fact that the other changes in the electrolytes were not affected by salt restriction would indicate that the hypochloremic alkalosis and hypopotassemia is not connected with the pressor effect of DOCA.

Perera and Blood (1946), following up the clinical observation that hypertensive patients appeared to tolerate salt deprivation better than normal subjects, found that the weight loss, chloride output, and urine volume, which follow twenty-four hours of rigid sodium restriction is significantly less in hypertensive than in normal subjects. This observation would suggest strongly that the hypertensive subject may be secreting excess of electrolyte-controlling hormones, but it has already been pointed out that excess of the antidiuretic hormone has also been frequently demonstrated in many cases of hypertension, and that, according to the views expressed here, hypersecretion of the one must lead to hypersecretion of the other. A further possibility is introduced by the work of Shorr and Zweifach, who have reported that excess of both VDM and VEM are present in essential hypertension, and that the former has antidiuretic properties.

Interest in the value of rigid sodium restric-
tion in the treatment of hypertension has recently been stimulated by Kempner's enthusiastic reports of the results of the treatment of a very large number of cases of hypertension and renal disease by means of his "Rice Diet" regime. (Kempner 1944a, 1944b, 1946, ). This diet contains about 250 mgms. of sodium, 20 Gms. of protein, and about five Gms. of fat, with a limited fluid intake, and consists mainly of rice, fruit juice and sugar. Kempner's observations have extended over a number of years, include a very large number of cases, and dramatic results were often observed. He reports that this regime brings about marked subjective and objective relief in about 60% of cases, and that nitrogen balance can be maintained on this diet. Schwartz and Merlis (1948) have reported that nitrogen balance cannot be maintained on this diet, but in view of the large number of cases which have been maintained on this diet for long periods by Kempner it would seem unlikely that this is actually the case, as signs of starvation would surely have been noted by now.

Opinion is divided among other investigators regarding the value of this form of therapy, but no others have observed such a large number of cases as Kempner. Many believe that the virtue of the diet lies in rigid sodium restriction, and Bryant and Blecha (1947) have reported good results in 100 cases of hypertension by the use of equally rigid sodium restriction with a free fluid intake and a
more normal amount of protein and fat. Dock (1946) has reported similar results, and Wheeler et al. (1947) have reported that mild sodium restriction with a large fluid intake gave good results in chronic congestive failure, and noted that much the best results were obtained in hypertensive failure.

The consensus of opinion at the present time seems to be that rigid sodium restriction or the rice diet is useful when sympathectomy is contraindicated or has been unsuccessful, but that this sort of diet is very difficult to maintain or to endure for a prolonged period.

In the experimental field Grollman and Harrison (1945) reported that rigid sodium restriction had a pronounced hypotensive effect in rats with experimental renal hypertension, and that the survival time was markedly increased by this measure.

Rigid sodium restriction has been found, as would be expected, to be dangerous in some patients in whom renal function is severely damaged, as excessive loss of sodium chloride and uraemia may result. It is also of interest that Weston et al. (1948) and Currens et al. (1949) have found that renal function and blood flow decreases in patients treated with a low sodium diet, yet the blood pressure falls. Such a result is incompatible with the concept of a renal origin for hypertension.

It is obvious that this form of treatment must have the effect of causing a great increase in the
output of the electrolyte-controlling hormones of the zona glomerulosa. Were this not the case the body would speedily become depleted of sodium and chloride, and uraemia and death would result as in adrenal insufficiency. Such a result has only occasionally been reported, and then in cases where renal function was severely impaired. Confirmation could be obtained by the histological examination of the cortex of a patient who had died while undergoing this type of treatment.

There seems to be no doubt that Kempner has secured better results than other investigators by the use of his "Rice Diet". As this diet must be very close to starvation level, and as it is well established that starvation is a stimulus for the secretion of more sugar hormones and may sometimes be of use in inducing a remission in rheumatoid arthritis, it is possible that the stimulation of the production of more sugar hormones by the use of this diet may be partly responsible for the benefit obtained.

It is now known that the administration of large doses of ACTH to the human subject will produce, as well as hypersecretion of the sugar hormones, hypersecretion of the electrolyte-controlling hormones and the same effects on the electrolytes as DOCA. A rise in the blood pressure has been reported in one case by Hench, but it is remarkable that this is the only report of this effect so far.
It would appear that the simultaneous hypersecretion of the sugar hormones may usually mask the effects of the hypersecretion of the electrolyte-controlling hormones. There is no report of the effects of ACTH in hypertension so far, but it would seem likely that, owing to the greater sensitivity of the hypertensive patient to an increase in the blood and tissue sodium and salt and water retention, a definite rise in the pressure would be produced.

This discussion inevitably leads to the conclusion that, as neither DOCA nor excessive amounts of the endogenous electrolyte-controlling hormones can cause a pressor effect in the absence of a normal sodium intake, the pressor effects of these hormones are mediated by their action on electrolyte and water balance, and that, for some unknown reason, the hypertensive patient is more sensitive to the retention of salt and water than the normal person.

It is also clear that the above considerations do not in any way invalidate the possibility that there may be excessive secretion of the electrolyte-controlling hormones in hypertension, because in the presence of a normal sodium intake slight excess of these hormones could cause retention. This effect is inhibited if there is no sodium to retain, so that even a great increase in the secretion of these hormones can cause neither retention nor a pressor effect.

The tendency to retain salt and water, the
changes in the electrolytes in hypertension similar to those caused by DOCA reported by Selye (1947), the excess of antidiuretic hormone found in many cases by Pendergrass et al. (1947) and by Ellis and Grollman (1949), all support the view that the hypertensive patient may have slight overactivity of both posterior pituitary and zona glomerulosa.

It is also possible that, as the secretion or the injection of extra quantities of the sugar hormones has a hypotensive effect, the secretion of the two groups of hormones in hypertension may be unbalanced owing to the secretion of excess of the electrolyte-controlling hormones.

It has previously been pointed out that there is reason to believe that hypersecretion of the antidiuretic hormone, by causing the retention of water, also causes hypersecretion of the electrolyte-controlling hormones in order to preserve the osmotic pressure at the expense of an increase in the volume of the body fluids. Any other cause of water retention could act in the same manner. It is therefore not possible to determine whether the fault is in the posterior pituitary or in the glomerulosa.

As Rydin and Verney (1938) and O'Connor and Verney (1942) have shown that emotion can activate the posterior pituitary and cause the secretion of the antidiuretic hormone, it would seem possible that hypersecretion of the antidiuretic hormone in hypertension may be of central nervous origin.
The cases of striking retention of emotional origin which are occasionally seen are certainly evidence that lesser degrees of retention could easily result from nervous causes.

Animal studies have also suggested that there may be a disturbance of the water and electrolytes in hypertension. Landis and Abrams (1947) reported that rats with renal hypertension reduced their sodium intake when allowed freedom of choice, and Eichelberger (1943) found that in the hypertensive dog the muscle sodium tended to be elevated at the expense of the potassium. Rats with renal hypertension were found by Schaffenburg and Selye (1948) to have the same changes in the blood as are induced by DOCA and salt.

It is particularly notable that salt and water retention, increased output of antidiuretic hormone in the urine, and changes in the blood similar to those caused by the administration of DOCA and salt or large doses of ACTH have been noted in both renal and essential hypertension. There is no indication of the incidence in each group, but the fact that the disturbance in the water and electrolytes is similar remains. It is also notable that Kempner treated cases of essential or malignant hypertension and of renal disease by the same methods, and obtained striking results in all. This would suggest that hypersecretion of electrolyte-controlling and of the antidiuretic hormones may take place in both essential and renal hypertension.
It is therefore possible that a factor of an undue increase in the volume of the interstitial fluid may play a part in the causation of hypertension, and that this factor is a major one in those cases which are found to respond well to drastic restriction of the sodium intake. In accordance with this view, it would appear to be the case that the production of hypertension in the experimental animal or in man by means of the administration of DOCA and salt is to a large extent due to the production of retention, or perhaps to the presence of excess sodium in the tissue cells.

A theory is advanced elsewhere that the retention of undue amounts of fluid or sodium in the connective tissue and muscle cells of the arterioles may predispose the vessels to the occurrence of hyaline degeneration in the subintimal connective tissue, and that, at the same time, it is possible that the sensitivity of the vessels to constrictor influences is increased. This explanation is only a tentative one, but it is in accord with some of the experimental evidence, though this assumption perhaps is hardly justifiable in the present state of our knowledge.

Whatever the true answer may be, there does appear to be a fair body of evidence to suggest that the retention factor is one of importance in hypertension, particularly because of the results which have been obtained by means of drastic restriction
of the sodium intake. At the time of writing Sapirstein et al. (1950) have reported that the administration of hypertonic saline instead of drinking water to the rat will result in hypertension after a month. This observation would seem to be of some possible significance, and tends to support the above argument.

**Summing-up.**

The preceding discussions, as was to be expected, have failed to marshall more than circumstantial evidence for the concept that essential hypertension is a manifestation of faulty adaptation to prolonged stress. Nevertheless, on general grounds alone, it is a most attractive hypothesis, and one which is in clear accord with clinical experience.

It has been concluded, by a somewhat roundabout route, that there is some justification for Selye's theory that there may be an imbalance between the sugar and electrolyte-controlling hormones in hypertension, and that excess of the latter is secreted and may play a significant part in many cases. The evidence indicates that the hypersecretion of the electrolyte-controlling hormones is most likely to be secondary to hypersecretion of the antidiuretic hormone, and that the blood pressure of the hypertensive subject is very sensitive to an increase in the volume of the interstitial fluids. A tentative theory to account for the deleterious effects of the
retention on the vasculature has been advanced elsewhere.

It would appear to be the case that retention may play a major role in those cases which respond well to drastic sodium restriction, and that, in those cases who do not respond to this treatment, the process has either gone too far or other mechanisms are concerned. The dramatic effects which have been secured by Kempner with the use of the Rice Diet are difficult to account for on the grounds of lowering of the blood pressure alone, and would suggest that the relief of the retention, and perhaps increased production of the sugar hormones as well, may also be playing a significant role.

Though it is logical on many counts to suspect the adrenal cortex as a possible origin of essential hypertension, there is no clear evidence that this gland may play a primary role except in cases of tumour or hyperplasia of the cortex. It is, however, possible that more cases of hypertension may be caused by a mild form of cortical hyperplasia than is thought, and that such cases are commonly overlooked. In such cases it is probable that hypersecretion of the electrolyte-controlling hormones and the resultant retention plays a major role in the pathogenesis of the disease.

The recent developments concerning the secretions of the adrenal medulla are of great interest, but whether they are of importance or not clearly
depends on whether such an abnormality of the secretions of the medulla is a rare event or a common one. It seems probable that if excess of nor-adrenaline were a common cause of hypertension the results of sympathectomy would be very much better than they are.

The discovery of the two "vasotrophic principles" by Shorr and his co-workers is also a development of which the importance or otherwise in relation to hypertension will become clear in time. There is no doubt that this work would have attracted considerably more attention had it preceded the discovery of the renin-hypertensin pressor system.

It has not been possible, on the available evidence, to attribute the development of essential hypertension to any particular cause, and it would seem likely that this disease is due to the interaction of both nervous and humoural factors, of which the latter are very probably of endocrine origin.

It has not been possible to limit the scope of this discussion to the "essential" variety of hypertension, as the data often does not distinguish clearly between essential and other types. That this should be so is inevitable, as a diagnosis of essential hypertension is usually made by a process of exclusion. Indeed it is not at all impossible that several, or even many, further aetiological varieties of hypertension are hidden in that great group labelled "essential" for lack of a better name.
CONCLUSION.

Having reached thus far, it will be apparent that this thesis cannot be readily summarised. It is therefore proposed to offer, instead, a brief commentary.

The opinions expressed in this thesis are the result of a careful firsthand examination of the original papers dealing with the very wide variety of subjects involved. This extensive survey has enabled the author to present what is hoped to be a clear and comprehensive analysis of the state of our existing knowledge of the adaptive mechanisms. Owing to the highly controversial nature of many aspects of this work, and the undoubtedly speculative character of many of the conclusions which have been arrived at, it is not inconceivable that much may be unacceptable on the grounds of lack of evidence. It is, however, also true that any attempt to co-ordinate and interpret the available data regarding a subject which cannot be else than vital to our continued existence is at least worth attempting.

Though most of the opinions expressed are open to question, it may be pointed out that the purpose of this work is to take stock of our existing knowledge, to delineate its limits, and to indicate the problems requiring further investigation.

The submission of this thesis in its present hypothetical form may perhaps best be justified by
the following quotation:

"The value of a theory does not wholly depend upon its truth, but is rather to be measured by the fruitfulness of the lines of investigation that it opens. Indeed, a theory may be wholly erroneous, and yet it may lead to the most important discoveries."

(Victor C. Vaughan, 1893).

It is therefore hoped that this work may be the prelude to the clinical and experimental investigation of the many unsolved problems which arise out of this thesis.

No concrete proposals for a programme of research have been discussed here, as the subjects demanding investigation are so diverse. To append a list of projects would obviously be valueless, and it is felt that points requiring further elucidation are sufficiently well defined in the text.

Finally, it is felt that we are, perhaps, beginning to understand a little about those vital forces which have hitherto been referred to as the 'vis medicatrix naturae'.

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