TOPLEY AND WILSON'S PRINCIPLES OF BACTERIOLOGY AND IMMUNITY

THIRD EDITION

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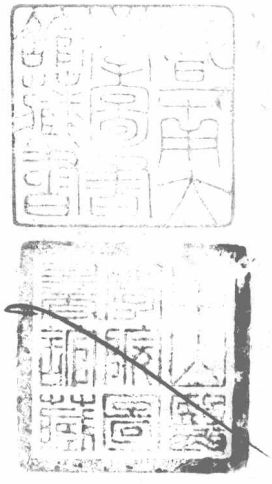

To

K. T. AND J. W.

PRINCIPLES OF BACTERIOLOGY AND IMMUNITY

VOLUME II

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PART III

INFECTION AND RESISTANCE

CHAPTER 42

TYPES OF IMMUNITY

THE term *immunity*, used as we use it here, needs definition. As plain English, it does not mean what it says. This does not matter very much because, as Whitehead points out so aptly in his *Introduction to Mathematics*, the scientist shares with Humpty Dumpty the privilege of paying words extra and making them mean what he likes. But if we are to avoid confusion we must at least give our words definite orders and see that they are obeyed. It happens that the state suggested by the word that we have chosen as a generic label for the phenomena we wish to study is one about which we know very little, except that it exists. We have indeed not bothered very much about it. Complete natural insusceptibility to infection removes the relationship between the particular host and parasite concerned from our field of interest, except in so far as we can learn from any instance of this kind something of the genetic laws that determine the transmission of this innate and complete resistance. Our main business is with those interactions between parasite and host that are characterized by a fluctuating equilibrium, and with the factors that shift this equilibrium, so that sometimes the parasite, sometimes the host, gains the upper hand. *Resistance* would be a better word than *Immunity*; but *Immunity* will serve well enough so long as we make it quite clear that we are using it to denote the resultant of two opposing systems, and that this resultant can assume any value from zero to infinity.

And our name misleads a little because of its associations. It happens to have been frequently applied to the data obtained by a particular kind of technique, and there has been a tendency to confuse technique with subject-matter. The special methods devised by the immunologist—if he must accept the unpleasing name that custom has given him—are applicable to problems with which he has no concern; while the field proper to his study extends far beyond the limits that would be imposed by any definition in terms of the particular technique employed. The student of immunity is concerned with all data relating to the mechanisms involved in infective disease, by whatever means they are obtained. Any account given at the present time must stress unduly a particular set of phenomena, simply because they are the only phenomena that have as yet been adequately studied; but this is a historical accident that will be remedied by time.

The phenomena that present themselves for study are derived from the most

diverse sources. Some come to us from epidemiology, using that term in its widest sense. Under natural conditions different animal species show a widely differing incidence of certain infections. Thus, anthrax is in the main a disease of herbivora. Of the animals dying of anthrax in this country in 1914, 733 were cattle, 5 were sheep, 32 were swine and 25 were horses. In Australia and South America sheep are more commonly affected; but Algerian sheep are stated to be highly resistant. Tuberculosis is one of the commonest natural infections of man and cattle. It is common in pigs and in fowls. It is relatively uncommon in sheep, goats, horses and dogs. It is stated to be very uncommon as a natural disease in rabbits, guinea-pigs, rats and mice. Among mankind there are well-marked racial differences in its incidence and severity. In eight of the great cities of the United States in 1920 the mortality from tuberculosis among the white population varied from 0·794 to 1·216 per 1,000 living; among the coloured population it varied from 2·855 to 4·205 per 1,000. Such instances could be multiplied *ad nauseam*.

The epidemiologist also records differences in the incidence and fatality of various infective diseases at different ages, suggesting in many cases an increase in resistance with age. He notes also that repeated attacks of the same infective diseases are in some instances very rare, as in measles, or smallpox, or diphtheria, or typhoid fever, while in others they are relatively common, as in influenza, or pneumonia, or the common cold.

Other data come to us from clinical medicine in the narrower sense. Infections that, in their usual course, progress slowly to death or recovery sometimes assume a fulminating form. Such a protean infection as tuberculosis shows the widest diversity in the varying prominence of its local and general manifestations. And, in any infective disease, why do some patients die and others recover?

For the immunologist these are crude data that require analysis. Using his own methods he re-examines the phenomena presented by natural infection. Sometimes he transforms the picture they present. He finds, for instance, that the recorded frequency of natural tuberculosis in various animal species does not in all cases reflect their relative resistance to experimental infection (see Chapter 59). He discovers also that there may be a diversity of immunological states within a single clinical syndrome. This is true of tuberculosis; there are different types of the tubercle bacillus, and a given host species is more resistant to one type than to another. It is true of lobar pneumonia. For the immunologist this is not one disease but several, each caused by a significantly different type of pneumococcus; and he notes that the statement that second attacks of pneumonia are not uncommon may belong to the Baconian category of a truth that has in it a mixture of a lie. Again he finds that enteric fever is not one but many; and his attempts at interference are planned accordingly.

Another important change that the immunologist makes in the clinical and epidemiological picture is in regard to the character and extent of the association between any given parasite and the host species that it infects. He finds that the real range of interaction includes states of equilibrium in which the host shows no overt signs of disease. Whether we call all these conditions latent infections, or refer to many of the hosts as healthy carriers, matters little. No hair-splitting definition will help us much. The significant thing we have learned is that in some infections, such as measles, contact between a previously uninfected host and the virus of the disease usually results in a clinically characteristic attack, so that the epidemiological picture gives us a reasonably adequate description of

the biological association, while in other diseases, such as cerebrospinal meningitis or poliomyelitis, the clinically diagnosable cases form so small a fraction of the total number of infected persons that they might almost be regarded as occasional accidents in an association that, in its modal form, induces no such serious effects.

In re-examining the data that he receives from the field and from the ward, the immunologist relies in large part on experiments on animals. When he tries to interpret his data he is forced to rely almost entirely on this fundamental method of study. He cannot advance without some simplification of his problems, some control, at least, over the innumerable variables that determine the incidence and results of infective disease as it occurs in nature.

By such experiments he has found that he can increase the resistance of animals by infecting them with sublethal doses of a given pathogenic organism, or by injecting an organism that has lost its power to kill—though here he was forestalled by Jenner's experiment of vaccination in man—or, more safely and conveniently, by injecting dead organisms or their products. From analogy, and from the fact that he can demonstrate similar changes in the tissue fluids, he concludes that this artificial immunization in animals is essentially similar to the natural immunization that occurs during an attack of an infective disease. Since the tissues of the naturally infected or artificially immunized host play an active part in bringing about this increased resistance, he calls it *active immunity*. In some cases he finds that he can transmit this resistant state to a normally susceptible animal by injecting into it the serum of another animal that has been rendered immune. Since the tissues of the recipient appear to play a relatively passive part, he calls this *passive immunity*. He also finds that immunity of this kind is sometimes transmitted naturally from a mother to her young, either by the passage of the protective substances *via* the placental vessels, or by their ingestion during the first days or weeks of life in the colostrum. This he calls *congenital passive immunity*.

And so, if he has a taste for classification, the immunologist can draw up some such list as this:

1. Innate Immunity.

2. Acquired Immunity.
   - (*a*) Active.
     - (α) Naturally acquired.
     - (β) Artificially induced.
   - (*b*) Passive.
     - (α) Naturally acquired (congenital).
     - (β) Artificially induced.

Innate, or Genetic, Immunity.

Of innate as opposed to acquired immunity, little need here be said. We have noted that different animal species may display wide differences in their resistance to various bacterial parasites, or to their toxins. This species immunity is of great practical importance in relation to the communicability of infective disease from animals to man, or from one animal species to another.

There can be no doubt that differences in innate resistance also occur within any animal species, one individual differing from another in this biological character as in any other. Of the extent of these differences and of the laws that govern their inheritance we as yet know very little. Within recent years a number of workers have attempted to study this problem by direct experiment, and their results indicate that it is possible to increase or lower the average resistance of a given strain of rats, mice or other experimental animals, by selective breeding. (See for instance Webster 1923, 1924*a*, *b*, 1925, 1933*a*, *b*, Pritchett 1925, 1926*a*, *b*, Lambert and Knox 1928, Irwin 1929, 1933, Irwin and Hughes 1931, 1933, Lambert 1932, Schott 1932, Gowen 1933, Gowen and Schott 1933*a*, *b*, *c*, Schütze *et al.* 1936, Hill *et al.*, 1940, Lurie 1941, Gowen and Calhoun 1943).

Experiments of this type are, however, subject to great technical difficulties. The obvious method of obtaining a strain of animals with a high genetic resistance is to infect an adequate sample with the bacterium under study, breed from the survivors, and repeat the process through several subsequent generations. This plan has, in fact, been followed by some of the workers referred to above; but it is clearly open to serious sources of error. In testing the resistance of our original generation we shall certainly alter it, and the effect of this alteration will not be confined to the parent animals. The surviving females will pass on a temporary passive immunity to their young; and, since most of the species commonly employed in such tests attain sexual maturity within a few months at most, this congenital passive immunity may persist until the F_1 generation are tested. A much more serious source of error is that the survivors will often be carriers of the organisms with which they were infected. Either the male or female parent may thus infect the young, inducing in them an acquired active immunity, or adding it to the congenital passive immunity already present. If this source of error is avoided, by mating the original sample of animals at random, and testing them after they have been separated from their young, the number of animals that must be employed, and the resulting labour, are enormously increased; since it will only be by chance that both parents of any one litter will be found to possess a resistance above, or below, the average.

The papers referred to above describe various attempts to overcome, or minimize, these technical difficulties; and they are very fully discussed in a recent monograph by Hill (1934). His conclusion is that, while possible errors of the kind we have mentioned render doubtful many of the observations that have been recorded, a presumptive case has been established for the existence of genetic differences in resistance within a breed or species, as well as between breeds or between species. In regard to the degree of these genetic differences, within a strain or breed, it is much more difficult to arrive at any just conclusion. Some of the differences recorded have, in fact, been quite trivial; but a few have been of a relatively high order.

As an example of the latter we may quote results recorded by Webster (1933*b*). By selective breeding, carried out through several generations, he was able to obtain a particularly resistant, and a particularly susceptible strain of mice, both originally derived from the strain that has been bred for many years at the Rockefeller Institute. The organism against which they were tested, in each successive generation, was *Salm. enteritidis*. The susceptible strain finally developed showed a mortality of 85 to 95 per cent. when infected with this organism, while the resistant strain showed a mortality of the order of 15 per cent. It is of interest to note that the difference in resistance between these two strains was non-specific, in the ordinary bacteriological sense. Thus the susceptible strain showed a mortality of 63 per cent., when tested against *Past. septica*, 80 per cent. when tested against Friedländer's bacillus, and 38 per cent. when tested against the pneu-

mococcus, while the corresponding figures for the resistant strain were 35 per cent., 45 per cent. and 16 per cent. respectively. On the other hand the susceptible strain showed a mortality of 40 per cent., when tested against the virus of louping-ill, as compared with a mortality of 60 per cent. in the resistant strain; so that the genetic factors concerned, whatever they may be, do not seem to operate against all types of infection, though they are operative against many.

Webster (1937) was later able to develop three strains of mice which he regarded as genetically stable in their reactions to *Salm. enteritidis* and to the virus of St. Louis encephalitis—one susceptible both to bacterium and virus, a second susceptible to bacterium but resistant to virus, and a third resistant to virus but not to bacterium. The resistance displayed by the animals resulting from various cross-breeds of these strains were in accord with the hypothesis that susceptibility to the two infective agents is regulated by two distinct sets of inherited factors (see also Church 1939).

Schütze, Gorer and Finlayson (1936), who have made tests on Webster's resistant and susceptible strains, record rather different results. The resistant strain showed a lower mortality than the susceptible when tested against *Salm. enteritidis* or *Salm. typhi-murium*; but when the two strains were tested against the pneumococcus, or against *Past. septica*, there was no significant difference in their behaviour. The discrepancy between these results and those recorded by Webster may be due to the fact that Schütze and his colleagues infected their mice by intraperitoneal injection, while Webster used the intranasal route. In Schütze's experiments both strains were equally susceptible to the virus of louping-ill.

We are still largely ignorant of the defence mechanisms whose effectiveness is determined by genetic constitution. Gorer and Schütze (1938) found some evidence that in a strain of mice resistant to *Salm. typhi-murium* the specific antibody response to the "H" antigen was better than in a susceptible strain, but this relation did not hold for "O" antigen, nor for the "H" or "O" antigens of *Salm. enteritidis*. Lurie (1941) on the other hand, working with inbred strains of rabbits, of low and high resistance, demonstrated that both the degree of cellular response to invasion by the bovine tubercle bacillus, and of skin response to the injection of heat-killed bacilli, was higher in the tuberculosis-resistant strains (see p. 1299). In inbred strains of mice selected for resistance to *Salm. typhi-murium* the degree of resistance was found by Gowen and Calhoun (1943) to be correlated with the mean number of leucocytes circulating in the blood. A large number of circulating leucocytes, however, is probably a manifestation of a general not of a specific resistance to the organism, for, as Reich and Dunning (1941) showed in rats, the numbers of leucocytes may be correlated with general fitness for survival.

Severens, Roberts and Card (1944) studied the defence mechanism in two breeds of hen, which as chicks aged 1–10 days were respectively susceptible and resistant to infection with *Salm. pullorum*. All the demonstrable differences in the reactions of the two breeds were connected with lymphocytes. Age for age, the number of circulating lymphocytes, the rate of their normal increase after hatching, and the number present in the tissues of the spleen, were all greater in the resistant breed of chick. Moreover, splenectomy reduced both resistance and the circulating lymphocytes in the resistant chicks, but had little effect on the susceptible. The resistance was not due to a greater bactericidal power of the blood, although blood lymphocytes were observed to be phagocytic. It is suggested that the greater availability of lymphocytes may have increased the resistance by providing large numbers of precursors for macrophages in the tissues of the resistant chicks.

It would be unwise to expect that an increase in strain resistance would be determined by a change in a single group of mechanisms. For example, Hill, Hatswell and Topley (1940) bred mice from the survivors of a certain dose of the endotoxin of *Salm. typhi-murium*, and repeated the procedure for ten generations. The tenth generation was highly resistant to the toxin as compared with control unselected mice, but in spite of this it had not acquired any resistance to infection with the living bacillus.

Acquired Immunity.

It is with acquired immunity that we are here mainly concerned; and our interest lies particularly in those reactions that we can induce, and study, in the laboratory. Before discussing these mechanisms in any detail, it will, however, be well to consider briefly the general difference in behaviour displayed by immune and susceptible animals.

Grades of Immunity.

We have noted that the kinds of immunity in which we are most interested are seldom absolute. To keep our ideas clear and precise we may consider briefly the grades of immunity that can, in fact, be demonstrated, remembering always that they shade into one another by imperceptible degrees.

Fig. 236 gives, in diagrammatic form, a rough classification that will be sufficient for our immediate needs. It represents an infection of the invasive type, associated

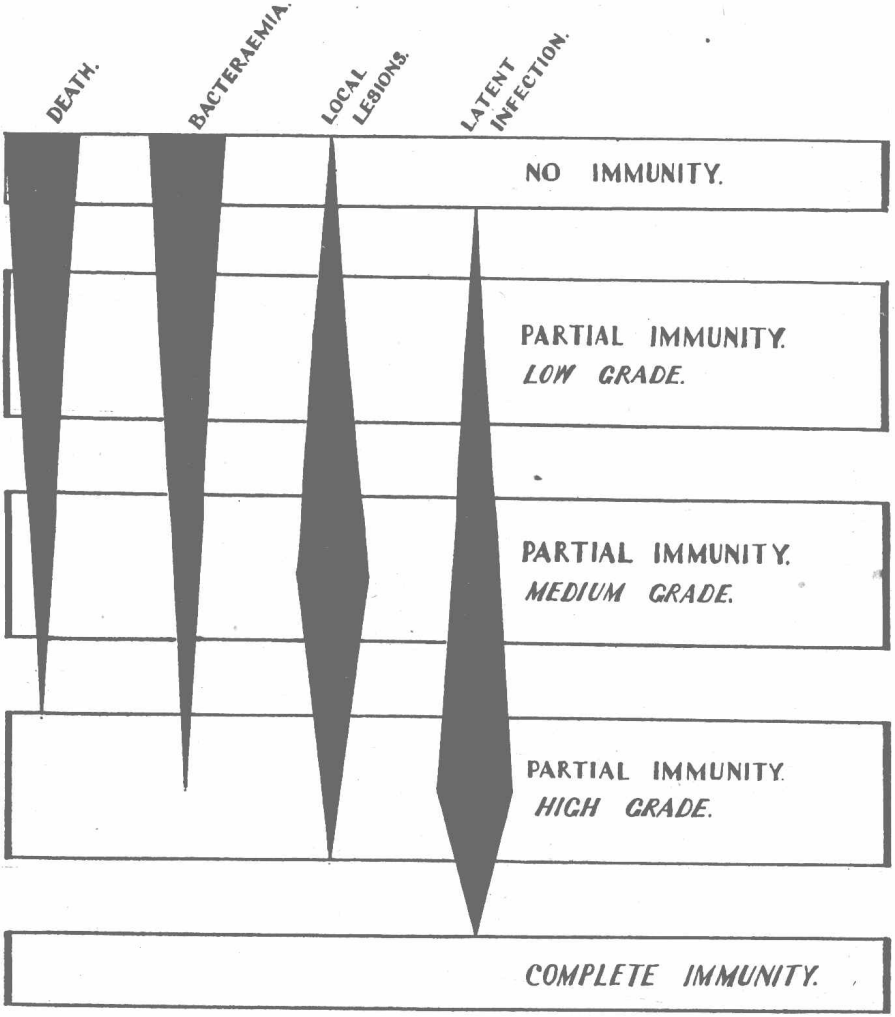

FIG. 236.

with a bacteræmia (an invasion of the blood stream by micro-organisms) as well as with local lesions; but it can easily be modified to meet the case of a toxæmic infection.

The width of the black wedge-shaped areas at any level may be taken to represent the chance of death, and the degree, or frequency, of bacteræmia, of local lesions, and of latent infections, in a sample of individuals possessed of approximately the same grade of immunity.

Thus, starting with the completely susceptible, we may assume that all, or almost all, infected individuals, will develop an acutely fatal bacteræmic infection. Local lesions will be infrequent, and minimal when they occur. There will be no latent infections.

Passing to our next arbitrary grade—partial immunity of low degree—we find fatal bacteræmic infections becoming less common, local lesions more frequent and more pronounced, and a small but increasing number of latent infections.

With partial immunity of a medium grade we find bacteræmia and death much less frequent, local lesions common and relatively extensive, and latent infections increasing in frequency.

With partial immunity of a high grade, death no longer occurs, bacteræmia is infrequent and, when it occurs, is slight and transient. Local lesions are becoming much less frequent and, when they occur, much less extensive. Latent infections reach a maximum frequency and then begin to decline.

Finally we reach the ideal—perhaps never fully attained—of complete or solid immunity. The host is entirely impervious to all attacks of the parasite.

It will not have escaped attention that the grades of resistance that we have labelled as partial immunity are compatible with severe and often fatal infections, and that many infective diseases in their common clinical form might be regarded as occurring in partially immune persons. This view is almost certainly the right one. The syndromes that normally characterize such diseases as typhoid fever, or lobar pneumonia, are expressions of partial immunity. They would not occur in a completely susceptible population attacked by a fully virulent parasite. The latter proviso is, of course, necessary. We may logically use the term immunity to express the relation of any given host to any given parasite, but events are determined by a balance—the balance between the virulence of the parasite and the resistance of the host.

The conception that infective disease, as we usually see it, is an expression of partial immunity, and that minor increases in immunity tend to increase the frequency of milder infections, is of sufficient importance to justify a few illustrative examples, drawn from experimental data.

It was noted by Smith and Moore (1892) that normal and actively immunized rabbits respond very differently to the subcutaneous inoculation of *Pasteurella septica*. Normal rabbits develop a rapidly fatal septicæmia. Immunized rabbits may develop large local abscesses, but show much less tendency to succumb to an acute generalized infection. More recent studies by Jones (1924) afford a good illustration of active immunity in all its grades. The normal rabbit is highly susceptible to *Pasteurella septica*, dying of a generalized septicæmia after the subcutaneous or intratracheal inoculation of 0·01 ml. of a broth culture. In the latter case pulmonary lesions are slight or absent. In rabbits partially immunized by a single injection of a killed vaccine a similar intratracheal injection of living culture is followed, in most cases, by a severe and fatal pneumonia, usually associated with a suppurative pleurisy and pericarditis. In rabbits immunized by repeated doses

of vaccine, intratracheal injections of living culture are usually without effect, while subcutaneous injections lead to the formation of localized abscesses followed by recovery.

Similar phenomena have been recorded in other bacterial infections. Thus Wadsworth (1904) found that the intratracheal injection of virulent pneumococci into normal rabbits was followed by a rapidly fatal septicæmia without local lesions, while similar injections in partially immunized rabbits were often followed by a characteristic pneumonic consolidation.

Differences of the same kind have been observed when strains of pneumococci of varying virulence have been injected intratracheally into normal rabbits. Thus Gaskell (1927) found that strains of high virulence gave rise to a rapidly fatal septicæmia without obvious pulmonary lesions; those of lower virulence to a fatal lobar pneumonia; those of still lower virulence to a patchy lobular consolidation, grading into an entire absence of reaction as the strains employed approached the region of complete avirulence.

The Relation of Immunity to Epidemiology and to Clinical Medicine.

Immunity is essentially an applied science. Its primary data are drawn from clinical medicine, and its outstanding achievement is that it enables us to do things, to interfere intelligently in the natural course of infective disease.

It must, therefore, remain in the closest touch with the field and with the ward. Its hypotheses, based largely on experiments in the laboratory, must stand their trial under field conditions. And here we are faced with a difficulty that is not shared by the more exact sciences. The relations of physics to the mechanical industries are superficially of the same kind as those of immunology to medicine, but actually they are very different. If a result obtained in the physical laboratory suggests a useful application to wireless reception or to aviation, or to any other practical and utilitarian end, it can be tried out with a reasonable certainty that its actual effect will be sufficiently obvious. It may succeed at once, or fail decisively at once, or succeed after adjustment; but in any case definite answers will come back from the field to the laboratory, and both parties to the transaction will learn something from their success or their failure. In medicine this is not always the case, simply because the practice of medicine is a much more difficult thing than any kind of mechanical industry, or indeed than any industrial process at all.

It may be quite easy to tell when an immunological procedure is an unqualified practical success. It is much more difficult to tell whether it is a partial success, or an unqualified failure. And this cause of confusion, which in truth affects the immunologist in the laboratory almost as much as the physician in the ward, is so important that it deserves a separate chapter.

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