An Address

ON

THE IMMUNITY PROBLEM AND ORGANIC EVOLUTION,

AND THE ATTITUDE OF CIVILIZED COMMUNITIES
TO DISEASE.

DELIVERED BEFORE THE OXFORD MEDICAL SOCIETY.

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A RIGOROUS analysis of the conceptions formed by different individuals of the process by which immunity against disease is brought about in the individual and in the race would, I venture to think, reveal a certain amount of uncertainty, even in the minds of members of a learned society, as to the exact relationship between the individual or acquired form on the one hand, and the racial or natural form of immunity on the other.

And yet, until we have realized the steps by which acquired immunity or direct adaptation to disease has been developed in the individual, we have left a large gap in our knowledge of the history of human progress.

By this I do not mean that we should discuss the biochemistry of the immunity reaction. For our present purpose it does not matter whether the struggle between the body cells and the disease organisms takes place at close quarters and depends on a contact reaction between phagocytes and bacilli, or whether it occurs at longer range between the fixative and digestive secretions of the defensive cells and the toxins of the disease organisms after these have been shed into the blood stream.

We are not concerned with amboceptors or with haptophore and toxophore groups, or with endotoxins and exotoxins, except indirectly. We are concerned rather with the manner in which certain capacities of "defence" on the part of the body cells are exercised in response to certain capabilities of attack on the part of the disease organisms, and more especially with differences in the making and in the bringing into action of this offensive and defensive machinery.

As a matter of fact, many of us have a more consistent, if not a more fully detailed, conception of the indirect or racial than of the direct or individual form of the immunity response.

We know that races become naturally immune to lethal diseases—such as tuberculosis or yellow fever, in which recovery is difficult—by a process of selection of the more naturally resistant individuals, and, although we do not know the origin of these individual differences in natural susceptibility and still call them "spontaneous" variations, we do know that their origin is a matter of breeding and a question of the transmission of hereditary characters, and that it is only influenced indirectly by environmental factors.

We know also in the same way that the capacity to recover from non-lethal diseases—such as measles or scarlet fever—is a question of natural endowment, a question of racial evolution, a sort of half-way step between natural insusceptibility to attack on the one hand, and the purely individual non-inherited form of acquired immunity on the other.

My purpose this evening is to try to analyse our conception of that form of individual adaptation known as Acquired Immunity, to see how it stands when compared with Natural Immunity from the evolutionary point of view, and with other use acquirements made by the individual to changed conditions of life.

In the first place, we start by recognizing certain features about immunity. We appreciate the fact that the body cells of the individual acquire these new characters by the exercise of an innate capacity of recovery from disease, and the real question awaiting solution is, How does the exercise of a capacity of recovery bring about in the cells which exercise it a state of insusceptibility to subsequent attack by the same disease organism?

At first sight it looks as if the exercise of innate capacity of one kind—namely, a capacity to recover—

has resulted in the establishment of another kind of capacity, a capacity to resist invasion. Whereas, if we regard the state of artificial immunity which results from recovery from disease not as a new capacity but as a use acquirement on the part of the defensive or body cells, then it is necessary to account for its persistence or transmission in heredity to the cell descendants of these cells, for, as we know, modern biological conceptions deny the possibility of the hereditary transmission of acquired characters.

Hence it is very important to know the fundamental nature of this newly acquired character, this capacity to resist invasion. We want to know whether it does represent a use acquirement, and, if so, what is the essential nature of a use acquirement. We want to know whether the method by which the defensive cells acquire this artificial immunity against subsequent attacks of the same disease is the same method as that by which the nerve cell learns or acquires a new form of neuro-psychic response.

In both cases alike (from the individual point of view) a new adjustment has been made as the result of the exercise of an innate capacity which in the case of the defensive cells is that of recovery from disease.

I.

Now the first proposition that I wish to put forward, and that I hope to substantiate, is: That "becoming different," the assumption of new characters on the part of any individual cell or group of cells is in every case the outcome of variation and selection among units of a certain order, size, and complexity.

Just as the evolution of new characters by any race or species is the outcome of a process of variation and selection among the germ cells from which the individuals of those species spring, or just as the acquirement of new characters by any cell group or organ during the lifetime of the individual is the outcome of a process of variation and selection among the cells of which the organ is composed, so also the acquirement of a new character on the part of the individual cell is the result of a process of variation and selection among the intracellular protein groups of which the individual cell is composed.

Thus while the capacity on the part of any individual organism or individual cell to make use acquirements depends on the exercise of a capacity to vary, either among cells or among cell parts, the nature of the use acquirement made is decided by the nature of the environmental stimulus towards which this capacity to vary is exercised.

The factors which bring about adaptation in the individual are environmental change in interaction with capacity to vary, either on the part of somatic cells or on the part of the intracellular elements which compose the individual somatic cells. Just as in racial adaptation it is the germ cells which vary.

II.

And the second proposition that I wish to put forward is: "That in every case of the assumption of a new character by any individual cell or cell group the ultimate test of the nature of the new character assumed—that is to say, the criterion as to whether it has come about by use acquirement or as an innate variation—must be the order of units amongst which the change has occurred and the presence (or absence) of destruction and regeneration among them during the process."

It is only by applying this test, it is only when we know the order of the units making the change, and know also whether during the process of making it they do or do not undergo death and replacement by fitter units, that we can say whether the new character is a use acquirement or an innate variation, whether, in fact, it is due to "inter"-cellular or "intra"-cellular variation and selection.

For we must remember that an adaptation which is a use acquirement on the part of the individual may be an innate variation on the part of the cells in which it arises.

This, of course, involves a reconsideration of what we mean by a use acquirement. It means that we must judge of a use acquirement not from the point of view of the individual organism in which it appears, but from the standpoint of the individual cells which make it. We must judge of it, in fact, not by its manifestations, but by its mode of origin.

Judged, then, by this test, by the size and quality of the units which make the adaptation and by the way in which it is made (that is to say, whether the making of it has been associated with destruction and regeneration of individual cells or by a reconstruction and rearrangement of intracellular parts), the ways of making use acquirements in the individual human being are few. In fact, the defensive cells and nerve cells seem almost alone in this capacity.

We may illustrate this conception of direct adaptation as a process of intracellular as opposed to intercellular variation, by two or three of the so-called use acquirements made by the individual.

The occurrence of muscular hypertrophy in response to increased muscular effort has been regarded as an excellent example of an acquired character, and when regarded solely from the point of view of the individual it is so. It arises in response to extra calls for muscular effort, that is increased stimulation, during the lifetime of the individual. It disappears when the stimulus ceases to operate and it is not transmitted to offspring.

But the method by which it is brought about is not the same as that by which acquired immunity is brought about. In the enlarging muscle the increased volume is due to multiplication of voluntary muscle cells and not to the occurrence of new characters in the muscle cells themselves. The increased nerve stimulation and the increased blood supply are responded to, not by variation in muscle cells, but increased cell division of muscle cells. Thus, although the individual acquires a new character, a larger biceps, the individual muscle cells do not acquire any new characters, the increased size of the muscle being due to increased numbers of muscle fibres.

Here, then, during the process of making the acquirement, although there is no injury or death, but only a proliferation of muscle cells, there is no intracellular variation in the muscle cells themselves. The hypertrophy is the result of a quantitative and not a qualitative change in cell division, the result of the exercise by the muscle cells of a highly-developed, innate capacity to undergo cell division, when stimulated in a certain way.

The characters acquired by epithelial tissues when transferred from a mucous to a skin surface, or vice versa, when transplanted, in fact, from an aquatic or moist to an aerial or dry environment, may be taken as another example. A portion of epithelial tissue, or a skin graft, transplanted to a moist mucous surface loses its horny stratified character or squamous cell arrangement and becomes a layer of mucus-secreting columnar cells.

I say epithelial tissue because we have no reason to think that the fully-grown, functionally-active epithelial cells themselves undergo this change. What happens is that the younger epithelial cells which spring from the undifferentiated "mother" cells grow up into this new condition in harmony with the changed environment, while the older, fully developed cells perish and are thrown off. Young undifferentiated epithelial cells inherit a capacity of developing in one of two directions, according as the environmental conditions favour one or the other line of growth.

Thus in this case also a supposed example of the origin and transmission to cell descendants of a new character or acquirement turns out on examination to be an example of hereditary development along one of two alternative lines.

In the making of this acquirement a destruction has taken place of those cells which are unable to adapt themselves, and a proliferation and multiplication of those cells which are capable of surviving and of functioning under the new conditions. Again, there has been *inter* not *intra* cellular selection.

NEURAL ADAPTATION.

Now let us contrast these supposed examples of use acquirement with the case of the nerve cell responding to quantitative and qualitative alterations in the stimuli of light or sound or to new nerve stimuli, still confining ourselves, of course, to the life-history of the individual. Here we have the most perfect example known of a typical use acquirement, the result of adaptation on the part of individual cells to altered environmental conditions.

From our present point of view there are two main features about this process of neural adaptation of special interest.

First, it occurs in perfection in a cell (like the nerve cell) which of all animal cells possesses the greatest capacity for rearrangement of its internal molecular composition.

The researches of Marinesco, Gustav Mann, Hodge, and others into the changes in the Nissl bodies and nuclei and other component parts of nerve cells, as the result of fatigue, all bear witness to a capacity for rapid change in the protein intracellular substance.

That which is true of fatigue in lesser degree is true also of response to altered stimulus, to "use acquirement" in greater degree. For if we ask ourselves the question, What is the difference between a renewed response to an old stimulus and a new response to a new stimulus? we are bound to conclude that the difference is a matter of degree. It is a question of the amplitude of the swing of the metabolic pendulum.

Moreover, that which is true of the nerve cell is true of the nervous system as a whole. When a higher level neuron group, or when the brain as a whole learns a new language, it makes a "use acquirement." Not only so, when it forgets an old language it also makes a negative adjustment, and much of our mental equipment is made up by substitution, by a process of forgetting an old and learning a new mode of response.

Neuro-psychic adaptation rests on the possibility of alternative nerve channels, on the selection and establishment of one out of a number of possible nerve routes or synaptic paths for the passage of the neural wave. Our notion of voluntary action as the outcome of deliberation and choice is in harmony with this view.

Further, all this takes place in a tissue the component cells of which in the adult human subject are incapable of cell division, and as a consequence are incapable of handing on the acquirements they have made to any cell descendants.

In the case of the nerve cell a very high capacity for intracellular change has been evolved at the expense of capacity for cell multiplication and regeneration. Just the reverse of what has happened in the case of the muscle cell. And along with absence of cell division and cell regeneration goes the equally important absence of cell destruction during neuro-psychic adaptive response.

The process of making use acquirements on the part of the neurons to changes in environmental stimuli—as long, at all events, as those changes fall within the limits of nerve cell capacity—is unaccompanied by any injury to, or death of, the neurons. This is a very important fact, and is in striking contrast to the wholesale destruction and regeneration of cells which takes place in other tissues when exposed to new conditions.

When we also recall the fact that, although there is no destruction and regeneration of individual nerve cells during the process of neural adaptation, yet that destruction and reconstruction does occur on a large scale among the intracellular protein elements of which the nerve cells are composed, we are led to the conclusion that these marked differences in the behaviour of cells during adaptive response must be associated with a difference in the method whereby the adaptive response is made, that is, with a difference in the size and kind of units which vary and undergo selection when exposed to the new conditions.

Judged, then, by the standard laid down, the neuro-psychic response fulfils all the conditions of a true "use acquirement" both when regarded from the point of view of the individual organism and of the individual nerve cells. Variation and selection take place among units of an intracellular and not an intercellular order. The adaptive response is not accompanied by any destruction or regeneration among the nerve cells or the units concerned. It is brought about by the stimulus of environmental change in interaction with the exercise of a capacity for intracellular variation on the part of individual nerve cells, and it is not hereditarily transmitted.

COMPARISON OF IMMUNITY REACTION AND NEURO-MUSCULAR RESPONSE.

We are now in a position to compare the immunity reaction with the nervous and muscular responses from the same point of view.

There is no more striking use acquirement from the individual point of view than that by which, after recovery

from disease, the individual acquires immunity against subsequent invasion by the same disease organism.

From the individual point of view such an adaptive response fulfils all the tests of a "use acquirement." It is brought about in response to environmental change, and it is not transmitted to offspring.

But it is necessary to examine the reaction, not only from the point of view of the individual, but also from the point of view of the body cells which make the adaptation, and more especially from the point of view of that somewhat ill-defined group of wandering and fixed cells which have intimate connexions with the blood and lymph streams, and which we call the defensive group of cells.

The immunity reaction, as a whole, falls into two great divisions: The natural immunity, which comes about through the selection of more resistant individuals during racial experience of disease, and the acquired immunity, which results from the exercise of an innate capacity of recovery after individual experience of disease. Just as the response of the central nervous system is made up of two primary divisions—the racially-acquired innate method of reflex and instinctive action, and the individually acquired ideo-volitional mode of response.

It is chiefly with the second or acquired aspect of the immunity reaction that we are now concerned. And although it will be necessary to compare the acquired with the natural form in its mode of origin and mode of action, it is chiefly with differences between them in completeness, in persistence, and specific relationships, in so far as these illustrate the different phases of a "use acquirement" that we are now interested.

Acquired immunity, again, like immunity as a whole, also assumes two more or less distinct aspects.

On the one side we have the short range cellular reaction between phagocytes and disease organisms, and on the other hand the long range blood reaction between the fixative and digestive secretions of the defensive cells and the toxins of the disease organisms after these have been shed into the blood stream.

The first takes place for the most part locally against organisms like the tubercle and the leprosy bacilli, which rely for their offensive powers on the elaboration of intracellular toxins. In the second, the disease organisms manufacture exotoxins, which circulate in the blood stream, and to which the defensive cells respond by the formation of antibodies.

These two aspects represent the *antimicrobial* and the *antitoxic* divisions of the acquired immunity reaction.

Now it is of interest from our present point of view that the persistence of acquired immunity bears some sort of relationship to these differences in mode of action of the defensive cells.

For instance, the immunity which follows a localized reaction like vaccinia, or a localized streptococcal or staphylococcal infection, or a disease like tuberculosis or osteomyelitis, characterized by inflammation and perhaps suppuration, is less persistent than the immunity which follows a generalized reaction like small-pox or measles. In the one, phagocytosis or local destruction of defensive cells as well as disease organisms occurs to a considerable extent. In the other the reaction is more general, and destruction of body cells may be absent.

Or if we regard the two phases from the exotoxic and endotoxic point of view we find the same relationship. Thus, if we examine the reaction made to an organism like the tubercle bacillus which secretes little or no exotoxin and against which it is difficult for the body cells to manufacture an efficient antibody, and in which resistance must take the form of a local tissue reaction, and recovery takes place by the destruction of the bacilli at close quarters, then we find that in tuberculosis acquired immunity is often a question even of local distribution—it is incomplete and of short duration; in fact, recovery from tuberculosis is made up of a series of localized reactions against localized attacks by tubercle bacilli of varying degrees of virulence. These reactions are followed by phases of incomplete and transitory immunity, and these again by recrudescences of the local disease.

On the other hand, in a disease like small-pox or measles, the disease organisms secrete an exotoxin, and the defensive cells liberate fixing and neutralizing antibodies, and the struggle is fought out in the blood stream and body fluids. The persistence of acquired immunity under these condi-

tions is much greater and generally lifelong. But even in measles and scarlet fever the persistence of the immunity which follows recovery varies considerably.

I have, through the kindness of colleagues in general practice, collected some records which suggest an hereditary or familial element in some cases.

1. Whooping-cough.

1. Two brothers. Suffered from whooping-cough in childhood. Again more severely at public school.
2. Father. First attack in infancy. Second attack, aged 30 (?), during daughter's illness—slight.
- Daughter. First attack, aged 3—severe. Second attack, aged 16—moderate.
3. Mother. First attack in childhood—severe. Second attack, first week after confinement—moderate.
- Infant. Also had whooping-cough.
- Son. First attack, aged 7. Second attack, aged 14—mild.

2. Measles.

1. Mother, aged 35. First attack, aged 4—mild. Second attack, aged 25—much more severe.
- Six children. Two have had measles twice or three times.
- Annie. First attack, aged 3—moderate. Second attack, aged 8—very severe. Third attack, aged 11—slight.
- Winnifred. First attack, aged 6 months—moderate. Second attack, aged 2½ years—moderate.
- No other cases of plural attacks ancestrally or collaterally.
2. E. B., aged 6. First attack, aged 5—severe. Second attack, aged 6—mild.
- Sister. Also has had two attacks of measles.

3. Scarlet Fever.

1. Brother and sister. G. S.: First attack, aged 7. Second attack, aged 14. M. S.: First attack, aged 16—slight. Second attack, aged 25—severe.

In these cases the persistence of the acquired immunity—that is to say, the number of generations of cell descendants to which the new character of insusceptibility to reinvasion is handed on—bears some relation to the completeness with which these defensive cells reacted and exercised their capacity of recovery, since mild attacks in childhood were generally followed by severe attacks in later life.

Moreover, this fact that early loss of acquired immunity runs in families suggests that the early loss is associated with an hereditary difference in the capacity of recovery by the exercise of which acquired immunity is brought about.

For it is, as we know, only in the individuals of those races which have evolved some capacity of recovery by racial experience, and only in those diseases of which the race has had previous adequate experience, that acquired immunity is present as a mode of adjustment to disease.

It will be a matter of considerable interest to ascertain whether, and if so, to what extent, this hereditary transmission of innate capacity of recovery follows Mendelian lines. For if it does, then we may expect to find Mendelian features in the persistence of the acquired immunity which results from its exercise.

Thus, then, we may state in general terms that the persistence of acquired immunity depends to a great extent on (1) the number and kind of body cells which have exercised the capacity of successful response, (2) the completeness with which the response has been made, and (3) on the extent to which the characters so acquired have been transmitted to the cell descendants of the cells which acquired them, just as the completeness and persistence of natural immunity both depend on the amount of experience which the race has had of disease and the stringency of selection it has undergone in regard to it.

Further, when in acquired immunity the capacity of recovery has been exercised under normal conditions of response—that is to say, when the reaction has been made to an organism of a full degree of virulence normal to its species, and where the reaction has not been cut short by the premature destruction through treatment of the disease organism or its toxins in the body of the host—then the protection afforded by recovery is usually lifelong and as durable as that afforded by natural immunity.

Further, acquired immunity, like natural immunity, is a specific reaction, but in both forms the protection afforded by recovery from invasion by a certain disease organism extends to the attacks of different varieties or strains of the same organism within certain limitations. Thus the acquired immunity which follows vaccination protects against small-pox, and natural susceptibility to small-pox also applies to vaccinia.

There is yet another point of interest about the relationship of acquired to natural immunity.

If a large number of non-immunized individuals possessing innate capacity of recovery are exposed at the same time to the infection of a certain disease, only a certain number will contract the disease on that occasion, while of those who escape some will contract the disease on a future occasion. Whereas if a large number of naturally susceptible individuals—that is to say, individuals belonging to a race that has had no experience of the disease and who consequently do not possess any innate capacity of recovery—are exposed to the same disease at the same time, they will all contract it at once.

This fact, that susceptibility to invasion varies more in individuals who possess an innate capacity of recovery than in individuals who do not possess this capacity, suggests that this capacity of resistance itself varies in potency and efficiency at different periods of the individual life-history: at one time it enables its possessor to resist invasion, while at another it only enables him to recover after invasion; and whereas the older established form of natural immunity is either fully present or wholly absent, the more recently evolved form of capacity of recovery is present in a more irregular and capricious manner—in a more active or in a less active condition.

Insusceptibility a Use Acquirement.

We have now critically examined acquired immunity from the point of view of the cells which acquire it, and we have compared it with natural immunity, both in its mode of manifestation and mode of origin, and we find clear evidence of the operation of variation and selection in the production of acquired immunity, just as we find clear evidence of the operation of the same factors in the production of natural immunity. We also know that from the point of view of the individual the immunity which succeeds individual experience of disease is a pure "use acquirement."

How can we reconcile these two conceptions of acquired immunity? How can we reconcile its function in the individual as a use acquirement with its origin in a process of variation and selection? Only, I think, by remodelling our conception of a "use acquirement." It is only by regarding a portion, at any rate, of the acquired immunity reaction as the result of a process of variation and selection on the intracellular scale that we can harmonize these contrary views.

If we suppose that in the making of the "use acquirement" of insusceptibility to subsequent invasion the body cells exercise a capacity of varying intracellularly (that is, in the construction and arrangement of the protein groups which compose their protoplasm) when stimulated by changes in the nutrient fluid which surrounds them, if we suppose further that that particular molecular composition and arrangement which survives and persists in each cell is the one which is best suited to the altered nutrient conditions brought about by the toxin of the disease, and that therefore the particular kind of intracellular response selected will depend on the kind of disease organism to which it is made, then we are able to understand why this new and acquired form of cell metabolism is transmitted to cell descendants. It is so transmitted because it really arises as an innate variation among the intracellular units in the individual cells which acquire it.

So regarded, innate capacity of recovery or resistance to disease on the part of the body cells becomes innate capacity to vary intracellularly when exposed to new conditions introduced by disease organisms. And this capacity to vary, although possessed in different degree by all the individuals of a race that has had sufficient experience of the disease in question, remains latent in such individuals until roused to exercise by exposure to disease. Thus, by the exercise of this capacity for intracellular variation on the part of the cell and by the selection of the most appropriate kind of molecular response a new character arises in the cell, that of a capacity to resist reinfection, representing from the point of view of the individual organism a "use acquirement."

Moreover, by so regarding individual reaction to disease, we are bringing the use acquirement of the immunity reaction into some sort of relationship with the use acquirement of neural response which we have already seen reason to think is also the outcome of a process of

variation and selection among the intracellular elements in nerve cells.

Just as the latitude of the neural response is determined by the hereditary limits of innate neural capacity, so the latitude of the individual immunity reaction is determined by the extent of the hereditary capacity of recovery or resistance to the disease.

But the question remains, How much of this insusceptibility to subsequent invasion is due to "intra"-cellular and how much to "inter"-cellular selection? How much, in fact, is represented by use acquirement and how much by innate variation?

As pointed out previously, our test for this problem must be the order of units among which variation and selection occur, and the presence or absence of destruction and regeneration among the individual cells concerned in the response.

When judged by this standard the acquired immunity reaction again falls into two divisions: An antimicrobial or phagocytic side, characterized by local tissue reaction to organisms which chiefly manufacture endotoxins in which destructions and regeneration of wandering cells occur and local reaction, inflammation, and suppuration may be present; and an antitoxic or humoral side, characterized by general body fluid response to organisms which secrete exotoxins in which local reaction is insignificant and cell destruction absent.

Judged, then, by this test, the antimicrobial or phagocytic side of the immunity reaction represents innate variation, and the antitoxic or humoral side of the reaction represents "use acquirement," although, when regarded from the body cell point of view, both arise through a process of variation and selection, in the one case among intercellular and in the other among intracellular units.

It is interesting to note also that of these two divisions of the acquired immunity response the phagocytic or antimicrobial is an older character phylogenetically than the more recently evolved antitoxin reaction.

It is also interesting to note that the two most prominent instances of use acquirements in the human individual—the neural adaptation to changes in nerve stimuli and the immunity reaction on the part of body cells to the toxins of disease organisms—have both arisen in two fields of human activity in which development has in historic times been most rapid and in which selection has been most stringent. Mental activities and evolution against disease have exercised a predominating influence on modern civilization.

Thus, then, a critical examination of the immunity response leads us to the conclusion that all forms of immunity—the natural and the acquired—arise in a process of variation and selection among units of different size and complexity.

In the racially acquired form of natural immunity these units are the germ cells from which the more resistant individuals spring. In the antimicrobial aspect of acquired immunity response they are those individual body cells which react to the disease organisms. In the antitoxin aspect they are the intracellular elements of which these cells are composed.

Judged from the point of view of the individual organism, adaptation to disease is a "use acquirement"; judged from the point of view of the units which undergo adaptation, it is a process of innate variation.

The Immunity Problem from the Bacterial Side.

Probably much more light will be thrown on the difficult problem of the mode of origin of the immunity reaction when more is known concerning the way in which disease organisms adapt themselves to changing conditions, and gain or lose in virulence.

When we know whether exalted virulence in bacteria is brought about by innate variation or use acquirement, by interbacterial or intrabacterial variation and selection, we shall probably also know how body cells become immune.

Following the principles laid down, we must first ascertain the order of units among which the variation and selection process takes place during bacterial adaptation. And to do this we must ascertain the prevalence and incidence of cell destruction and cell regeneration among disease organisms when they undergo adaptation to the defensive activities of different hosts on the one hand and to different culture media on the other.

We know already that in most cases the process of invading the resistant human or animal organism by disease organisms is associated with a considerable death-rate among the invading organisms. We also know that a considerable number of generations of organisms must live and perish in the culture fluid or in the partly immunized host before a strain is born of a virulence capable of flourishing under the new conditions.

But we do not yet know whether, under any circumstances, individual disease organisms themselves acquire increased offensive capacity when exposed to altered nutrient conditions. We do not know whether the increased or diminished virulence is obtained by innate variation among the bacteria or by use acquirement on the part of individual organisms. A knowledge of these facts would indicate the order of units among which variation and selection is taking place.

A comparison, if such were possible, between the death-rate among disease organisms when acquiring exalted virulence by repeated passage through different hosts of varying degrees of immunity, and the death-rate among the same organisms when acquiring exalted virulence by growth in different culture media, would go far to determine the relative share taken by intercellular and intracellular variation in these two forms of adaptation. It is a suggestive fact that in order to bring about increased offensive capacity or exalted virulence in any strain of disease organism it is necessary to pass the organisms through a series of hosts of different degrees of immunization or to grow successive generations in different culture media. In both cases the essential requirements are a large number of bacterial generations exposed to different environments. These requirements are incompatible with direct adaptation, but favour the occurrence of intercellular variation and selection.

Organisms which cause disease are organisms of enormous fertility and very great variability. They are capable of a far greater and more rapid relative increase than the body cells to which they are opposed.

Further we must not lose sight of the fact that if it is to flourish as a race each species of pathogenic disease organism must possess the capacity, not only to multiply rapidly within the body of the host, but also to pass from the body of one host to another after the death of the first. It must be able to survive during transit through air, earth, or water, if it is to bridge the gap between intracorporeal and extracorporeal life. In this sense, then, the task required of a disease organism is greater than that required of a defensive cell.

Now this very marked fertility and variability among disease organisms is itself suggestive of adaptation by intercellular as opposed to intracellular selection during bacterial acclimatization.

For we know that among disease organisms as amongst animal cells the destruction of unfit and the multiplication of fit varieties are just the two conditions which favour the selection of more virulent strains of organisms during the progress of disease and that these conditions are incompatible with adaptation by "use acquirement" which presupposes a capacity on the part of each individual organism or cell to persist and adjust itself to the new conditions.

The crucial difference between indirect adaptation by innate variation and direct adaptation by use acquirement is this: In the first, the organisms which are exposed to the new conditions perish and are replaced by organisms of greater resistance. In the second, the organisms which are exposed to the change themselves undergo the adjustments necessary to adapt them to it. The first is a *pre-experimental*, the second a *post-experimental* change.

We can hardly doubt, therefore, that when in the process of invading the human or animal organism, and while still exposed to the resistance of body cells and body fluids disease organisms become adapted to their new environment, and develop strains of altered virulence, they do so for the most part by the old method of the natural selection of more resistant individual organisms. But there is some evidence that the other, the direct method of individual use acquirement, is not altogether absent among some unicellular organisms when exposed to altered conditions.

Although susceptible of either explanation Ehrlich's experiments in the immunization of trypanosomes against fuchsin and arsenic suggest an increased struggle for

existence among the organisms during the process of chemo-immunization, and Ehrlich himself suggested that the adaptation was brought about by a partial starvation of individual trypanosomes by a blocking of their nutritive receptors by antibodies derived from the cells of the partially immunized hosts.

But we may also recall the observations of Metchnikoff and Dallinger and others on the effect of environmental change on unicellular animal organisms. The researches of Cohn, Balbiani, Danysz, and many others have shown that infusorians and other protozoa do become adapted to nutrient media of different chemical and even toxic composition by a gradual process of acclimatization, and, if this process is sufficiently gradual, adaptation is brought about without causing the death of the organism.

Dallinger showed that the same thing occurred in changes in the physical environment. He gradually acclimatized infusoria to a water temperature of 23° C. without causing their death, and later to a temperature of 70° C.

Metchnikoff says, in regard to Davenport's and Neal's experiments on the acclimatization of stentors to four times the lethal percentage of mercury chloride, that the immunity cannot be attributed to the selection and persistence of those stentors which possess a natural resistance to the sublimate, but that it is the result of a gradual and direct chemical influence on the protoplasm of the stentors which, once acquired, enables all the animals to survive doses lethal to unacclimatized control individuals.

The experiments of Stahl are also very suggestive from this point of view of acquired immunity. Plasmodia of myxomycetes were habituated to and were finally attracted by solutions of glucose of a strength formerly injurious to them, and to which they manifested negative chemotaxis, and Metchnikoff brought about the same result with arsenical solutions. In this case, as in Dallinger's infusoria, the adaptation seemed to be associated with hydrolytic changes, the protoplasm of the adapted individuals contained less water.

Thus the evidence points strongly to the possibility of adaptation to environmental change taking place in some unicellular animal organisms by a process of individual use acquirement unassociated with the death of any of the organisms exposed to the change, and therefore independent of any process of variation and selection among the organisms concerned. Possibly the same explanation may apply to some extent to pathogenic organisms.

If the conception of a use acquirement which I have just put forward be true, then we must regard the adaptive change on the part of these organisms under such conditions as the outcome of a process of variation and selection in, and of reconstruction and rearrangement of, the intracellular protein elements of which the organisms are composed.

Function and Adaptation.

It may be thought that in selecting the neural response as an example of use acquirement I have confounded normal function with direct adaptation. But when we come to analyse our conception of function we realize how it merges into use acquirement by intracellular variation, and how both spring from the fundamental property of irritability in all protoplasm and its capacity of response to stimulus.

The alternating or partly overlapping cycles of anabolism and katabolism which we call function, or response to stimulus, either proceeds along lines of hereditary cell potentiality, in which case we call it normal function, or it proceeds along lines and in a direction away from original cell potentiality, when it represents the making of a new acquirement.

In both cases there is a "becoming different," a "changing of state" on the part of the cell in response to environmental influence of some kind or another.

Adaptation implies shifting the mode or plane of functional response, and this shifting is done in the case of direct adaptation or "use acquirement" by the action of environmental change, not in originating but in selecting one particular mode out of a number of modes of action which in the intracellularly varying cell cluster round the habitual mode of normal response. After a time this particular mode becomes established as the normal mode of response under the new conditions, and we then call it altered function.

Pfeiffer has shown that the adaptive movements of bacteria under the influence of increasing stimulation obey the same psycho-physical law as that which governs the response of the nervous system to alterations in nerve stimuli; both reactions conform to the Weber-Fechner law. This is an important fact, and suggests that the two reactions have a common origin in the fundamental property of irritability common to all protoplasm. In this sense adaptation and function are essentially one.

Every nerve cell above the reflex and instinctive level makes a use acquirement when it responds to changes in a nerve stimulus, and every group of neurons which makes new acquirements, which forgets an old and learns a new language, is establishing a new response to a new stimulus, and in doing so it is carrying on normal function. The reason why normal function and the making of new acquirements are, in the case of the nerve cells, one and the same thing is that the nerve cell possesses the capacity of intracellular variation—in other words, of educability—to a marked degree.

Another example will make this even clearer. The pigmented skin cells of the frog (as Lord Lister showed) respond to alterations in the intensity of the light stimulus by changes in the distribution of pigment in the chromatophore skin cells. This is their normal mode of response, their normal function, and each time that the pigment cell responds thus, every time that it changes intracellularly and concentrates or diffuses its pigment granules, it also makes a use acquirement. The response occurs among units of an intracellular order, and it is not accompanied by injury, death, or regeneration of the cell as a whole under normal conditions. The alternating cycles of cell response in this case represent acquirements which correspond with the lines of hereditary cell activity.

Thus, "use acquirements" can be brought about in several ways—by the simple rearrangement of intracellular parts as well as the destruction of old, and the reconstruction of new and different intracellular parts. Both methods involve intracellular change and intracellular selection.

Under the old régime of natural selection, the evolution of a new kind of response meant variation among individuals. It involved the destruction of old and the selection of more fully adapted individual organisms during the process of readjustment to the new conditions of life. Under the new régime of "use acquirement" the evolution of a new response means variation among intraindividual or intracellular units; it means the substitution of new for old parts in the machine, instead of the destruction of the machine itself.

Just as the rapidity with which races become adapted to new conditions depends on the rate of destruction of the unfit and the regeneration of the more fit, so the rapidity with which the individual organism or the individual cell acquires a new character and adjusts itself to new conditions depends on the rate of intracellular variation and intracellular selection or of intracellular rearrangement.

It is well known that the process by which the individual cell adjusts itself to new conditions occupies a considerable time. It is a gradual process of becoming accustomed to the environmental change which must not be too violent or too rapid; if it is, then it involves the death instead of the readjustment of the cell. The time is taken up by the process of variation and selection which goes on among the intracellular elements during this process of adjustment.

If the variations are large and discontinuous and in the right direction, the use acquirement will be rapidly made, the new response will be rapidly learnt. If the variations are small and fluctuating, or if the stringency of selection set going by the environmental change is not great, then the cell will be a long time in adjusting itself or in making the use acquirement.

In both cases, in functional discharge and in use acquirement, the limits within which functional activity can be maintained or adaptive response made are both determined by cell potentiality, or, in other words, by the hereditary capacity of the cell for intracellular variation.

It is, of course, true that in many adaptive responses some cells, like some unicellular organisms, are more apt at readjustment than others. This means that such cells

differ in capacity for intracellular variation. This means also that such responses are partly indirect. In such reactions the principle of intercellular or interorganismal selection is still present, and if the difference in capacity of adjustment is sufficient to cause death, or injuriously affect regeneration and cell division in some of the cells then this principle comes into active operation and the process of making the adaptation descends to the intercellular level.

It is, in fact, one of the essential conditions of the making of a pure use acquirement that all the cells or unicellular organisms concerned in the reaction shall be able to readjust their internal composition and mode of action sufficiently to enable them to live, and to avoid injury under the new conditions, otherwise the units which vary in capacity and are selected are cellular and not intracellular units and the making of the acquirement is associated with the destruction of unfit cells.

Neural adaptation to changes in nerve stimuli entirely fulfils these conditions. So also (if our conception of it is true) does that portion of the acquired immunity reaction which is unaccompanied by the destruction or injury of any body cells.

THE ATTITUDE OF CIVILIZED COMMUNITIES TO DISEASE.

If, then, the acquirement of the immune state be a type of adaptive response in general—if we are right in regarding all adaptation as either individual or racial, direct or indirect, and as the result of variation and selection, either among cells or in cells—then it is clear that such a view must largely influence our conception of the true attitude of civilized communities to disease.

Among primitive societies the problem of adaptation to disease has been almost entirely a question of racial evolution under the control of natural selection. Savage peoples, in order to escape death from disease, must be naturally immune. Capacity to recover is of no avail unless the conditions of mutual protection and co-operation are present under which alone recovery is possible.

Hence under such primitive environmental conditions the acquirement of the immune state by individual experience and recovery is of little importance as a factor in adaptation against disease. Half measures and part adaptations are useless; it is necessary to be wholly and innately immune. For any individual to acquire immunity against disease two things are necessary: He must possess some innate capacity of resistance, and opportunity must be present for its exercise. But as civilization advances conditions of life arise which allow of these factors coming into play. The screening and protecting influence of individual acquirement modifies the stringency of natural selection, and, as Baldwin, Morgan, and others have pointed out, it directs the lines along which organic development shall proceed.

Conditions which conduce to recovery from disease, and which therefore favour adaptation by use acquirement, are, broadly speaking, the care of the sick during recovery on the one hand, and improved medical treatment, especially along bacteriological lines, on the other.

It is to the principle of "use acquirement" involved in all such measures of co-operation and environmental control that I wish to draw attention.

Advances in our knowledge of the prevention and the treatment of disease; improved methods of treating the sick and favouring recovery—these constitute a great object lesson in adaptation by "use acquirement."

Advances in external sanitation by which disease organisms are banished from the environment, measures of internal sanitation, such as serum and vaccine therapy, by which the disease organisms are destroyed or their virulence reduced after they have gained an entrance into the body—all such measures lead us further and further away from the old régime of innate variation and natural selection. The necessity for being immune by nature becomes less as the possibilities of becoming immune by art become greater.

But some one will ask, What bearing has all this discussion about the intimate nature of acquired immunity on the practical question of the best way of treating disease? What does it matter, some one will say, as long as we become insusceptible, whether we acquire immunity by a process of intracellular variation and selection during individual life or whether we are born immune through

the operation of natural selection during racial experience of disease?

It matters just because the immunity reaction is a type of all adaptive response, and, since evolution is largely adaptation to a widening environment, a true solution of the immunity problem supplies the key to many other evolutionary problems also.

When narrowed down to essentials, there are only three ways of undergoing adaptation to environmental change, just as there are only three ways of becoming immune against disease:

1. Either adaptive change is entirely the result of external influence and the organism is as clay in the hands of the environmental potter.
2. Or the organism initiates and directs its own adaptation independently of outside interference.
3. Or adaptation is the result of the interaction of environmental influence and cell potentiality.

Now the immunity problem sheds some light here. We know that the toxin of the disease organism does not directly build up by chemical influence the immune response in the body cell. Nor does the body cell evolve the immune state in the absence of the stimulus of the disease organism.

The state of acquired immunity is the outcome of the exercise on the part of the body cell of a capacity to become different, to vary intracellularly, in not one only but in several directions, when stimulated by the toxin of the disease organism. When this hereditary capacity to become different, to vary intracellularly, is inadequate to meet the new conditions, "use acquirement" is impossible; the cell perishes, and the process of adaptation sinks from the intracellular to the intercellular level.

The problem for the social reformer is how to promote the adaptation of the social organism to its environment without sacrificing the interests or the lives of the individuals during the process of reform. The problem for the physician is how to bring about immunity and resistance to disease in the individual organism without at the same time injuring or destroying the body cells and so producing illness or disease itself.

The problem for both is how to raise the adaptive response to the intracellular level. Both must build on innate capacity for response, on capacity to vary or become different, in fact, on educability. Both alike should try to accomplish the result by stimulating the exercise of this capacity on intracellular and intraindividual lines, and should only resort to intercellular and interindividual struggle with its attendant destruction of competing units when intraorganismal methods have failed or are incompetent to produce progress.

Now this cannot be done by a return to older methods. A return to crude individual competition and natural selection would only serve to destroy the forces of co-operation and mutual protection, which are essential conditions for the exercise of the capacity of recovery and the production of acquired immunity from disease, just as they are essential also for the making of "use acquirements" in many other fields of human activity. Hope for future progress lies in the extension of the method of adaptation by "use acquirement" and environmental control, in the improvement of environmental conditions and the banishment of disease organisms from the human environment by measures of external sanitation, and in the destruction or the reduction of the virulence of disease organisms by vaccine- and chemo-therapy, if they should obtain a foothold in the body.

These are the methods of use acquirement and environmental control, and the methods by which more and more adaptation to disease on the part of the human race will be brought about.

And if, as I have already said, we may regard the great immunity reaction as a type of evolution and adaptation in other fields, if we may regard natural immunity through natural selection as a type of the earlier methods, and artificial immunity through the exercise of individual capacity to profit by experience and through environmental control as a type of the methods of the future, then, bearing in mind the success that has been achieved by these latter methods in the struggle against disease, we may look confidently to an extension of use acquirement and environmental control in other fields, rather than to a

return to innate preadaptation and natural selection, remembering always that both methods depend on innate capacity of some kind or other—capacity of being already adapted before experience, on the one hand, or capacity to become adapted and to learn by experience on the other.

Since innate capacity of recovery in the immunity reaction, like capacity to learn or educability in all adaptive responses are matters of heredity and breeding, it is essential in discarding the older method of natural selection that we take steps to safeguard the transmission and production of innate capacity by some measures of Eugenic control.

A Clinical Lecture

ON

AN ANALYSIS OF FIVE HUNDRED CONSECUTIVE OPERATIONS FOR ACUTE APPENDICITIS.

DELIVERED IN THE POST-GRADUATE COURSE AT THE MANCHESTER ROYAL INFIRMARY.

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IN the BRITISH MEDICAL JOURNAL of January 25th, 1908, I submitted an analysis of 100 consecutive operations for acute appendicitis. To these I have added 400 operations since performed, the present list including, therefore, all the operations I have undertaken in the acute stage of appendicitis between January 1st, 1906, and October 28th, 1911.

SEX.

The series comprised 285 males and 215 females. Much stress has in the past been laid upon and theories invented to account for the alleged great preponderance of appendicitis in the male over the female sex. I believe, however, that many slight attacks pass unrecognized in the female, in whom, owing to the menstrual function, slight abdominal pain is not held of so much account as in the male, where all abdominal pain is abnormal. Moreover, many attacks of appendicitis coincide in their onset with that of menstruation, and are, therefore, all the more likely to be overlooked.

AGE.

The average age was 26.3 years: of males 25.3, of females 28.1. The oldest patient was 77, the youngest 3.

Age Periods.	Males.	Females.	Total.
1 to 5 years ...	6	5	11
5 to 10 " ...	24	13	37
10 to 20 " ...	83	53	136
20 to 30 " ...	74	55	129
30 to 40 " ...	49	48	97
40 to 50 " ...	32	17	49
50 to 60 " ...	13	17	30
60 to 70 " ...	1	6	7
70 to 80 " ...	3	1	4
	285	215	500

PREVIOUS ATTACKS.

One hundred and forty-two patients gave a history of one or more definite previous attacks, that is, 28.4 per cent.

DURATION OF SYMPTOMS PRIOR TO OPERATION, WITH RESULTS.

In all cases the duration of the disease has been calculated from the first severe abdominal pain. It is well