THE
JOURNAL OF
COMPARATIVE PATHOLOGY
AND
THERAPEUTICS.

VOL. XVII.—No. 4. DECEMBER 31, 1904. PRICE 2s. 6d.

THE EVOLUTION OF IMMUNITY.

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My object, in this paper, is to endeavour to suggest some thoughts which force themselves upon us when we set ourselves to enquire into the problem of the origin of the phenomenon known as immunity, and first of all let us be perfectly clear as to the meaning of that term.

When we look carefully at the various species of highly organised animals with a view to ascertaining their specific differences, we find that it is not in structure alone that one species of animal differs from another. There are other characteristics no less striking that separate species, characters which are doubtless connected with their ultimate material structure, but which it is impossible in the present state of our knowledge to correlate with specific morphological variations. Thus we find that almost all vertebrate species of animals exhibit differences in their liability to diseases, differences either of degree or kind or of both. All vertebrate species have their own special mental qualities, exhibited by varying degrees of intelligence and acuteness of sense perceptions. Some appear to be possessed of almost human reason, at any rate they are extremely susceptible to educative influences, whilst others resist these influences almost entirely. In a word, specific differences embrace every possible variation in physiological activities, whether these be what we term mental, moral, or physical. Taking one only of these classes of variations, we may from that arrive at a definition of immunity which, with but slight verbal alteration, would be applicable to all.

It is convenient to take the physical differences as indicated in the power of resistance to disease, because this special aspect of immunity (and it is only one aspect) is of most importance to us as scientific students.

Two or three well-known examples will suffice.

Horses are very susceptible to glanders, it is the most fatal equine disease ; horned cattle are immune to glanders ; goats and sheep are intermediate. Some horses are more susceptible than others. Cattle and sheep are very liable to anthrax ; but Algerian sheep are almost immune to anthrax, and horses are not nearly as susceptible as cattle.

Tuberculosis, the most wide-spread human disease, exhibits great variation in its attacks upon animals. Cattle are most susceptible, while it is far less common in sheep and goats. Field mice are susceptible to tubercle, whilst house mice and white mice are resistant. Finally, man suffers from many conditions which do not attack the lower animals, and *vice versa*.

In the light of these facts relating to the varying incidence of disease, it is not difficult to frame a definition of immunity sufficient for our purpose. We may say that : "Immunity is that condition of an organism or tissue in virtue of which it is able to resist infection either partially or absolutely."

We are not concerned just now with the exact nature of this condition ; that is a complicated question which it is not my purpose to deal with now. The question I wish to ask is : Can we account in any degree for the origin of the phenomenon, or for the differences shown by animals in relation to it ? In other words, what can we discover as to the course of the evolution of immunity, and how have animals become immune ?

It is only necessary to state such a problem in order that its enormous importance should be realised. The possibility of becoming immune to destructive agencies and deleterious influences of any and every kind, is the greatest hope of mankind, and there can be no more interesting and important enquiry than that of how specific immunity has been evolved in the past, and how its evolution is progressing in the present.

When we come to look a little closer at the manifestation of this phenomenon of immunity, we at once discover that it presents itself in two perfectly distinct forms. It is seen that there are two forms of immunity to disease. For example, some species exhibit an innate immunity to certain infections, such as horned cattle to glanders, as above-mentioned. The immunity is inborn in the species. But there is another form of immunity which is not inborn but acquired, as an example of which may be mentioned the immunity of human beings to such diseases as smallpox, measles, and scarlet fever, after recovery from an attack of these conditions. This immunity is acquired naturally by the individual who recovers. (There is also an acquired immunity, the result of specific treatment by inoculation, but this we have not to consider now).

Immunity is therefore (*a*) innate, or (*b*) acquired, and the problem to which I wish to draw attention now is first, how is innate immunity evolved ? and second, how is the power of acquiring immunity evolved ?

It will simplify matters if we restrict ourselves to the evolution of immunity to disease in human beings, because we have more facts on this aspect of immunity than any other, and we may be quite certain that the same laws have produced immunities to other influences.

We may select smallpox, tuberculosis, and measles, as well-known diseases to investigate, and our own race, the Anglo-Saxon, as a case in point.

It will at once be evident that smallpox and measles are on a different footing to tuberculosis, for, whereas the patient who recovers from an attack of the two former is relatively or absolutely immune from future infection, the exact opposite is the case in tuberculosis—one attack renders the patient more liable to a second.

As the case of smallpox is complicated in this country by the prevalence of vaccination, I will leave that for the present and consider the other two, measles and tuberculosis, against which we have no specific treatment as yet, and whose effects on a race may therefore be traced as those of any other factor which contributes to the evolution of any race.

Measles may be said to be endemic in most civilised countries, though by no means equally common. "It is liable to some epidemic extensions, the recurrence of which in European communities is characterised by striking periodicity. In isolated communities the disease will occasionally die out altogether, but after the lapse of some years, during which a susceptible population has been growing up, the importation of a fresh case is liable to result in a fresh outburst which may rapidly assume pandemic proportions. This was well illustrated in the case of the Faroe Islands, into which, after an immunity from measles lasting sixty-five years, the disease was re-imported in the year 1846, with the result that in the course of five months more than three-fourths of the entire population were attacked; and the same thing in even more marked degree was seen in Fiji in the year 1875, when the disease was imported into the country, it is supposed, for the first time. In this instance, so extensive was the outbreak, and so rapid was its spread, that more than one-fourth of the population actually died of the disease within three months."¹

Such a catastrophe as that which occurred in Fiji is nowadays quite unknown in Great Britain although measles is constantly with us. It is here considered, apart from its sequelæ, a trifling complaint, which most children recover from with no further treatment than any careful mother may carry out. And yet, recollect, it is extremely common. What do these facts mean, but that our race has become immune, not to measles, but to the danger from measles; in other words we have evolved the power of acquiring immunity to measles, a very different thing from evolving immunity to the disease itself, and a thing which obviously neither the inhabitants of Faroe or Fiji had evolved. Introduced into a new locality for the first time, measles is seen to be an extremely fatal condition. If that locality be isolated the inhabitants become immune for a time, and then again susceptible, while in a large community such as ours what takes place is that in course of time the race is able to survive the disease, although it never becomes immune to the infection. Coming amongst the Fijians, one-

¹ "Encyclopædia Medica," Vol. VII., pp. 348, 349.

fourth of the population died forthwith, because they had not had time to evolve the capacity for acquiring immunity against it.

So that, whatever the exact explanation may be, which is the problem before us, it is very evident that the result of long continued exposure to the ravages of measles has resulted in the evolution amongst Englishmen of a greatly increased power of resistance to the effects of measles, a power, in other words, of acquiring an individual immunity, without which evolved power a race exhibits a great mortality from this infection. It is quite evident, also, that we shall never evolve immunity against the infection, but that as time goes on we shall exhibit an increased capacity to resist the effects, that is an increased power of acquiring immunity.

The history of smallpox is from the point of view of race evolution on similar lines.

"Smallpox is known to have been indigenous in Eastern countries for nearly two thousand years, its earliest records coming from India and China. The first appearance in Europe seems to have been in the sixth century, when fatal epidemics broke out in southern France and northern Italy. England appears to have been first severely visited about 1241, and at this time the disease was widely spread through Europe. From Europe smallpox was conveyed to the American continent, first to Mexico in the year 1527, where it raged to a fearful extent, destroying millions of victims, and spreading thence to other parts of America, which it gradually overran."

"Smallpox has been one of the greatest, if not actually the greatest, of the scourges of mankind; no form of disease has been more destructive of life, none has brought more misery in its train. In Europe not a decade passed in which the disease did not overrun great tracts of country, decimating the inhabitants in its progress. In England in the seventeenth and eighteenth centuries a large proportion of the medical literature bears upon the treatment of smallpox, showing that that disease was the common form of illness which the physicians of those days were called upon to treat." Nowadays in this country one may be many years in practice without seeing a single case.

"The records of the mortality from smallpox in the eighteenth century show that it accounted for nearly one-tenth of the total mortality, that neither age nor sex nor social conditions afforded protection, and that of those who recovered from it the number permanently scarred or disfigured formed so large a proportion of the population that unmarked persons were comparatively few." Indeed, to be unmarked constituted in a woman a claim to be considered a beauty.¹

At the present time in European countries smallpox has been robbed of much of its terror owing to the introduction of vaccination, which is an artificially acquired immunity, but, even apart from vaccination, smallpox is not the scourge it was formerly, that is to say, the death rate from it is not so high in those attacked. The population remains susceptible to its infection, but has evolved the power of resisting its effects to some extent, so that a greater proportion of cases recover. Just as in the case of measles, so in smallpox, there is no sign of any evolution of an innate immunity,

¹ "Encyclopædia Medica," Vol. II., pp. 213, 214.

people are as naturally susceptible as ever; indeed, susceptibility is almost universal, but, as in measles, where a nation has been exposed to its ravages for many generations, they gradually evolve the power of acquiring immunity in individuals, and so reducing the death-rate percentage of cases.

What about those races into which smallpox is introduced for the first time? History has no more striking records than those relating to this matter. The experiment has been carried out upon such a colossal scale, and with such dire results to the nations, that he who runs may read. As we have said, they are literally decimated when first exposed to smallpox. Indeed, so powerful is the smallpox poison in a new blood that even the attenuated virus of vaccination is more than a nation unused to smallpox can stand, and, as in the case of the Esquimaux, they will die from it. We, who have had smallpox among us for centuries, are evolving a capacity to recover from infection, a capacity which enables us to make use of vaccination as a safeguard, because that attenuated virus causes us as a rule no more than a temporary and slight discomfort, while at the same time it confers an immunity which lasts for some years. Our resisting power to smallpox is not yet on a par with that to measles, but it is proceeding upon precisely similar lines, and for precisely the same reasons. What those are we shall see presently.

But now consider the case of tuberculosis for a moment. Tuberculosis is the most widespread of all human diseases, and the majority of the higher vertebrates are also susceptible. It has been said that 7 per cent. of mankind die from its effects. It is due to an infective organism, and in its most common form—consumption—the disease “for very many centuries has ravaged the Old World, especially such crowded parts of it as England. But Englishmen now increase and multiply in cities and towns, the natural breeding places of consumption; whereas, under like conditions the inhabitants of the New World, where consumption was unknown till recently, perish. When infected with consumption by white men they tend to extinction everywhere, even in rural districts.” Whole tribes of native races have perished as the result of their first contact with this white man’s scourge. But the white man crowds himself in millions into the slums of London, Manchester, Glasgow, Edinburgh, and numbers of other large cities, and still increases and multiplies.

Now note: one attack of consumption does not confer a lifelong immunity upon the patient, as is commonly the case in measles and smallpox; on the contrary, one attack of any form of tuberculosis leaves the patient more susceptible to the disease than he was before. In order that he may have a chance of survival, he must be taken out of infectious surroundings and tended with the utmost care. The patient recovered from smallpox can face an epidemic with impunity, but the tubercular patient who has recovered must avoid the source of the evil. How then is it possible for Englishmen to increase and multiply under the conditions of our slums which are so favourable to tuberculosis? Obviously the only possible answer is that a great evolution against tuberculosis has occurred, but in this case what has been evolved is an inborn or innate immunity. No increased power of resistance is to be found; the explanation is that the infection itself is resisted. The race does not recover from the infection, as it does

from measles ; it resists it. In the one case the capacity to recover, the power of acquiring immunity, has been evolved ; in the other case the capacity to resist, an innate immunity, has been evolved.

Such then are the facts of the case. What is the argument of the problem? How have these results come about? How is immunity evolved?

It is quite clear that it would be ridiculous to place this problem outside the scope of any other phase of physical evolution. The explanations of the evolution of one part of man's nature are to be applied to all parts. Those explanations during the past hundred years have centred themselves round two main views, the Lamarckian and the Darwinian, and it becomes of great interest from the point of view of the general question of evolution to see which theory is capable of affording an explanation of the evolving of immunity.

"Only two theories of evolution are possible, or even thinkable. All other theories, of which several have been enunciated, are from the nature of the case, mere variations of those two."

"Evolution must proceed by the transmission of inborn traits, or of acquired traits, from parent to child, and by their accentuation during succeeding generations. Even if we regard the course of evolution as designed and predestined, no other method is thinkable, because no other traits than the inborn and the acquired exist in living beings." "Lamarck, because he first formally enunciated it, gave his name to the one theory ; Darwin, for the same reason, gave his to the other."¹

Lamarck held that characters which have been acquired during the life of the parent are transmissible to some extent to the offspring, and that the accentuation of these transmitted traits during successive generations was responsible for evolution. In other words, the Lamarckian view is "that variations arise through the transmission of parental acquirements to the child, and that evolution results from the repetition of this process during succeeding generations."²

Darwin, although he thought that some acquirements were transmissible, perceived that this explanation was utterly inadequate for all the facts, and insisted that variations in offspring occurred quite apart from any previous acquirement by the parent ; that they arose independently of any known law, and hence are termed spontaneous variations. He further insisted that evolution was mainly due to the selection by Nature of those variations which gave their possessors some advantage in the struggle for existence, and so it comes about that Darwinism is summed up in the phrase, "The survival of the fittest by Natural Selection in the Struggle for Existence."

The modern followers of Darwin go further still, and assert that Lamarck was entirely wrong ; that acquired characters are never transmitted, and that Darwinism, therefore, is the whole solution of evolution. "It is curious that during every age men have accepted as a belief the method of evolution as laid down by Lamarck, but have sought to improve their own plants and animals in the manner described by Darwin."² That is to say that breeders select well-marked spontaneous variations to breed from, not animals which acquire new characters in their adult life.

¹ "Alcoholism."—G. Archdall Reid, pp. 7, 8.

² *Ibid.*, p. 8.

Now apply these two views of the method of evolution to the phenomenon of immunity.

According to Lamarck, characters acquired by the parents are transmissible to the offspring. Disease is an acquirement; so is immunity to disease after recovery from an attack. We should expect on this view that diseases against which the individual cannot acquire immunity would be transmitted, whilst in the case of the parent becoming immune that immunity ought to be transmitted likewise. It is at once apparent that the facts of the two diseases we have considered, measles and smallpox, do not accord with these expectations. Generation after generation of parents acquire a life-long immunity to measles as the result of an attack, and yet the children of these parents are born still susceptible to the infection. They are just as liable to measles as were their parents who acquired immunity. The children in their turn have to acquire their own immunity. The same is true of smallpox. True, the succeeding generations of offspring exhibit an increasing power of recovery from these diseases, but that cannot be explained by the view of Lamarck. On the other hand, if a parent acquires tuberculosis, his children on this view should be born with tuberculosis, which they are not. If tuberculosis were transmissible from parent to offspring, it is quite obvious that in each succeeding generation there would be more and more consumptives, and the race would progressively degenerate. We have seen that as a matter of fact the precise opposite is the truth; that the longer the race is exposed to the disease, the less severe is the result, the fewer the deaths. Immunity to tuberculosis could not be evolved on the Lamarckian hypothesis, because the individual does not acquire it to transmit.

Lamarckianism, then, offers no explanation of the evolution of immunity, nor does it explain the origin of the power of acquiring immunity.

Turning now to Darwinism, the doctrine of the survival of the fittest in the struggle for existence, we are at once impressed with the thought that, if this doctrine be true, disease must be a potent factor in the evolution of man, for it is the most ruthless of all selecting agencies. In the struggle for life against infectious disease, other things being equal, it is the fittest which survive, and the fittest in this case are those individuals who are naturally immune, or who possess the greatest capacity of acquiring immunity. In the case of measles and smallpox, out of five hundred persons attacked a certain number will be able to recover from the disease, that is, will be able to acquire immunity against it. We see that their acquired immunity is not transmitted, their children also take measles and smallpox; but the power of acquiring immunity, because inborn, is transmitted to the offspring, and, inasmuch as the parents are selected, the power of acquiring immunity tends to increase in succeeding generations. The most susceptible die out, leaving the least susceptible to carry on the race, and this selection of the fittest acting over many generations will gradually result in the evolution of an increased power of recovery, of acquiring immunity. Hence, the longer measles and smallpox and other similar diseases act upon a population, the more will the unfit be eliminated and the less susceptible will successive generations be. Hence the general law that "Every race is resistant

to every deadly disease strictly in proportion to its past experience of it."¹ Hence Englishmen can live and multiply although constantly exposed to measles and tubercle, where whole tribes are wiped out on their first introduction to these infections.

In the case of tuberculosis, a disease against which the individual acquires no immunity, what should we expect on the principle of the survival of the fittest? Obviously that only those who possess an inborn immunity will survive, and that the most susceptible will perish. The inborn immunity is transmitted to offspring, and, on account of the elimination of those who have it not, in each succeeding generation there will be a greater proportion of immune individuals. They are selected by nature to carry on the race, which for this reason gradually evolves an inborn immunity. Hence, numbers of Englishmen can live and multiply in badly lighted and ill-ventilated slums, although constantly exposed to the tubercle bacillus, whilst the native, even in the open wilds, is carried off in large numbers. "These diseases are so prevalent within their areas of distribution that no man escapes infection unless he be immune, nor death unless he be resistant."

Plainly there has been great evolution against disease, but also plainly it has not been by the transmission of acquirements, but by the elimination of the unfit by natural selection.

The conclusion we are inevitably driven to, therefore, from a study of the past history of the relations of man to infectious disease, is, that both innate immunity and the power of acquiring immunity are evolved in the same manner as are other characters, namely, by natural selection of the fittest to survive.

"If the effects of disease are transmissible, then their effects must accumulate generation after generation. The son must start with the parent's constitution plus the effect of the parent's disease, the grandson must start with the son's constitution, plus the effect of the son's disease, and so on. It is plain on this hypothesis that a race afflicted by any disease should undergo evolution or degeneration, evolution if the disease tends to strengthen the individual against subsequent attacks by conferring immunity, degeneration if it tends to weaken him. On the other hand, if the effects are not transmissible, then a race afflicted by deadly disease would change equally, would undergo evolution equally, but not degeneration. For men differ individually in their power of resisting disease. Deadly disease is therefore a selective agency. It weeds out the less resistant to it, leaving the race to the more resistant. Therefore, on this other, this Darwinian hypothesis, a race afflicted by a disease should grow more and more resistant to it. Moreover, since resisting power against one disease does not imply resisting power against any other—for example, since resisting power against consumption does not imply resisting power against malaria—every race should grow resistant only against the particular death-dealing diseases by which it is afflicted."²

If I have made myself clear, it will be seen that the evolution of immunity to any given noxious agency is brought about by precisely similar means as the evolution of any other human characteristic.

The naturally immune are selected to carry on the race, in so far

¹ "Alcoholism."—G. Archdall Reid, pp. 9, 51.

² *Ibid.*, pp. 34, 35.

as that special agency is a selecting one. Those who can acquire immunity likewise survive, and that power is reproduced in their offspring. In the one case an inborn immunity is evolved, in the other an increased capacity of resistance. In both cases the result of continuous selection by disease, acting on any race, is to make that race resistant just in proportion to its past experience of the condition.

To tubercle then we are becoming naturally immune; the susceptible have perished and are perishing. To measles we are still susceptible, but its dangers are a thing of the past, and the longer we are subjected to the infection the more resistant shall we become, because the least resistant perish.

And, so, taking resistance to disease as the test of fitness, the evolution of immunity is the result of the operation in the sphere of disease, as in all other spheres, of the great law of natural selection by survival of the fittest.

GLANDERS.¹

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HISTORY.

ACCORDING to Bass,² the earliest recorded reference to glanders is found in the writings of Aristotle, who describes the only disease of the ass under the term *μηλιν* (*melis*). The description is meagre, since the passage merely states that the disease begins about the head, with a purulent discharge from the nose, and proves fatal when it extends to the lungs. But the same author has also been credited with a knowledge of farcy owing to his statement that horses develop abscesses.

In the writings of the next six centuries no reference to either glanders or farcy has been identified, and the disease is next mentioned by Apsyrtus, who lived during the fourth century of the Christian era. Apsyrtus appears to have employed the term *μαλιν* (*malis*) in somewhat the same sense as the English word distemper, and he distinguished four forms of the disease, viz., moist, dry, articular, and subcutaneous. It is probable that the first of these was glanders, and the second farcy. Assuming this to be correct, Apsyrtus, as Bass points out, was not only acquainted with glanders but also believed that the disease was contagious, and actually recommended the segregation of affected animals in order to prevent the disease from spreading. It is worth noting, however, that, like many subsequent writers up to comparatively recent times, Apsyrtus described glanders as an easily curable disease.

Glanders appears also to have been known to Hippocrates, who was a contemporary of Apsyrtus, but his writings contain no reference to the disease except a prescription for it. He is also said to have pronounced the disease incurable during its advanced stages.

¹ This article forms part of the Harben Lectures, 1904. The full report of the Lectures will appear in the "Journal of State Medicine," Vol. XIII.

² Deutsche Zeitschrift für Tiermedizin, Bd. 19, p. 218.