Observations

ON THE

NATURE OF THE IMMUNITY REACTION.

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PERHAPS one of the most striking examples of cell adaptation to changed conditions is afforded by the response made by the cells of the organism to the attacks of disease. Somatic cells and body fluids acquire new characters in response to external influences, and the characters so obtained are transmitted to the cell descendants of the cells which acquire them, and the condition known as "acquired immunity" is the result.

It becomes important, therefore, to inquire whether the conditions under which the response against disease is made throw any light on the essential nature of the process by which all "use acquirements" are made by cells exposed to altered conditions of life. Whether, in fact, the examination of the conditions of the immunity reaction suggests the occurrence of any variational or selectional process among the cells, or the component parts of the cells, exposed to the changed conditions, or whether it suggests a more direct relationship between the change in the environment and the change in the cell, a readjustment of the internal relations of the cell to the changed environmental relations, brought about in some way by a direct action of the environmental stimulus on the cell structure, wholly independent of any preliminary experimentation in adaptation, or any testing of adaptational steps by any standard of fitness afforded by the welfare of the cell as a whole, or the welfare of the organism of which it forms a part.

Although, as will be shown later, the distinction involved in the terms used is probably an artificial one; although, as we shall be able to show, the origin of new characters by "variation and selection" on the one hand, and by "use acquirement" on the other, is fundamentally one and the same process, yet, for our present purpose, the question to be considered is: Whether the new characters which arise in certain body cells as the outcome of a response to attacks by disease organisms owe their origin to "variation" among the cells or to a "use acquirement" on the part of the cells exposed to the change.

Since the appearance of these new characters represents an adaptive change on the part of the cells concerned, this involves the further question, whether all cell adaptation to altered conditions of life is a "use acquirement" or a "variational and selectional" process, or a "mixture of both."

Although there is no complete agreement among pathologists as to the number and kind of body cells that should be included in this group of what I propose to call "defensive cells," yet all agree that those cells which are to be found at some stage or other of their life-history in the blood or lymph streams should certainly be included in such a category.

It matters little, from our present point of view, whether the struggle between the defensive 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" on the one hand, and "the toxins of the disease organisms," after these have been shed into the blood stream, on the other.

It makes no real difference to the special problem of the origin of new cell activities and new cell capacities, whether we discuss the immunity problem in terms of amboceptors and haptophore and toxophore groups, or whether we describe it simply in terms of toxins and antitoxins. The essential point is that the immunity reaction itself consists in the exercise of certain capacities of defence on the part of the body cells in response to the exercise of certain capacities of offence on the part of the bacilli or cocci or protozoa which cause the disease. The question, therefore, is whether the new characters which arise on both sides are "use acquirements" on the part of

the individual cells concerned, whether they arise as favourable "variations" among some of the cells during the cell proliferation which accompanies the struggle, or whether they arise as favourable "variations" among the living units, the physiologically differentiated parts which compose the individual cells. Partly by a process of chemo-therapy and partly by growing the organisms in partially immunized hosts, Ehrlich established a strain of trypanosomes immune to certain substances, and capable of transmitting the immune character to their cell descendants for many generations. He states, in reference to this new strain, that it is of little consequence whether it arose as a "mutation" or as a fluctuating "variation." However this may be, it certainly is important to know whether this new character, this immunity against arsenic and fuchsin, was acquired by the individual trypanosomes during growth under the new conditions, or whether it arose as a favourable variation among some of the trypanosomes during the increased struggle for existence and the destruction of trypanosomes brought about by the change in the environment.

Ehrlich³ himself not only brought forward evidence to show that there is an increased struggle for existence among the organisms during the process of chemo-immunization, but he also suggested that it was brought about by a partial starvation of individual trypanosomes by the blocking of their nutri-receptors by antibodies derived from the cells of the host.

We know that when a struggle for existence occurs, together with a multiplication of the contending organisms, the conditions are present which favour the origin and selection of favourable varieties of new characters, rather than the establishment of use acquirements.

Thus, then, in regard to the disease organisms there is presumptive evidence that they adapt themselves to new conditions, and acquire new characters by a process of "variation and selection" during the process of struggle for nourishment between themselves and the body cells of their host.

Another important fact has been established concerning the immunity response. Largely through the labours of Ehrlich and his co-workers it is becoming increasingly clear that the process by which the body cells respond to disease organisms and their toxins is the same kind of process, slightly modified, as that by which they respond to nutrient material.

In order that it may assimilate nourishment the cell must sooner or later get into intimate cell contact with the material it is to assimilate. The same thing is true in the disease response. The cell treats the disease organism and its secretions as so much proteid material, suitable or unsuitable for assimilation. It is attracted to or repelled from it, and if the circumstances of the reaction allow of such a process, it ingests and assimilates the bacillus by a process of phagocytosis. The cell endeavours to treat the toxin in the same fashion. It fixes and neutralizes it by a complex machinery of amboceptors and digestive complementary molecular groups shed into the blood stream.

The essential point is that the "defensive" cells, when occupied in resisting disease organisms and their secretions, are engaged in a response in which they, or their ancestors, have had some experience in an allied nutritional form, and of which the immunity reaction is a "variant."

After these preliminary remarks we may now examine more closely the conditions under which the disease response takes place.

We know that in the case of all adaptive responses made by higher organisms to changes in their environment (provided that the change be not too sudden or too violent) the essential elements in the conditions of response are a certain rate (generally a considerable rate) of increase in numbers, and a certain rate (generally a considerable rate) of mortality among the individuals exposed to the change. We shall find a corresponding high birth-rate and high death-rate among the "defensive cells" exposed to the attacks of disease organisms.

In every disease, due to microbic infection, there is an incubation period intervening between the entrance of the disease organisms into the body and the commencement of the invasion phase of the disease. During this variable period there are reasons for thinking that the disease organisms are engaged in cell multiplication, and in the

elaboration of toxins, haptophore and toxophore groups, to fit the nutri-receptors of the defensive cells.

The invasion stage itself is marked by severe symptoms which indicate a more or less profound change in the environment of the body cells, due, in Ehrlich's language, to the anchoring of the disease organisms or their receptors to the side chains of the body cells.

The succeeding stage of illness, with its periods of remission and intermission, is associated with recurring sheddings of saturated, and the reanchoring of regenerated receptors on both sides, with a mutual neutralization of the toxophore and antibody groups on either side. This process may end in recovery by crisis, in which a sudden fixation and neutralization of toxin occurs, together with a more or less wholesale destruction of the disease organisms, or it may end in lysis, a more gradual but essentially similar process, in which the disease organisms and their toxins are neutralized and destroyed in successive stages.

Under certain conditions some of the organisms worsted in the struggle may retire to tissues or situations in which they are less exposed to attack, or they may succeed in surrounding themselves with protective capsules, or they may remain quiescent in the more resistant spore form, and under favourable conditions of lessened resistance on the part of the host may again become active and bring about a relapse, or, in "variational terms," screened from immediate attack, they undergo cell multiplication, and vary in the direction of, or acquire greater virulence, as they become armed with more virulent toxophore and more efficient haptophore receptors and renew their attack on the defensive cells.

Such are the phases of the disease response; the very step-like interrupted character and the varying intensity of the process suggest the operation of "variation and selection" among the contending cells and disease organisms. If recovery were wholly synonymous with the increasing development by exercise of a capacity of "defence" by the body cells, and the decreasing exercise of a capacity of "offence" by the disease organisms, no adequate explanation seems forthcoming of these sudden changes in the intensity of the process, or of these rises and falls in activity on both sides.

If, on the other hand, recovery denotes the origin of additional adaptations arising as variations, in or among the defensive cells, and relapse, recurrence, and death indicate further variation in offensive capacity in the disease organisms, then the alternation between the inactive and the active phases in disease coincides with the transitional stages between increased variation on both sides.

In the course of every disease, at some stage or other, there are some traces of death and injury amongst the body cells. We need only recall the high rate of mortality among the polymorph leucocytes which occurs in suppuration. Such a high rate of mortality may itself be evidence of a powerful positive chemiotaxis on the part of the cells, and it may indicate a successful reaction.

There is also the desquamation and the exfoliation of the older epithelial cells of skin or mucous membrane in the exanthematous fevers. The muco-purulent secretion thrown off by the mucous membranes when invaded by micro-organisms of many kinds; the loss of staining reaction denoting death in the aggregations of phagocytes and giant cells, which surround imprisoned colonies of tuberculous and other bacilli, both are associated with the defensive reaction and the recovery process.

The phenomenon of phagolysis, especially of macrophages, described by Metchnikoff, and regarded by him as a necessary preliminary to the liberation of cytases into the blood stream by phagocytes, affords direct evidence of cell mortality whatever may be its intimate relation to the bactericidal property of immunized serum.

All these phenomena provide examples of the high cell death-rate which accompanies the disease process. But there are important indications that what is true of the defensive cells as a whole in the disease response, is true also of their physiologically differentiated cell parts.

There is every reason to think, judging from the analogy of the division of nuclear material in germinal reproduction, that such a physiological differentiation of molecular cytoplasmic and nuclear structure exists in every cell, even though we may not be able to recognize it in any

structural modification under the microscope. The very fundamental facts of immunity, as interpreted by the most sound and far-reaching of all the theories hitherto propounded (that is, Ehrlich's), strongly suggest the occurrence of differentiation.

Ehrlich has shown that there must be a shedding into the blood stream of some such physiologically differentiated portions of defensive or body cells, that there must be a throwing off of molecular groups of a highly complex and specific stereo-chemical composition—for example, amboceptors, since bodies of this kind can be recovered from the blood stream in combination with the toxin groups, which they have "fixed," and from which, by appropriate means, they can again be split off. Further, these same bodies, in the shape of receptors, while still in organic union with the body cells, serve to anchor the toxophore groups to these cells in the same way that, under normal conditions, as nutri-receptors they anchor nutrient material to the same cells.

The fundamental facts concerning disease as a whole point in the same direction. The bodily wasting which means cell destruction, or destructive changes in cell parts, the haemolysis, the cytotoxicity, all these processes are closely associated with the disease response.

Cell regeneration and cell proliferation are both also constant characteristics. We need only recall the regeneration of red blood corpuscles, of leucocytes, of lymphocytes, of microphages, of macrophages, and of tissue cells.

But besides the regeneration of individual cells destroyed by the toxins of the disease organisms, there is also an abundant regeneration; in fact, an over-reproduction of physiologically differentiated cell parts. The enormous volume of antibodies and antitoxins found in the blood stream, in proportion to the dose of toxin administered during the process of immunization, affords abundant evidence of the regeneration and reshedding of such molecular groups by the body cells exposed to the activities of the disease organisms.

This conception of the process of cell destruction which occurs during disease, as representing a mortality-rate among imperfectly adapted cells, and as the discarding of so much unfit material, and the process of cell regeneration as a process which is useful in favouring the origin by variation of more fit and more fully adapted cells, is, I think, in harmony with general biological conceptions.

If, on the other hand, we conceive of the adaptive changes arising in cells, exposed to the attacks of disease organisms, as so many direct reactions made by the cells to an environmental change of a chemical kind, and as so many "use acquirements," then it is not easy to account for the cell destruction which undoubtedly figures so largely in the disease response; for if the cell as a whole, when exposed to such a chemical change as that brought about in the nutrient medium by the toxin of a disease organism, readjusts its molecular constitution, and brings it into harmony with the change in the environment, there is no necessity for the destruction of the cell. If, on the other hand, the fully-formed cell exposed to such changes cannot so adjust itself, while some of the younger and less highly differentiated cells can so adjust themselves, or are already so adjusted, then the principle of "variation and selection" is at once introduced into the adaptive response.

It is admitted by all, even by those who uphold the "direct adaptational" view of the immunity response, that the process of adaptation by "use acquirement" is a gradual change, and that it occurs in stages in which the more perfectly adapted succeed the less perfectly adapted.

The crucial difference between "direct adaptation or use acquirement" and "indirect adaptation by variation and selection" depends on the conditions under which the response is made, and these in the case of the disease response are as follows:

In the "direct" or "use acquirement" form the adaptation is made by the individual cell or the physiologically differentiated parts which compose the individual cell exposed to the environmental change, whereas in the "indirect" or "variational form" the adaptive change is not made by the individual cells exposed to the new conditions; these, being unable to undergo the required molecular readjustment, perish, while the new characters arise, as adaptive variations, in the younger cells or

"mother cells" stimulated to active cell division by the destruction and removal of the older cells.

Look at the facts, however, as we may, we are always coming across struggle for existence, cell destruction, and cell regeneration in recovery from disease. They occur not only among individual phagocytes, but also among the physiologically differentiated cell groups, the amboceptors and receptors which compose the phagocytes.

Moreover, there is a quantitative side to this relationship, between struggle and recovery in the disease response. A high cell birth-rate and a moderate cell death-rate are characteristic of a successful response and of recovery, whereas a low cell birth-rate and a wholesale cell death-rate or injury-rate are characteristic of the unsuccessful response in which there is no time for the readjustment of cell parts, or for the origin of new and more fully adapted cell varieties.

It is very necessary to bear in mind this cell destruction when deciding between "use acquirement" and "innate variation" as possible causes of the origin of new characters in somatic cells in response to disease.

Conditions involving injury and death of numbers of individual cells are really incompatible with the origination of new characters by "use acquirement." The nerve cells, which are capable of making use acquirements in the highest perfection, do not undergo injury as cells or perish in the process of acquiring new modes of response to changes in nerve stimuli. On the other hand, a high rate of multiplication among organisms, together with a high rate of mortality among those which are less perfectly adapted, strongly suggests that a process of adaptation by selection is going on in consequence of some change in the conditions of life.

Consequently we are led to believe that both the "direct" and "indirect" forms of adaptive response are present during the response to disease—the immunity reaction.

Moreover, we are not without direct evidence of the fact that the body cells, and especially those of them which form the defensive group, are as a whole (like the highly variable disease organism to which they are exposed) very variable as regards these defensive capacities.

There seems to be no hard and fast line of demarcation between "natural immunity" on the one hand and "acquired immunity" on the other. Among naturally immune races, some individuals exhibit this natural refractoriness to certain disease organisms in a higher degree than others. In acquired immunity the artificially-acquired immune state persists longer in some individuals than in others in reference to the same disease.

There are, indeed, indications that, through the operation of natural selection, this variability in capacity of response to disease organisms and their secretions on the part of the defensive cells has assumed a selection value among the body cells, just as a corresponding variability in capacity of offence and defence against the attacks of body cells has assumed selection value in the case of the disease organisms.

ACQUIRED IMMUNITY.

The foregoing statements must now be submitted to the test of experience, and the various kinds of immunity must be considered, especially that state of resistance to subsequent invasion which results from recovery from any one of the zymotic diseases, and is known as "acquired immunity."

The individuals of certain races which have had a sufficiently long experience of certain non-lethal diseases such as scarlet fever and measles, possess an innate capacity, not to resist invasion, but to recover from the disease if exposed to infection, in a greater degree than individuals belonging to races which have not had experience of such diseases.⁴ This means that the body cells of such individuals are enabled by the exercise of the innate capacity of recovery to transmit to their cell descendants another kind of capacity, or the same capacity in a more perfect form, namely, a power to resist invasion—that is to say, a capacity to become adapted after experience to any given environmental change, is transmitted to cell descendants (not to offspring) as a capacity of preadaptation to a subsequent occurrence of the same change, independently of preceding experience by such cell descendants.

Further, it is well known that the degree of persistence of the immunity so acquired stands in direct relation to the specific nature and activity of the disease organism causing the disease, in so far as that specific character is associated with a capacity to establish widespread and intimate relations with the body cells of the host—in so far, in fact, as specific character goes with capacity to bring about generalized systemic infection.

Thus while reaction to the small-pox organism (which, as shown by the generalized rash, causes widespread infection) results generally in a lifelong immunity, reaction to the organism of vaccinia results in a more transient immunity.

Moreover, in vaccination the degree of persistence stands in direct relation to the number and size of the vaccine pustules, that is to say, to the volume and intensity of the reaction made. In this way vaccination reduces the persistence of acquired immunity because in vaccination use is made of an organism which has undergone varietal change and reduction in virulence.

Vaccine therapy, on the other hand, increases the persistence of "acquired immunity" by inducing a wider and more complete response on the part of the defensive cells to the disease organisms or their toxins.

Again, the persistence of "acquired immunity" in any given case is reduced by any kind of treatment which tends to destroy the disease organism or to reduce its virulence soon after it has gained an entrance into the body. Such chemo-therapeutic treatment acts by qualitatively and quantitatively reducing the reaction made by the organism to the disease. Thus after treatment by salvarsan in early stages the Wassermann reaction in the syphilitic patient becomes negative, and the immunity to subsequent reinoculation by the *Spirochaeta pallida* is less persistent than in cases in which the disease has pursued a longer course.

Antitoxin treatment probably acts in the same manner. The toxins formed by certain organisms which grow on the surface of the mucous membranes are fixed in the blood stream at an early stage of the infective process. Thus the reaction made against the disease organisms is limited to the blood stream, and its volume and intensity is thereby reduced.

Thus in the treatment of diphtheria by antitoxin, the saturation and fixation of the toxophore groups in the blood stream of the patient, by the foreign amboceptors furnished by the immunized animal, restrict the reaction to the body fluids, and prevent that intimate cell contact between toxophore groups and defensive cells, through the medium of sessile receptors, which would have occurred if unsatisfied amboceptor groups had not been injected in the shape of antitoxin. Consequently under such circumstances the body cells do not experience the same intense stimulation, and so do not respond so effectively, or suffer the same starvation, and so respond by cell regeneration and cell variation and selection, according to whichever view we adopt of the origin of new adaptive characters in somatic cells, when exposed to new stimuli.

This association between persistence of acquired immunity and intimacy of cell contact between toxins and defensive cells is also illustrated in an interesting manner by the suppurative diseases.

As a rule, and speaking generally, the pyogenic infections (that is, diseases associated with suppuration) do not confer an acquired immunity of long duration. The recurrence of localized staphylococcal and streptococcal infection foci is common in the same individual. This coincidence, which appears at first sight contradictory, is probably due to the fact that the reaction under such circumstances is a more or less localized response, limited, as far as cell contact goes, to the body cells and defensive cells in the neighbourhood of the foci of infection. This interpretation is rendered probable by the fact that in these diseases those attacks confer the longest immunity in which the infection is most generalized. Thus, septicaemia is more protective than localized abscess.

We may summarize the foregoing facts by saying that in "acquired immunity," when the capacity of recovery is exercised under normal conditions of response—that is to say, when a complete reaction has been made to a disease organism of a degree of virulence normal to its species—then the resulting immune state is usually lifelong, whereas, when the capacity of recovery has been exercised

under abnormal conditions of response—that is, where the reaction has been incomplete, or made towards a disease organism of reduced virulence, or where the reaction has been cut short by the early destruction of the disease organism or its toxins in the body of the host—then the resulting immunity may be transient.

In certain chronic or subacute diseases in which the offensive powers of the disease organism and the defensive capacities of the body cells are more evenly balanced, the slight immunity acquired may be so transient as to permit of frequently renewed infection. Thus, in tuberculosis the disease response is made up of a series of invasions or recrudescences, alternating with a series of partial or local recoveries; and the object of vaccine-therapy in such diseases is to stimulate the body cells to a larger and fuller reaction, with the hope that a more persistent and more complete state of immunity will so result.

So far we have been considering instances of what may be termed a normal relationship between the conditions under which the recovery from the disease has taken place and the persistence of the immune state which follows the recovery so made.

It is, however, necessary to mention certain exceptional cases in which this normal relationship is interfered with, or, at any rate, has the appearance of having been disturbed.

In certain individuals belonging to races which have had experience of, and therefore have undergone evolution in regard to certain diseases, an attack of any of the zymotic diseases such as scarlet fever or measles (generally a mild attack in childhood) may be succeeded by a second, third, or even a fourth attack, generally more severe, in adult life. Although more observations are needed on this point, there is some evidence which tends to show that this peculiar tendency to reinfection sometimes occurs in several members of the same family. In these exceptional cases the capacity to recover persists, while the acquired capacity to remain immune against subsequent infection is diminished or lost.

This leads us to consider the whole question of the persistence of “acquired immunity,” and to inquire what it is that occurs, when susceptibility to infection by any disease returns after a period of insusceptibility following recovery.

One point about this loss of “acquired immunity” seems well established—it has no necessary connexion with, and therefore is not caused by, any relaxation of the stringency of selection of resistant varieties of defensive cells. Thus the infection of small-pox may be entirely absent from the environment for long periods of time, and yet the immunity acquired against subsequent infection by one attack of the disease may be lifelong, whereas the infection associated with vaccination may be repeatedly introduced into the body, and the “acquired immunity” which results from vaccination, and revaccination, may be transient.

At the same time we are ignorant of the way in which the immunity of short duration conferred by vaccination differs from the immunity of longer duration conferred by an attack of small-pox. The difference cannot be wholly and entirely one of completeness or intensity of reaction, for the immunity to revaccination while it lasts is as complete as the immunity to reinfection by small-pox while it lasts. Moreover, the loss of “acquired immunity” seems to take place gradually and not suddenly. Individuals gradually become more susceptible to revaccination as time elapses since the last vaccination was practised.

It is interesting to compare this continuous fall in resistance in “acquired immunity” with the irregular and apparently sharply differentiated phases of susceptibility and insusceptibility to disease which occur during the lives of non-immunized individuals, who, although susceptible, and although exposed to infection on frequent occasions, only contract certain diseases under special conditions as yet imperfectly understood.

Apparently these irregular alternations of susceptible and insusceptible phases only occur in individuals who, through racial experience of disease, have inherited some innate capacity of recovery. For if a number of individuals belonging to a race which has not undergone any adaptation to a disease are exposed simultaneously to infection,

all, or the great majority of the individuals so exposed, at once contract the disease, that is, they are found to be all susceptible at the same time. This curious fact again points to the intimate connexion between capacity of recovery and the immune state which results from its exercise.

When we compare these exceptional cases with the constant association which undoubtedly exists between the completeness and intensity of the recovery reaction, and the duration of the immune state which results from it, we are led to perceive some relationship, not only between the persistence of acquired immunity and the exercise of the capacity of recovery from which it results, but also in a somewhat ill-defined manner between this varying state of susceptibility to infection during the individual life and the possession of an innate, racially derived, capacity of recovery, even although that capacity has not been exercised by the individual possessing it.

It will be interesting to know whether, in a reciprocal manner, the capacity of recovery undergoes any corresponding increase or decrease during these positive and negative phases of higher resistance and increased susceptibility, whether, in fact, such an individual recovers more easily if he contracts a disease during a period when he is only slightly susceptible, than he does if he contracts the same disease during a period of greater susceptibility.

Though it is difficult to explain all the cases in this way, it is of course possible that some of these irregular cases, in which infection occurs at one time and not at another in susceptible individuals, depend on the dose of infection received, and the route by which it gains entrance into the body. That is to say, an inherited capacity of recovery may be equal to successfully resisting a small dose of infection, but may be unable to deal with a larger dose rapidly introduced, until the capacity has been strengthened by exercise during actual experience of the disease.

But if we explain the facts in this way we are compelled to regard “acquired immunity” as a more complete form of the capacity of recovery, by the increased exercise of which the immune state itself has been brought about. We must, in fact, regard “acquired immunity” resulting from recovery from disease after individual experience, as the same thing as the “natural immunity” which results from the recoveries made by favoured individuals during racial experience of the same disease. This would mean that a capacity exercised in response to the stimulus of “use” has been converted into a capacity exercised in response to the stimulus of “nutrition.” Or, in other words, that a pre-experiential character, a preadapted capacity to resist invasion, arises as the result of the exercise of a post-experiential character, a capacity to recover after invasion. This, as we know, is a reversal of the order in which these two capacities have been evolved.

In reference to this difficulty, the question arises whether we are not still under some misconception as to the fundamental nature of the process by which “use acquirements” are brought about, and, as we shall see later, there are many strong reasons for concluding that the process of direct adaptation by “use acquirement” is itself the result of “variation and selection” among the physiologically differentiated parts of which the individual cell is composed, the result, in fact, of variation and selection on the intracellular scale.

However this may be, we must also remember that the recovery capacity, from the exercise of which immunity of the acquired kind results, is itself an innate, inherited character, which has arisen, like other congenital characters, during racial experience of disease.

There are some other isolated clinical facts bearing on the question of the duration of “acquired immunity,” but they are not sufficiently understood or sufficiently co-ordinated to be of much service from our present point of view.

In conclusion, it is desirable to analyse critically our conception of “acquired immunity.”

Do we regard the artificially-acquired immune state as a *progressive* change, a gain in some quality, a more perfect form of the capacity of successful resistance, or do we regard it as a *retrogressive* change, a loss of some quality or character which previously rendered the body cells susceptible to invasion by disease?

In terms of the side-chain theory, does “acquired

immunity" depend on an increased formation by the body cells of ambo-receptors which in the shed form fix, and neutralize the toxophore groups as soon as formed by the disease organisms in the blood stream, and so prevent infection on any considerable scale?

Or does "acquired immunity" depend on the loss of the already formed ambo-receptors, and the absence of any regeneration on the part of the body cells of those ambo-receptors which originally served as nutri-receptors, but which have been made use of by the haptophore group of the disease organism to anchor the toxins to the body cells, and which, therefore, only serve under the altered conditions to render the body cells vulnerable or susceptible to the disease organisms?

Or does "acquired immunity" depend on both these conditions? That is to say, does the exercise of the capacity of recovery result in the increased formation of ambo-receptors, which, when shed, are capable of directly neutralizing the toxins immediately they are formed, together with the cessation of any further regeneration of the same susceptible kind in the persistently sessile form?

There are still some facts which suggest that even this conception of "acquired immunity" as a double adaptation, the result of both "progressive" and "retrogressive" changes, is still imperfect, if it is limited to one group of cells—the defensive cell group.

In the first place it seems very probable that all the cells in the individual organism are concerned in the immunity response.

Though certain types of cells or cell groups have become, through evolution, more fully adapted than other cells to respond to the attacks of disease organisms and their secretions, and though it is upon these cells that the brunt of the attack falls, yet all the other cells, even the highly specialized nerve cells, are drawn into the struggle in certain circumstances, owing to their affinities for nutrient material of complex proteid composition analogous to that which form the secretions of disease organisms.

Thus we are led to regard "acquired immunity" as that adaptive change in the body cells and body fluids of any organisms which results from the exercise by some or all of the cells of the organism of a capacity of successful response to the activities of certain disease organisms.

The completeness and the persistence of the immune state so acquired bears a direct relationship to the number and kind of the body cells which have exercised this capacity of successful response, and the completeness with which the response has been made by those cells, and the fullness with which the characters so acquired have been transmitted to the cell descendants of the same cells.

Absolute and persistent immunity, therefore, means the possession on the part of all the body cells of efficient means of defence or the absence of susceptibilities permitting attack, or of a combination of both these characters. In many, probably in most, individual organisms in relation to many, probably to most, kinds of disease organisms, this state of complete adaptation does not exist in all the body cells at one and the same time in one and the same individual organism.

Finally, we conclude that the condition of "acquired immunity" so brought about is in some cases and in some diseases the result of direct adaptation on the part of the body cells exposed to changed conditions. It is the result of a process of "variation and selection" of an *intracellular* kind. In other cases it is represented by adaptation of an indirect kind on the part of the body cells exposed to environmental change, the result of a process of "variation and selection" of an *intercellular* kind.

Or it may be due to a combination of both these factors.

It is, indeed, possible to differentiate somewhat more closely diseases against which it is possible to acquire immunity on the one hand and diseases to which adaptation can only be brought about by natural immunity during racial experience on the other.

Reid⁴ has shown that, speaking generally, the diseases to which adaptation is brought about by acquired immunity after individual experience are diseases like small-pox or measles, which are characterized by acute infection, due to extracellular toxins (exotoxins) secreted by the disease organisms into the blood stream. While the diseases in regard to which acquired immunity is impossible or

difficult, and to which adaptation is brought about by natural immunity evolved during racial experience, are the more chronic infections, like tuberculosis and leprosy, in which the disease organisms do not secrete exotoxins in any quantity, while between these two extreme groups there are numerous diseases of an intermediate type in regard to which adaptation is brought about by both kinds of immunity, natural and acquired.

It is interesting therefore, to find that, approaching the subject of acquired immunity from another side, we have already reached the conclusion that the artificially acquired immune state which follows individual recovery from disease is partly the result of direct adaptation by use acquirement, and partly the result of indirect adaptation by innate variation among body cells.

Moreover, we found that it was in the chronic infections, like tuberculosis, characterized by destruction and regeneration amongst the body cells, that intercellular variation and selection occurred, and that adaptation was largely indirect.

While it was chiefly in the acute infections, like small-pox and scarlet fever, in which exotoxins were secreted by the disease organisms and antitoxins and antibodies were elaborated by the defensive body cells, and in which the evidence of cell destruction was less marked, that adaptation was chiefly direct and variation and selection of the intracellular kind.

This means, speaking broadly, that the antitoxin side of the immunity reaction represents the individual use acquirement, or *direct* form of adaptation, and the intracellular phase of variation and selection, while the phagocytic side of the immunity response represents the racial or innate and *indirect* form of adaptation and the intercellular phase of variation and selection.

It means, further, that, as we have already seen, the immune state is the result of one kind of adaptation in one group of diseases, and of another kind of adaptation in another group, and of both kinds of adaptation combined in a third group.

NATURAL IMMUNITY.

We must now consider that form of resistance to disease known as natural immunity, and compare, from the adaptational point of view, the conditions under which it occurs with those under which "acquired immunity" exists.

In the first place, "natural immunity," unlike the "acquired" form, does not depend on the previous exercise of any capacity of recovery by the immune individual. It is an innate character, and arises through the selection of more resistant individuals during racial experience of disease, and, like all *innate* as opposed to *acquired* characters, it is transmitted from parent to offspring.

But while these are the conditions under which "natural immunity" occurs in the ordinary way, there are certain further facts which are of interest from our present point of view.

It is well recognized that the line which separates the "naturally immune" species or variety of animals from the "non-immune" species or variety is a very narrow and apparently an arbitrary one.

For instance, albino rats are said to be immune to anthrax; whether this be entirely so or not, it is probably true that albino rats present a greater immunity against anthrax infection than wild rats. Now the essential difference between albino rats and wild rats is one of pigment. The whole question of pigmentation in reference to immunity requires further investigation. It is, however, difficult to understand how the absence of pigment in the body cells of any animal can be associated with an increased capacity of resistance to disease, or how the presence of pigment can assist the anthrax bacilli, or hamper the defensive cells in the disease response in such animals. Moreover, in the cancer reaction we find, on the other hand, the absence of pigment in the rat associated with increased susceptibility to cancer implantation. Thus Loeb found that he could grow sarcoma of a certain strain in albino rats, but not in ordinary rats (quoted by Gould in the Bradshaw Lecture).

If we regard "natural immunity," like "acquired immunity," as a state of adaptation brought about in different cases by a progressive variation, or a retrogressive variation, or by a combination of progressive characters of increased resistance with retrogressive characters of

diminished susceptibility of all body cells or of some kinds of them, then this peculiar association becomes more intelligible. Immunity to anthrax would then in the albino rat be a recessive variation, and would be associated with other characters of a recessive kind in the same animal.

In order to conceive of "natural immunity" as entirely due in any individual organism to entire absence of susceptibility to invasion, we must regard the body cells of such immune individuals as destitute of all receptors, all molecular cell groups of a kind susceptible to attack on the part of disease organisms and their toxins, both toxophore and haptophore groups. We must, in fact, regard the cells as destitute of all characters by means of which disease organisms are enabled to establish relations with them. Their nutri-receptors must be incapable of affording anchorage to the toxins of such organisms.

Having no vulnerable points, if disease organisms do gain entrance into the body, they can excite no reaction, and are treated as inert material or as food.

Such an example of "natural immunity" of the negative kind is afforded by the marsh turtle in regard to anthrax. This animal is naturally quite immune to the anthrax bacilli and its toxins, and seems to be quite unaffected by the injection of large doses of the poison into the body. Moreover, as the result of such treatment no antibodies and no antitoxins are found in the blood or body fluids.¹

The alligator, on the other hand, affords an example of "natural immunity" of the positive kind, in which the artificial introduction of anthrax bacilli is followed by the plentiful production of antibodies in the blood serum.

Such a negative form of "natural immunity" as that afforded by the marsh turtle would be paralleled in "acquired immunity" by those typhoid carriers, of which apparently a few are recorded, in which the typhoid bacillus can be demonstrated, but who give no Widal reaction.²

A "natural immunity," an insusceptibility of this kind really means an absence of established relationship, or rather the impossibility of establishing relationships between the body cells and the disease organisms to which the cells are insusceptible. In such circumstances there is no evidence of any reaction or defensive response by the body cells as the result of the introduction into the body of the disease organisms by natural or artificial means. It is either an immunity which precedes racial experience of disease, or it is the final stage of perfected natural immunity of the positive kind.

This conception of "natural immunity" under certain limited conditions as a negative state, a loss of susceptibility, derives some support from certain facts known about the responses made by organisms to food material and non-protein chemical substances.

Certain individuals and some species of animals are naturally immune to, that is, insusceptible to, the poisonous action of articles of food, alkaloids, and other substances. Thus the rabbit is insusceptible to belladonna, a chemical substance poisonous to other species of rodents. The entrance of this material into the body of the insusceptible animal is not followed by any symptoms of reaction. It is simply dissociated, and assimilated, or excreted by the body cells in the same way that ordinary food material is dealt with.

The presumption is, therefore, that if "natural immunity" under certain circumstances may be represented as a negative state, "acquired immunity" may be so represented also. But however large and important, or however small and unimportant, the part played by "natural immunity" of this negative kind in the disease response either in man or the lower animals, there can be no doubt as to the importance of the part played by "natural immunity" of the opposite or "positive kind."

This kind of natural immunity succeeds racial experience of disease out of which it arises, just as acquired immunity results from individual experience of disease.

It consists, as before outlined, in a perfected form of the recovery response, established during racial experience of disease, in which the body cells or the special defensive cells, or body fluids, or both, immediately respond in an adequate manner, and without the necessity for any preliminary training or reinforcement, to any attempt on the part of the disease organisms to invade the tissues. Unlike the negative form of "natural immunity" the positive form is an adaptation of a progressive kind. It is

due to the increased perfection of an old or the acquisition of a new character. Moreover it *succeeds* and does not *precede* racial experience of disease.

The greater number of examples (both in the human and other species of animals) of natural immunity to disease organisms and their toxins appear to be of this positive kind.

For instance, individuals belonging to immune races, and themselves naturally more or less immune to the tubercle bacillus, show a high opsonic index, that is to say, a high defensive capacity on the part of their defensive cells in relation to the tuberculous organism when inoculated with its toxins.

In many cases of natural immunity to different species of disease organisms in the lower animals the formation of antibodies and antitoxins in the blood in response to inoculation by the disease organisms or their toxins to which such animals are naturally immune, strongly suggests that the immune state is the outcome of an adequately adapted defensive machinery existing in the body cells of such animals. Interesting facts confirmatory of the view that "natural immunity" of this kind is a progressive adaptation, a state of more perfect defence, are derived from a study of the allied haemolytic and cytolytic reactions observed in such naturally immune animals.

Lastly, it is quite possible that "natural immunity" in some cases and under certain conditions may be due to a combination of the negative and positive forms. It may arise during the process of adaptive evolution against disease as a *progressive* change in one way, and a *retrogressive* change in another way; as a *gain* of a character in one direction and the *loss* of a character in another direction; as an *increase in defensive capacity* in some cells and a *diminution in susceptibility* in other cells.

Nor is this division of "natural immunity" into two kinds merely a matter of superficial interest. It assumes additional interest when regarded from the hereditary and evolutionary point of view. Thus regarded it becomes evident that the *positive* must have succeeded the *negative* form in the history of any species.

If, finally, we regard the "naturally immune" state as a whole, irrespective of any artificial division into kinds or varieties, and irrespective, also, of the different ways in which the different varieties may have originated, we find certain features for the most part the opposite of those found in the "acquired form."

Unlike "acquired immunity," *natural immunity* is transmitted from parent to offspring. It is almost invariably, under normal conditions at any rate, lifelong in duration, and so does not exhibit that variability in persistence which is characteristic of the acquired form.

From our present point of view the most important point about natural immunity is that it represents an *innate congenital* character or capacity. It arises during the growth of the individual, like other congenital characters, in response to the stimulus of nutrition, and independently of any individual experience of disease.

About this there can be no doubt, with the exception perhaps of the extreme negative variety which represents an entire absence of both individual and racial experience of disease, the naturally immune state is an adaptive state, the outcome of the selection of more resistant individuals during racial experience of disease.

RECAPITULATION.

Having considered "natural" and "acquired" immunity, and having examined and compared the conditions under which they respectively occur, we are now in a position to ask the final questions which it is the object of this inquiry to attempt to answer:

1. Is "acquired immunity" the outcome of *use acquirement* or of *innate variation*?
2. What is the fundamental nature of a "use acquirement"?
3. Does it originate in a biological process essentially different from that by which innate characters arise, and, if so, in what essentials do the two processes differ?

It will be convenient, in the first place, to consider the resemblance in the conditions under which "use acquirements" and "innate characters" originate.

In both cases the new characters arise during the gradual process of cell growth away from, rather than in

the direction of, the hereditary cell tendency. In both cases they arise from the interaction of two factors—*environmental change* on the one hand, and *cell potentiality* on the other.

All cellular variation must ultimately be explained in terms of interaction between outer and inner forces. But while in use acquirement the new character, the new variation is a reaction to the *use* factor in the environmental stimuli, and has the appearance of being a "direct" response, in spontaneous or innate variation the new character so arising is a reaction to the *nutritional* factor in the environmental stimuli, and has the appearance of being an "indirect" response.

Further, the study of the immunity and disease response has shown us that when the use and nutritional factors are combined in one and the same environmental stimulus, as in the case of the response made by the defensive cells to disease organisms and their toxins, then the new acquirements, or the new variations, whichever way we describe them, tend to arise as "direct" adaptations to the environmental change.

This fact suggests that, after all, although they differ as to the conditions under which they occur, the processes of adaptation by "use acquirement" on the one hand, and by "innate or spontaneous variation" on the other, are not two essentially different processes, but one and the same, taking place among cell parts in the one case and among individual cells in the other.

Thus, in the response made by the neuron to any change in the stimuli of sound, light, heat, contact, or any of those vibrations which constitute the various kinds of nerve stimuli, we encounter the process of "use acquirement" in the most highly developed form. Not only are the two factors, use and nutritional stimuli, widely differentiated in the environmental influence to which the nerve cell is exposed, but the response made by the nerve cell to the stimulus is widely and definitely differentiated in regard to these same two component factors also. For the neuron responds to the most delicate alterations in the use stimulus, while the nutritional stimuli, which reach it at the same time, remain constant or may vary in a contrary direction. Moreover, as a consequence of this differentiation and highly organized condition, the nerve cell has lost the power, at any rate, in adult life, in the fully developed form, to undergo cell division and therefore to transmit to cell descendants the acquirements which it has made.

Unlike the process by which adaptational change is brought about among other kinds of cells, and unicellular organisms, and to a certain extent also among the defensive cells, a process characterized by intercellular struggle for existence, cell destruction, and cell regeneration, and cell variation; the process of "use acquirement" by which a nerve cell becomes adapted to changes in the nerve cell environment is characterized by an absence of any struggle for existence, or of any injury or destruction to nerve cells, or of any regeneration of nerve cells, but it is characterized by changes of an intracellular kind, by new combinations in molecular groups, and by the discarding of less fit molecular groupings, and by the waning and waxing of Nissl bodies.

Both processes are alike in this, that they are due to variation and selection among units exposed to change, but in innate variation the "variation and selection" concern individual cells, while in "use acquirement" they are intracellular, and concern cell parts.

In the intercellular form the possibility of variation among cells as individual units is closely dependent on the degree of organization of the cells concerned. The more highly specialized and differentiated nerve cells are incapable of varying among themselves, since they are incapable of cell division, while the less highly organized phagocytes or disease organisms would seem to be capable during cell proliferation of innate variation.

In the intracellular form of adaptive response and variation we find the same conditions, for while the nerve cell as a whole is a highly specialized cell, the cytoplasmic substance of which the young and adaptable nerve cell is composed is highly labile and capable of much molecular change and rearrangement.

In both cases alike the modified capacities and the altered activities are due to the influence of environmental stimuli acting on hereditary potentiality, in one case of the

cell regarded as a unit, in the other case of the physiologically differentiated molecular biophores of which the cell is composed.

If we are right in thus regarding a "use acquirement" as a process of variation and selection in an intracellular form we should expect that any character so originating would be transmitted to cell descendants, just as the new characters which arise as the outcome of intercellular variation are so transmitted, and such, indeed, we find to be the case.

Whenever a new character arises in any cell as a "use acquirement"—that is, as a variation of a qualitative or quantitative kind during growth of physiologically differentiated cell parts—it is transmitted in cell division to the cell descendants of that cell. The facts concerning "acquired immunity" illustrate this point very fully. The acquirements made by the defensive cells during the exercise of the capacity of recovery are transmitted to the cell descendants of the defensive cells.

We also see the reason why acquirements made by the body cells of the individual are not transmitted to offspring, for only those variations which occur in or (since the process of origin is the same) only those acquirements which are made by the germ cells themselves are transmitted to germ cell descendants—that is, to new individuals. Acquirements made by body cells are only transmitted to the cell descendants of those body cells, and then only under definite conditions.

In fact, the transmission of new characters to cell descendants is so bound up with adaptation, and is of such vital importance to the welfare of the individual organism that it has itself come under the influence of natural selection and has come to possess selection value.

For instance, it has not apparently been to the interest of the individual that automatic and fixed modes of response acquired by nerve cells and the nervous system as a whole should persist indefinitely or be transmitted to nerve cell descendants. Hence the nerve cells have lost the power to multiply, and so do not transmit acquired characters.

It is not in the interest of the organism that muscular hypertrophies, the result of "use acquirements" should persist in the absence of the special stimulus which called them forth, hence "use acquirements" in the muscular system depend on a graduated exercise of a capacity of muscle cell division, in response to the use stimulus, and when the stimulus ceases to operate the muscle cells cease to divide.

In the response made by the defensive cells to disease organisms, on the other hand, it is to the interest of the organism that the capacity to resist disease should persist, hence the defensive cells transmit to their numerous cell descendants the new capacities which they themselves have acquired during the reaction to disease. And if in addition (as I think the evidence clearly shows) it is to the interest of the organism that the capacity to resist disease should persist in an economic form, that is in a form in which it can be immediately exercised without any necessity for a renewed exercise of the capacity of recovery, as it can be in the "acquired immunity" form, then we can understand how it has come about that this capacity to recover from infection has been converted into a capacity to resist invasion.

As to the change in character or form undergone by the capacity so converted, it may be due to changes in the defensive cells of a *progressive* kind, to a more perfect form of the recovery response in which a permanent machinery of defence is always ready, or it may be the outcome of a *retrogressive* change, a negative variation, a loss of susceptibility on the part of the body cells or some of them. In terms of the side-chain theory it may be due to a failure on the part of the defensive cells to reproduce susceptible receptors capable of affording anchorage to the haptophore and toxophore groups of the disease organisms.

It is very necessary to remember that the immune state and the capacity to recover are both adaptations, and that the whole disease response is an attempt at mutual adaptation on the part of two highly variable and extremely prolific kinds of organisms, the defensive cells and the disease organisms. In fact, the very life and death character of the struggle and the stringency of the selective process has placed a high selection value on both these capacities—Variability and Fertility.

But the different species—that is, the different morphological forms of the disease organisms—far outnumber the different kinds of the defensive cells; hence the same defensive cell must be adapted to and must be able to resist the attacks of many kinds of disease organisms. Hence it becomes necessary that the individual cell should obtain new defensive powers by “use acquirement”—that is, by varying “intracellularly” in response to environmental changes as well as by “intercellular” variation. Farther, in view of the changing capacities and changing activities of the disease organisms, a moving equilibrium or equality of adaptation can only be maintained by losing vulnerability in some directions and gaining increased resisting powers in other directions on the part of the defensive cells and the disease organisms. We know that in the struggle between individual organisms adaptation has been brought about by retrogressive as well as progressive variations; in fact, in some cases the former have outnumbered the latter. It is probable, therefore, that retrogressive as well as progressive variation has occurred on both sides during the struggle between individual cells and cell parts.

It is probable, in fact, that the advantages—the increased adaptive capacities which have arisen as the result of variation amongst the disease organisms, and the increased adaptive capacities which have arisen in defensive cells as “use acquirements”—both equally owe their origin to progressive and retrogressive variations, in the one case largely in the intercellular, in the other case largely in the intracellular as well as the intercellular field.

As before indicated, the crucial difference between “innate variation” and “use acquirement,” between “inter-” and “intra-” cellular selection is this: in the former the new characters do not arise in the individual cells exposed to the change, for, these being unable to make the adaptive response, perish, but in related cells which possess the more suitable capacities, and which therefore survive.

In the latter case, although the new characters arise in more fit physiologically differentiated cell parts the discarding of the older cell parts exposed to the environmental change does not necessitate the death of the cell as a whole.

But while they differ crucially in the kind of units which vary and which are selected, both processes are essentially alike, inasmuch as both depend on variation and selection.

The old question which Lamarck and Darwin set themselves to solve in the world of species still confronts us in the world of the individual organism. They were struck by the sharply accentuated discontinuity between species on the one hand, and they were troubled by transitional forms on the other. They asked the question, How does one specific character arise out of, merge into, and give rise to another specific character? Lamarck answered the question in one way, Darwin in another.

Modern bacteriological attitude to the evolutionary process as it affects the different varieties and different capacities of defensive cells is still in the Lamarckian stage, and the problem, moreover, is rendered even more obscure and more difficult by reason of the very fact that in the case of the body cell and the disease organism we are dealing with component parts of the individual organism, which are themselves unicellular organisms, and in such organisms the continuity between cytoplasm and nucleus is much more perfect than the continuity between body cells and germ cells in the multicellular organism.

Hence in unicellular organisms, such as the defensive cells, environmental change exercises through the cytoplasm a much more direct influence on nuclear activity. Hence variation assumes a more directly adaptive character. Hence, also, the greater difficulty in distinguishing between “innate variation” and variation due to “use acquirement.” Hence the great probability that they are both a process of variation and selection—one *intercellular*, one *intracellular*—and the further probability that the one process has arisen out of the other.

But the analogy between the progress of evolutionary thought in the ontogenetic and phylogenetic field goes deeper still.

Confronted by the difficulties to be surmounted in

accounting for “spontaneous” variation—that is, in associating germ-cell variation directly with somatic-cell variation, the result of environmental change—Weismann fell back on variation and selection among the different ids and determinants which he had already assumed in the germ cells, as forming the material basis of variation and hereditary transmission—that is, he fell back on variation and selection of an intracellular kind.

In like manner Ehrlich, confronted with the difficulty of accounting for direct adaptational response in defensive cells, has assumed the existence of a complex machinery of “receptors” in the defensive cells to explain the manner in which the immunity response to disease organisms is brought about.

There is therefore some precedent for going a step further and assuming, as we have now done, as a working hypothesis, a process of variation among the physiologically differentiated parts which compose the cell itself, together with a selection of the more favourable of the variations so occurring.

The result of the foregoing examination into the conditions under which acquired immunity occurs tends to show that the process by which the defensive cells acquire new characters and new capacities of offence and defence is a process of variation and selection, partly of an intercellular and partly of an intracellular kind.

It tends to suggest, in fact, that “use acquirement” is a form of adaptation to environmental change brought about by variation and selection among intracellular units instead of among individual cells.

REFERENCES.

¹ Metchnikoff, *Immunity*. ² Ledingham, Report to Local Government Board, 1910, p. 118. ³ Ehrlich, *Studies in Immunity*. ⁴ Reid, *Principles of Heredity*.

THE HULTON COLLIERY EXPLOSION.

BY

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HISTORY OF EVENTS.

THE explosion, lasting about a couple of seconds, produced a dull, heavy roar, distinctly heard four miles away, occurred on December 21st about 7.50 a.m., when the men had been working about an hour. I arrived about 8.20 a.m., and found the manager, Mr. A. Tonge, and the mechanical engineer and officials busily engaged in rescue work. Some colliery proprietors and Sir William Hulton, on whose land the pits are situated, were already on the scene, endeavouring to find out what was the matter, and anxious to give every assistance possible.

Drs. Blakemore and Russell, Leigh and Racker, were soon upon the scene, and we remained throughout the day attending to casualties. Medical men from all the surrounding districts were soon present and ready to render assistance.

The engine-house was prepared as an emergency station, while the Miners' Union room, lent by Mr. Roughley, was used as a temporary hospital under the charge of Dr. Mallett of Bolton Infirmary. Stretchers, splints, and surgical materials and blankets were supplied by the colliery officials. The Westhoughton district nurses, Nurses Gallimore, Jones, and Green, several nursing sisters of our ambulance division under Lady Superintendent Caldwell, together with ambulance carriages, were in attendance, so that the medical arrangements left nothing to be desired, and we were fully prepared to deal with any emergency. There were, in addition, a good number of well-trained ambulance men soon on the scene, who did good work on that and the succeeding days.

Hour after hour of anxiety was passed by the enormous crowd, uncertain as to the extent and consequences of the explosion, and doubts as to whether any would be found living became the current feeling, especially when the condition of the first casualty, brought up between 10 and 11, was seen—a youth, Gibson, aged 15. He was entirely nude, not a shred of clothing left on him. He was badly burnt all over, and thickly coated with coal dust. He was just alive, unconscious, and breathing spasmodically. There were no fractures or wounds; the hair was completely burnt off. He lived but a short time, death being due to the shock of the explosion.