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IMMUNITY TO TUBERCULOSIS*

BY

G. GREGORY KAYNE, M.D., M.R.C.P., D.P.H.

Tuberculosis Officer, Middlesex County Council

At the outset we should recognize the immensity of the subject and all its ramifications. We may divide it into natural immunity and acquired immunity, or, more correctly termed, natural resistance and acquired resistance. But, considering natural resistance first, we would need to discuss the influence of race, heredity, sex, and age, and even of different organs and tissues; the difference in resistance, if any, to the human and bovine types of bacillus; and, lastly, the mechanism by which natural resistance is effected. The mechanism of acquired resistance, if indeed it is different, offers an equally important problem, as does the hypersensitivity of the tissues which follows infection. How little do we know about the good influence of various environmental conditions on acquired resistance, and perhaps on natural resistance; and, on the other hand, about the bad influence exerted by malnutrition, intercurrent diseases, childbirth, and certain occupations. And this by no means exhausts the list. What part does resistance play in the development of phthisis as seen in the adult? How far do resistance and hypersensitivity determine the protean characters of tuberculous lesions, the varied clinical manifestations of the disease, and its puzzling epidemiological characteristics? And, finally, there are many problems involved in prophylactic immunization.

There is certainly, as yet, no consensus of opinion on the actual cellular or humoral mechanisms of either natural or acquired resistance among those intimately engaged in such research work. But it is possible to indicate the present trend of opinion on the roles of natural and acquired resistance in the evolution of tuberculosis in man, on the connexion between natural and acquired resistance, and on the relations between the latter and hypersensitivity.

Natural Resistance

Natural resistance has been defined as the inherent ability of the body to restrain the growth and bring about the death of the tubercle bacillus on first contact with it. It must have been evident for a long time that such inherent ability is present to a very different degree in different species of animals: rats, for instance, are highly resistant to tuberculosis, as are sheep, goats, and horses. But even in regard to man, "constitution" has since early times been considered to be very important in the development of tuberculosis. The discovery of the tubercle bacillus led to a swing of the pendulum, but the soil soon loomed on the horizon beside the seed. The

relative roles of soil and seed in relation to the various manifestations of the disease were not, however, clearly discerned. The discovery of the Koch phenomenon in the guinea-pig gave reality to the concept of acquired resistance; and, translated to man, this concept of acquired resistance following infection has for many years been regarded as all-important in connexion with those tuberculous manifestations that develop some time after the primary infection. Thus, while natural resistance might influence the course of the primary infection, the development of later lesions would be determined by acquired resistance. Acquired resistance would act by killing the bacilli freshly introduced into the body at the site of entrance, generally the lung; or, at least, by limiting the effects of the bacilli to the neighbourhood of this site. Moreover, acquired resistance, as demonstrated in the Koch phenomenon, appeared to act through hypersensitivity of the tissues, which developed at the same time. This hypersensitivity was identified with acquired resistance, and the changed state of the body following primary infection was called "allergy," this term including both resistance and hypersensitivity. Hypersensitivity was also held responsible for liquefaction of the so-called reinfection lesions, with resulting cavitation and bronchial spread. But we meet with difficulties at once. Does natural resistance cease to act and acquired resistance take over? If so, at what stage in the development of primary lesions or afterwards does this occur? Or does natural resistance continue to act? In which case, is acquired resistance merely a reinforcement of natural resistance, or does quite a different mechanism operate with the two? And finally, while we might assume that the principle of the Koch phenomenon is valid for reinfection in man from the outside, does it operate against bacilli derived from incompletely healed lesions in the body? We may recall that in syphilis it does not. What part is played by dosage of virus? There is evidence that no natural or acquired resistance will stand up to really immense numbers of tubercle bacilli. But, all other factors being equal, will natural resistance prove more effective than acquired resistance against large numbers of bacilli? All these questions cannot be answered yet, but observations in man during the past 25 years and further animal investigations have thrown some light on the relations between natural and acquired resistance, and on the role of inheritance in resistance.

Racial Resistance

During the last war it was noted that natives from African communities in which tuberculosis is unknown developed rapidly fatal tuberculosis when they came to Europe. This tuberculosis assumed the so-called childhood or primary type—that is, in addition to the lung lesion, extensive glandular involvement and generalization were found. The facile explanation was accepted that this was due to the fact that these natives had not been infected in childhood and had not therefore developed

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acquired resistance. We might, of course, have asked ourselves: If this was indeed the reason, why did not all infected European children die from generalized tuberculosis? However, further observations soon exploded this theory. First there was the work in South Africa among natives on the Rand (Publn. S. Afr. Inst. med. Res., 1932). Although 70% of the natives reacted positively to a very small dose of tuberculin on arrival at the mines they often succumbed to tuberculosis characterized by massive caseation of the tracheo-bronchial glands and extensive caseation of the abdominal glands, liver, and spleen. Yet in 50% of these cases calcified primary lesions were found. Moreover, the disease pursued the same rapidly fatal course whether the reaction to tuberculin was positive or negative on arrival at the mines. On the other hand, it was noted that if the natives stayed in their kraals the disease often remained quiescent. The explanation was offered that the rapidly fatal tuberculosis was due to overwork, undernourishment, and unaccustomed conditions in the mines. But this clearly could not explain it all, since not merely the outcome of the disease but its type was so different from what we see among civilized communities.

Then there are the findings in negroes in the U.S.A. The mortality rate among them is three to four times that among the white population. Moreover, Pinner and Kasper (1932), in comparing the pathological characters of tuberculosis in the negro and the white man, found that the primary type of tuberculosis with caseation of the hilar glands was present in nearly one-half of the negro adults. Yet Opie (1924) had shown that the incidence of calcified lesions among negroes is only slightly less than among white men. Here, too, environmental conditions were blamed for the rapidly fatal course of the disease; but, as already indicated when speaking of South African natives, environment could not account for the different type of tuberculosis; and, indeed, comparisons of negro and white populations, when the living conditions of the whites were certainly no better than those of the negroes, showed the same difference. Thus, although the role of environment cannot be entirely ruled out in these comparisons, there can be little doubt that a racial difference in resistance to tuberculosis exists, and that in negroes this difference shows itself by their inability to develop acquired resistance which would alter the character of reinfection lesions. In other words, if a negro overcomes his first infection he behaves to a later introduction of tubercle bacilli into the body as if it were a first infection. Thus the ability to develop and to maintain acquired resistance can form an integral part of what we call natural resistance.

In this connexion it is of interest to mention some observations of Lurie (1928). It is well known that rabbits are susceptible to the bovine bacillus and resistant to the human bacillus. Yet Lurie found that not only do human tubercle bacilli multiply readily in the rabbit but in the first week after inoculation they grow even more rapidly than the bovine organisms. Whereas, however, the human bacilli are soon destroyed by acquired resistance and the animal recovers, the bovine bacilli continue to multiply in the lung and kidneys until the rabbit succumbs to the disease. Therefore, what appears on the surface as the native resistance of the rabbit to the human type of tubercle bacillus really results from a specific resistance acquired during the progress of the infection; for at first no effective opposition to the multiplication of this organism exists. But it may well be asked, Why is this resistance not acquired against the bovine type of bacillus?

Individual Resistance

We have seen that there is evidence for a racial difference in resistance to tuberculosis. It is widely recognized that there are also differences in resistance among individuals of the same race, even among the highly sensitive guinea-pigs. Thus it is not rare to find among tuberculous negroes the typical phthisis of white people. All investigations relating to individual resistance and inheritance are exceptionally difficult, however, because it is impossible to rule out environmental differences. Even the similarities as regards tuberculosis among the identical twins studied by Diehl and von Verschuer (1933, 1937) might be explained by the fact that such twins are more likely than non-identical twins to have an identical environment. Recent experimental work of Lurie (1941) is highly significant in this

connexion. He studied the tuberculosis resulting from various modes of infection in generation after generation of six rabbit families inbred by brother-sister or parent-offspring mating and maintained under uniform environmental conditions. The six families fell into three groups—uniformly highly resistant, uniformly highly susceptible, and others intermediate in resistance. The resistance was found to be a function of genetic constitution which by itself determined whether under given conditions of natural respiratory contagion rabbits acquired (a) rapidly progressive primary generalized tuberculosis; (b) localized chronic ulcerative pulmonary tuberculosis, corresponding to bronchogenic tuberculosis, the common type seen in the human adult; or (c) a disease of a character intermediate between these two extremes. It is significant, however, that the resistance even of the most resistant strains could be overwhelmed by large doses of bacilli.

Apart from indicating the hereditary character of susceptibility to tuberculosis, these investigations appear to show that so-called natural resistance as well as acquired resistance may influence the type of lesion formed on first contact with tuberculosis; and thus they lead to the deduction that acquired resistance is but a reinforcement of natural resistance. Some authors in America (Israel *et al.*, 1941), no doubt influenced by these results, have postulated that apparent differences in the clinical manifestations of primary tuberculosis noted between adults in America and those in Scandinavian countries were due to a genetically higher resistance in North Americans. But, in the first place, it has not been established that the so-called different clinical manifestations of primary tuberculosis are really associated with a different pathological picture of primary tuberculosis: the pleural effusions or the apical infiltrations considered "primary" manifestations by the American workers did not occur soon enough after a change in tuberculin reaction to exclude the possibility that they developed after an insignificant but true primary complex. And, secondly, it seems very doubtful if we are justified in applying results obtained in rabbits by mating of an intimacy unknown among civilized human beings to the interpretation of factors influencing tuberculosis in man. Nevertheless, summarizing all that I have said, we may perhaps, on a broad biological basis, consider that resistance to tuberculosis might show itself in the following degrees. The lowest degree of natural resistance will not, on first contact with the bacillus, prevent an extensive primary complex with rapid generalization and death. A higher degree of natural resistance will lead to a primary complex with perhaps some dissemination, and recovery, but no acquired resistance, will follow; so that, as is the case with negroes and South African natives, described above, a fresh infection under bad environmental conditions will again result in a primary complex, this time with generalization and death. A still higher degree of natural resistance will cause a primary complex, recovery from which will give acquired resistance; and therefore any subsequent reinfection will not produce a primary complex but a parenchymatous lesion which tends to liquefy, cavitate, and spread by the bronchi. People still more naturally resistant might conceivably react to a first infection by developing the latter type of lesion at once, as postulated by some American workers. This concept, which, I emphasize, must for the present be considered as largely theoretical, involves one important assumption: that acquired resistance is the same as natural resistance, which it enforces, and that presumably when either natural resistance or a combination of natural plus acquired resistance reaches a certain level, hypersensitivity appears, causing liquefaction and cavitation. One supporting fact to be mentioned is that it is not extremely rare to meet with liquefaction of a primary pulmonary focus.

Allergy

This brings me to the phenomenon of hypersensitivity. The term "allergy," as originally coined, was applied to the difference between the body's response to a second or later dose of antigen (the tubercle bacillus or its products) and its response to the first introduction of the antigen. The term has been identified with hypersensitivity as shown in the Koch phenomenon and the tuberculin test. Resistance gained from a primary infection was considered to be due to this hypersensitivity, or at least to run parallel with it and be inseparable from it. These views have been greatly altered as a result

of the work of Rice Rich (1936) and his associates. As he puts it: "For many years it has been generally believed that the state of hypersensitivity is the chief mechanism of acquired immunity, the accentuated allergic inflammation having been regarded as the means by which the growth and spread of the bacilli are inhibited. The dangerous and destructive effects of hypersensitive reactions have always been very clearly recognized, but they were believed to be necessary evils that had unfortunately to be borne if one were to possess any acquired resistance at all." Rich, in experiments which are well known, succeeded in separating resistance from hypersensitivity. It has been shown that acquired resistance could be established without concomitant development of hypersensitivity; thus Pagel (1937) states that by treating animals with heat-killed tubercle bacilli he has produced immunity without hypersensitivity; and that (Pagel, 1936) such animals developed bronchogenic tuberculosis (the type comparable to phthisis in the adult) after virulent infection. It has also been shown that acquired resistance of a resistant hypersensitive animal could be transferred passively to a normal animal without concomitant transfer of hypersensitivity; and, finally, that when the hypersensitivity of a resistant animal was abolished by desensitization resistance remained intact. Nevertheless, it is probable that allergic inflammation enforces resistance by bringing to the site of reinfection, more quickly and in more concentrated form, factors that tend to fix the bacilli *in situ* and promote their destruction. It is generally agreed that allergy largely results from stimulation of the tissues by an antigenic component of the tubercle bacillus. Whereas, however, some believe that this component is different from that responsible for the production of resistance, others, like Pagel (1939), consider that hypersensitivity develops when antigen is in excess of antibody, and that this leads to tissue destruction with liberation of antibodies; while resistance due to surplus of antibodies causes no destruction of tissues. At all events, even if allergy is not an essential factor in the mechanism of resistance it appears to have a deep influence on the development of the disease in man.

Mention of the dissociation of resistance and hypersensitivity brings me to the tuberculin test. Allergy or hypersensitivity to the tubercle bacillus should not be identified with tuberculin hypersensitivity. The latter phenomenon appears to be quite unconnected with resistance, and its exact mechanism is still obscure, although our knowledge has advanced as a result of the work of Seibert and her associates. The tuberculin reaction does not represent anaphylactic sensitization to foreign protein, for in the latter phenomenon there is interaction of demonstrable antibodies with antigen, and sensitization of the cell cannot be demonstrated. The tuberculin reaction, on the other hand, is the result of sensitization of the cell itself, and antibodies cannot be demonstrated. The active principle responsible for the skin reaction is apparently protein in nature, and the origin of tuberculin hypersensitivity is connected with the tuberculous lesion; thus hypersensitivity tends to increase with extension of the lesion and to disappear with complete healing. It has even been shown that it is more marked in proximity to the lesion than in the body generally.

In view of what has just been said it is perhaps not surprising that tuberculin tests, both in clinical and in epidemiological work, sometimes give unexpected results. Those who condemn the test on these grounds should at least make sure that they use the purest material available—at present P.P.D.—prepared under rigid standards, and employ similar standards in carrying out and reading the test. Even when all this is done we may still find unexplained variations in the degree of hypersensitivity, or its absence, in persons who have certainly been infected. This should, however, spur us on to further work in order to elucidate this important phenomenon. For it seems clear that it is on the understanding of resistance and related phenomena that the future of tuberculosis control rests.

Mechanism of Resistance

I cannot conclude without referring to the intimate mechanism of resistance to tuberculosis, although I realize that I shall be entering, inadequately equipped, territory much explored yet little charted. Briefly what we have to ask is, What is the fate of the tubercle bacilli, and what part is played in this fate by cellular and by humoral factors?; and we must ask

these questions in regard both to natural and to acquired resistance. According to Pagel (1940, 1942) the fate of bacilli in natural resistance is represented by what happens to them when injected intradermally into the mouse. First the bacilli lose their envelope, being converted from basophilic into eosinophilic organisms; then they become granular and gradually disappear. Or they may remain indefinitely at the site of inoculation without multiplying. The fate of bacilli with acquired resistance, as represented in the Koch phenomenon, is quite different. They disappear rapidly—within a few days or even hours; a few small granules are all that remain. Tubercles form quickly—in from two to four days. The bacillus is now treated as a foreign body that cannot be absorbed, and the tubercles act as a barrier shutting off the bacilli from the rest of the body and the circulation.

Next we come to the thorny and still unsettled question of the relative importance of cellular and humoral factors. Pagel considers that the role of the cells is unimportant, if indeed they play any part at all, in connexion with both natural and acquired resistance. On the other hand, according to Lurie, a very important part is played by the mononuclear phagocytes. Pagel maintains, however, that earlier experiments by Lurie himself contradict this conclusion. At the same time, it must be emphasized that no bactericidal power has been demonstrated in the serum of animals either naturally resistant or made so as a result of infection.

There is one final point I cannot resist making. When I was consulting the Society's *Proceedings* I came across a discussion in 1925 on the control of tuberculosis and the milk supply. I read there the same emphatic evidence that is brought forward to-day by those who appreciate the seriousness of the problem, and, on the other hand, the same arguments against the pasteurization and boiling of milk, and the same expression of difficulties associated with eradicating the disease in cattle. It was more than disheartening to conclude that apparently little, if anything, had been done about it all since then. But I also heard one tuberculosis authority maintain, among others, that he was definitely convinced of the importance of partial immunization against pulmonary tuberculosis as a result of the ingestion of small numbers of bovine tubercle bacilli in milk, and, moreover, that he regarded this as one of the causes underlying the favourable alteration in clinical type and in death rate from human tuberculosis noted in recent years. I do hope that, in view of the present discussions on the safety of the milk supply, this view is no longer held by any responsible member of our professions, and that such travesty of one aspect of immunity will not be allowed to hinder an effective campaign for the eradication of tuberculosis in cattle.

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Dr. Charles B. Huggins, professor of surgery at the University of Chicago, has been awarded a prize of \$2,000 given by Dr. Charles L. Mayer and administered by the National Science Fund of the National Academy of Sciences. The prize was offered for the most outstanding contribution made during 1942 to present-day knowledge of factors affecting the growth of animal cells, with particular reference to human cancer. The advisory committee decided that this award should go to Dr. Huggins for his studies of the human prostate, with special relation to the cancers taking origin from this gland. A second Charles L. Mayer prize of \$2,000 for an outstanding study made in the same field in 1943 will be given, and entries and recommendations for this award should reach the office of the National Science Fund, 515, Madison Avenue, New York City, by Jan. 15, 1944. The advisory committee is interested primarily in fundamental studies on the factors influencing growth of animal cells rather than applications to any particular aspect of normal or abnormal growth.