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3. On the Mechanism of Genetic Resistance to Tuberculosis and its Mode of Inheritance[1,2]

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OVER the past 20 years, by bother and sister inbreeding of rabbit stocks for over eight generations and subsequent intrafamilial propagation, various races have been developed. These exhibit different native heritable resistance

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to tuberculosis, characteristic and constant for each race, irrespective of the mode of infection or the virulence of the tubercle bacillus used. Not all of the original races developed are still extant. Of the strains studied, races A and III were highly resistant to the disease, races F, C, Ca and FC were highly susceptible, while races B, D, H and AD were of intermediate resistance.

MECHANISMS OF GENETIC RESISTANCE

The pattern of the pathogenesis of the disease in these different races is most sharply revealed by natural airborne contagion. This is achieved either by exposing the different races simultaneously to rabbit roommates artificially infected with highly virulent bovine type bacilli (4) or by causing them to inhale the same numbers of these bacilli at a single sitting in an apparatus for quantitative airborne infection previously described (6). In the first instance, the susceptible families develop a single primary pulmonary focus which progresses rapidly, undergoes extensive caseation and fails to become encapsulated. Within a few weeks the draining tracheobronchial lymph nodes show caseation and the disease disseminates by hematogenous and lymphogenous routes. The metastatic foci thus originated progress without any effective opposition and the animal dies rapidly of a generalized tuberculosis, characteristic of the disease of white infants or of adults belonging to aborginal races which had not yet been subjected to natural selection by endemic tuberculosis. In the natively resistant rabbits the disease also originates as a single primary focus. However, the lesion in the lung progresses slowly, becomes encapsulated and eventually undergoes liquefaction, ruptures into the bronchi and, by intracanalicular spread of vast numbers of bacilli, gives rise to slowly progressive ulcerative pulmonary phthisis. The bacilli which escape into the lymph or blood cause few if any progressive lesions in the organs focalized, so that the draining lymph nodes and the other organs are not involved. The rabbits eventually die of a chronic disease which is localized at the portal of entry, the lung, and closely resembles the ulcerative pulmonary tuberculosis of the so called reinfection type in white European adults. The pattern of the disease in susceptible and resistant rabbits exposed to quantitative inhalation of bovine type tubercle bacilli is exactly the same as that seen in these respective races exposed to natural airborne contagion, with the single exception that the number of primary pulmonary foci which originate in the lungs is a function of the number of bovine type bacilli inhaled and the number that reach the terminal alveoli.

If bovine type tubercle bacilli are injected into the skin of susceptible and resistant rabbits (4), it is found that the mononuclear phagocytes of the resistant rabbits rapidly acquire an increase capacity to destroy the bacilli and are soon transformed into mature epithelioid cells harboring but few microorganisms. The small numbers of bacilli that escape the local lesion give rise to

chronic ulcerative pulmonary phthisis which eventually kills the animals in 14 to 15 months. On the other hand, the phagocytes of the susceptible rabbits do not readily acquire this capacity, and tubercle bacilli in great numbers swarm in their immature epithelioid cells 4 to 5 months after inoculation when the animals die of an extensive generalized tuberculosis. Associated with this more rapid development of acquired resistance against the multiplication of the tubercle bacillus in the tissues of the natively resistant animal, there is frequently but not constantly an increased capacity to develop, quickly and intensely, allergic sensitivity and antibodies against the tubercle bacillus and its products.

If human type tubercle bacilli are used in quantitative inhalation experiments on natively susceptible and resistant rabbits, it is found (8) that in the vast majority of the former, that had inhaled several thousand bacilli, there is a variable and often extensive pulmonary disease 5 months after infection. By contrast, in resistant rabbits simultaneously exposed and killed at the same time, only rarely is slight pulmonary tuberculosis observed, while in the great majority of these rabbits no tuberculosis at all is seen. Furthermore, while the lungs of susceptible rabbits at this time contain millions of viable tubercle bacilli, the lungs of the resistant rabbits are usually sterile and only occasionally show small numbers of microorganisms. It is noteworthy that the *initial* growth of tubercle bacilli in the lung is more retarded in the resistant animal. Again, as was found with bovine type tubercle bacilli, allergic sensitivity and antibodies tend to develop more rapidly or more intensely in the natively resistant races.

Parallel observations have been made with intracutaneous inoculations of BCG in susceptible and resistant rabbits (9), so that the response to this injection of the attenuated tubercle bacillus can be used as a means of selecting natively resistant and natively susceptible rabbits for breeding purposes. For the nodule at the site of inoculation of BCG in natively resistant rabbits develops quickly, reaches its peak rapidly and soon heals; whereas in susceptible rabbits this nodule grows more slowly, reaches its height tardily and heals much later. Again, the bacilli are more rapidly destroyed in the resistant animal and the development of allergic sensitivity and antibodies is accelerated in these animals. In fact, the larger initial size of the BCG nodule in the resistant rabbit is clearly attributable to the greater intensity of the allergic sensitivity developed by these rabbits in the first week after the intracutaneous inoculation of the several million viable BCG used. Whether the more rapid rate of development of allergic sensitivity and antibodies is the result of the accelerated native capacity for destruction of the bacilli in the tissues of the resistant animal or of the greater responsiveness of their cells to antigenic stimulation or to both has not yet been determined.

During the course of these studies it was observed that there is an incomplete

parallelism between the spread of intracutaneously injected India ink and resistance to tuberculosis (4). One of the most resistant races restricted the spread of the dye, while one of the most susceptible strains permitted it to spread much more widely. In an endeavor to determine to what extent connective tissue permeability determines resistance to the infection (5), it was found that the administration of estrogen, which reduces connective tissue and vascular permeability, retarded the dissemination of cutaneous tuberculosis and increased the resistance to the disease. On the other hand, the periodic administration of chorionic gonadotropin, which induced successive crops of corpora lutea in the ovaries and increased the connective tissue and vascular permeability, enhanced the disseminations of cutaneous tuberculosis and reduced the resistance to the disease. These sex hormones, while they affect the spread of the disease in the connective tissue in opposite directions, do not essentially influence the major factors concerned with resistance, namely, the rate of growth and destruction of the bacilli and the rate and intensity of development of antibodies and allergic sensitivity.

It was noted during the course of the latter investigation that tuberculosis in rabbits is accompanied by an hypertrophy of the adrenal cortex. Furthermore, just as in the case of connective tissue permeability, there was an incomplete parallelism between native resistance and the function of the adrenal cortex as indicated by its mass in relation to body weight (10). Thus the resistant race III is characterized by the possession of large adrenals whereas the susceptible FC strain possesses small adrenals. However, the C rabbits which are highly susceptible also have large adrenals. It is evident therefore that even if adrenal function is a factor in native resistance, it is only one of several. To ascertain whether the adrenocortical hormones play any role in resistance to the disease, cortisone in pharmacologic doses was administered to 10 rabbits of the susceptible race FC, and 10 of their litter mates served as controls (7). These two groups were then simultaneously exposed to the quantitative inhalation of human type tubercle bacilli. Cortisone treatment was continued in the experimental animals for about 5 weeks, at which time both groups were killed and the number, size and histological character of the primary pulmonary tubercles generated was determined. This method of assaying the effect of the cortical hormone on resistance was used because it was found to be the most accurate, rapid and quantitative measure of native resistance.

If bovine type tubercle bacilli of maximum virulence for the rabbit are quantitatively inhaled, it was shown that, irrespective of the genetic resistance of the animal exposed, the ratio between the number of bacillary units calculated as inhaled and the number of gross pulmonary tubercles developed within 5 weeks after infection is constant, namely 3 (6). It was demonstrated by a number of observers that only one of three inhaled particles of the size of

tubercle bacilli is retained in the alveoli of man or animals (1). It follows, therefore, that each viable unit of this bovine strain that is ingested by the alveolar phagocytes yields a visible pulmonary focus. On the other hand, if rabbits of different genetic resistance inhale human type tubercle bacilli, only a fraction of the bacilli retained in the alveoli multiply sufficiently to produce grossly visible pulmonary foci. Furthermore, and most significantly, the number of primary tubercles generated is a direct function of the native resistance of the animal (8). The greater the resistance, the fewer the tubercles generated, so that each race is characterized by a certain ratio between the number of bacilli inhaled and the number of primary pulmonary foci. Thus in the most susceptible race C one of 50 inhaled bacilli generates a tubercle; in the somewhat more resistant race FC about 100 are required; while in the most resistant race III only one of 600 inhaled bacilli yields a pulmonary tubercle.

Now by the use of this method it was found that cortisone in pharmacologic doses affects in a fundamental fashion all the essential mechanisms involved in the pathogenesis of tuberculosis. It greatly increases the number of tubercles generated by the inhalation of a given number of tubercle bacilli in a given race of constant genetic resistance. This is achieved by favoring the growth of the bacilli within the phagocytes. It suppresses nonspecific and allergic inflammation by virtue of the protective effect exerted by the hormone against agents which increase capillary permeability. As a result, the tubercles are greatly reduced in size by the suppression of their perifocal inflammation. This antiphlogistic influence, by suppressing the migration and ingrowth of cells and capillaries into the tubercles and by diminishing the communications between the focus and the rest of the body, tends to partially isolate the lesion and localize it at the portal of entry. The reduced capillary permeability and the lympholytic effects of the hormone may also be instrumental in the retardation of development of the caseous process and the diminution of antibody production which is characteristic of the cortisone-treated animals. For allergic sensitization, of which caseation is a part, has now been demonstrated to be at least partially mediated by antibodies. It is noteworthy that some of the effects of cortisone are similar to those of estrogen discussed above.

Thus an excess of the natural cortical hormone markedly influences native resistance to tuberculosis and acts as a double-edged sword. The very suppression of the inflammation, while it tends to isolate the infection from the rest of the body, nevertheless permits the local multiplication of the bacteria. For the phagocytes and the humoral agents concerned with combatting the infection arrive tardily and in low concentration. Furthermore, there is general agreement that cortisone administered during the course of immunization tends to lower antibody production which would also militate against the host. Again, while there is ample evidence that increased adreno-cortical function and cortisone stimulate phagocytosis of particulate matter and bac-

teria, the digestive capacity of the cells for the ingested microorganisms is markedly reduced whether these be tubercle bacilli, pneumococci, streptococci or even red blood cells. Hence, the bacteria can accumulate in the tissues in the absence of allergic inflammation or toxemia which are suppressed by the hormone.

The very fact that an excess of cortisone affects native resistance fundamentally both favorably and unfavorably would suggest that a proper balance between the adrenal and other hormones of internal secretion might exert entirely beneficial influences on this process. Indeed, experiments with minimal effective doses of ACTH, suggest that the resistance of certain inbred animals of low native adrenal function can be increased by corticotropin. Similar treatment of rabbits with higher genetic adrenal function has no effect. These observations were made in races FC and C, respectively. Furthermore, even in the FC race which is characterized by the low native adrenal function, the beneficial effects from ACTH, i.e., the reduction in the number of primary pulmonary foci generated by the inhalation of a given number of human type tubercle bacilli, can be obtained only within very narrow limits. A slight excess of ACTH may induce effects due to excessive secretion of cortisone-like hormones as suggested by a tendency for an increase in the number of tubercles generated by a given number of inhaled bacilli and by a constant diminution in the size of the primary pulmonary foci.

Thus genetic resistance to tuberculosis in different rabbit races is determined essentially by their varying native capacities to retard the initial growth of the bacilli within the phagocytes that ingest the microorganism and their subsequent varying innate ability to develop rapidly and intensely an increased power to destroy or inhibit the multiplication of bacteria. It is noteworthy that the intensity of this acquired resistance developed during the course of the infection tended to be superimposed on and determined by the native initial capacity possessed by a given race to retard the growth of the bacilli. This generalization applies to the resistance of these races to both mammalian bacilli, human and bovine; but it is particularly evident in the native resistance of these races to the human type bacillus to which the rabbit, as a species, is much more resistant than to the bovine tubercle bacillus.

The analysis of the pathogenesis of the disease in the different races suggests that the factors which determine resistance are multiple, and that no one single factor is invariably associated with resistance or susceptibility. Thus low connective tissue permeability and a high rate and intensity of development of allergic sensitivity and antibodies tend to be associated with resistance, but not invariably so. The sex hormones thus far studied exert opposite effects on the dissemination of the disease, but they do not affect the essential process of resistance, which is the rate of growth and destruction of tubercle bacilli in the tissues. There is some parallelism between adrenal size and native resistance,

but again not uniformly so. The adreno-cortical hormone, cortisone, exercises profound influences on the resistance to the disease, but these are not all in the same direction. Minute doses of ACTH can raise the resistance of certain races, but affect the resistance of other races not at all. Furthermore, even in the same race, corticotropin in slight excess may have an opposite effect.

INHERITANCE OF NATIVE RESISTANCE

It is clear even from the limited observations thus far made on the role played by some hormones in resistance to the disease, that the determinants of this genetic resistance are numerous, complex and interacting. In fact, the work of Wright and Lewis (12), Webster (11), Irwin (3) and Gowen (2) suggest that the factors involved in the inheritance of resistance to a number of infections are multiple and complex and that individual resistance cannot be explained according to a simple Mendelian formula. With the development of the method of assaying native resistance by the procedure of quantitative inhalation outlined above, an opportunity arose to ascertain the mode of inheritance of resistance to tuberculosis more rapidly and with more quantitative precision than was possible heretofore.

For this purpose two races were chosen, the highly resistant race III and the highly susceptible race C. When these two races are given a single intracutaneous inoculation of virulent, bovine type tubercle bacilli, race III dies of a slowly progressive ulcerative pulmonary phthisis, the C rabbits die of an acute massive nodular caseous pneumonia and generalized tuberculosis. The duration of the disease in the race III rabbits is about 2 to 3 times that of the C rabbits.

When these two races inhale human type virulent tubercle bacilli, H37Rv, quantitatively and simultaneously, many more tubercles are generated in the susceptible than in the resident rabbits when killed 4 to 5 weeks after inhalation. In race C, on the average, one primary pulmonary focus results from the inhalation of about 50 tubercle bacilli; in race III, over 600 isolated microorganisms, calculated as inhaled, are required to generate a single tubercle (Fig. 1).

As can be seen from Chart I, the log of the ratio between the number of bacilli inhaled and the number of tubercles generated in 14 rabbits of the C race ranged between 1.1 and 2.5 with a mean of 1.7 ± 0.09 and an arithmetic mean of 48 ± 10. It is noteworthy that in 9 of these 14 rabbits the log of this ratio was 1.6 to 1.8 and, in arithmetic terms, from 38 to 66 inhaled tubercle bacilli sufficed to generate a tubercle. As is evident, race C is a rather uniform strain in which the individual resistance, as measured by this method, varies within relatively narrow limits.

In 16 resistant race III rabbits the log of this ratio ranged between 1.9 and 3.6 with a mean of 2.8 ± 0.11 and an arithmetic mean of 640 ± 170 inhaled

tubercle bacilli for each tubercle formed. Clearly the range of individual variation in resistance in race III is far greater than that of C. Nevertheless, the "P" value of the difference between the means of these two races is 0.000 and statistically highly significant.

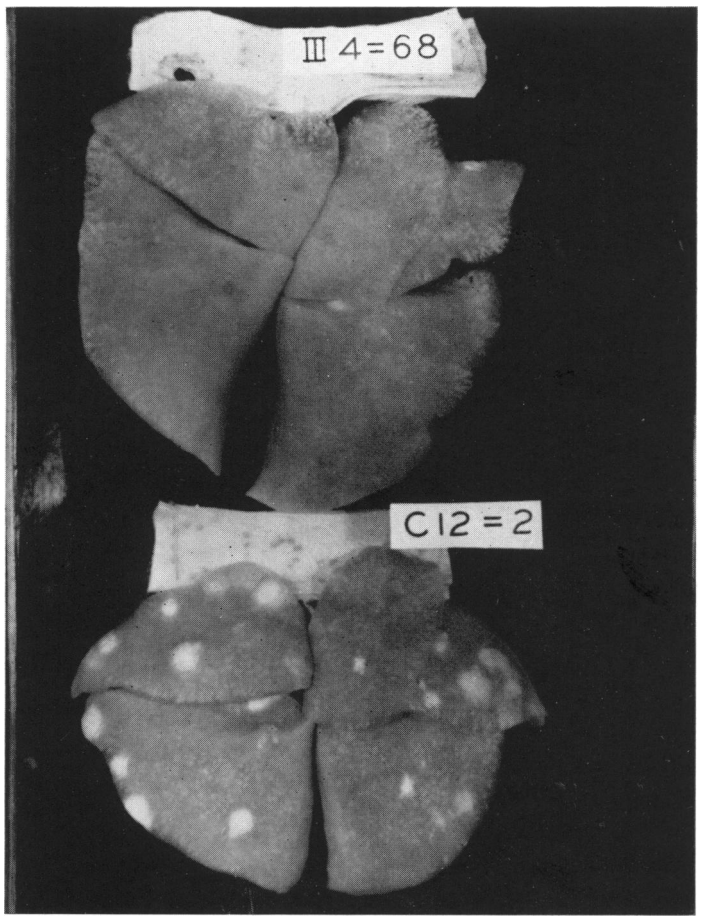

FIG. 1. The lungs of resistant rabbit III 4=68 and of susceptible rabbit C 12=2, 5 weeks after the simultaneous exposure to an estimated number of 981 and 1081 tubercle bacilli, respectively. Two tubercles were found in the resistant animal and 50 were counted in the susceptible rabbit. The ratio between the number of bacilli inhaled and the number of tubercles generated was 459 for the race III rabbit and 22 for the susceptible C rabbit.

When these two races were crossed, the average resistance of 13 rabbits of the F_1 generation was intermediate between these two extremes. The mean log of the ratio between the number of bacilli inhaled and the number of tubercles generated was 2.5 ± 0.09 with an arithmetic mean of 340 ± 84. This ratio is almost exactly half way between the 48 bacilli necessary for the susceptible

race C and the 640 required for the resistant race III in order to generate a single pulmonary tubercle in each, respectively. It is noteworthy that the spread of variation of the individual resistance of the F_1 generation of this hybrid is less than that of either parent strain. Clearly, therefore, the determinants for resistance are certainly not purely dominant or recessive Mendelian factors, but additive in nature. Statistically, the mean resistance of the hybrid IIIC is significantly different from the mean resistance of either the C or the III race; the "P" value of this difference in the first instance is 0.000 and in the second instance it is 0.03.

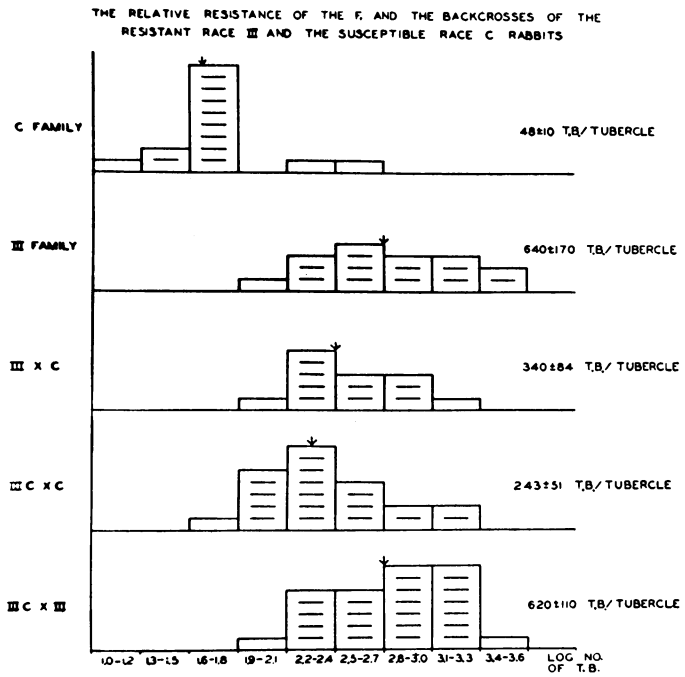

CHART I

When this hybrid IIIC is back-crossed to the susceptible race C there is a clear tendency for many of the individual animals of this back-cross to approach in their resistance that characteristic of the susceptible strain C so that on the average fewer tubercle bacilli are required to generate a tubercle in this back-cross than in the F_1 hybrid. The log of the mean ratio between the bacilli inhaled and the tubercles generated is 2.4 $\pm$ 0.09 instead of 2.5 $\pm$ 0.09 and the arithmetic mean is 243 $\pm$ 51 for this back-cross instead of 340 $\pm$ 84 which was the number of bacilli required to generate a single tubercle in the F_1 IIIC. Although 21 rabbits of the IIIC X C cross were studied, the range of variation in resistance was so great, from a log of 1.7 to 3.2, that the mean

resistance of IIIC was not significantly different from that of IIIC X C. However, the mean resistance of the IIIC X C was significantly different from that of races C and III.

When this hybrid IIIC was back-crossed to the original highly resistant race III, both the mean resistance and the range of individual resistance was

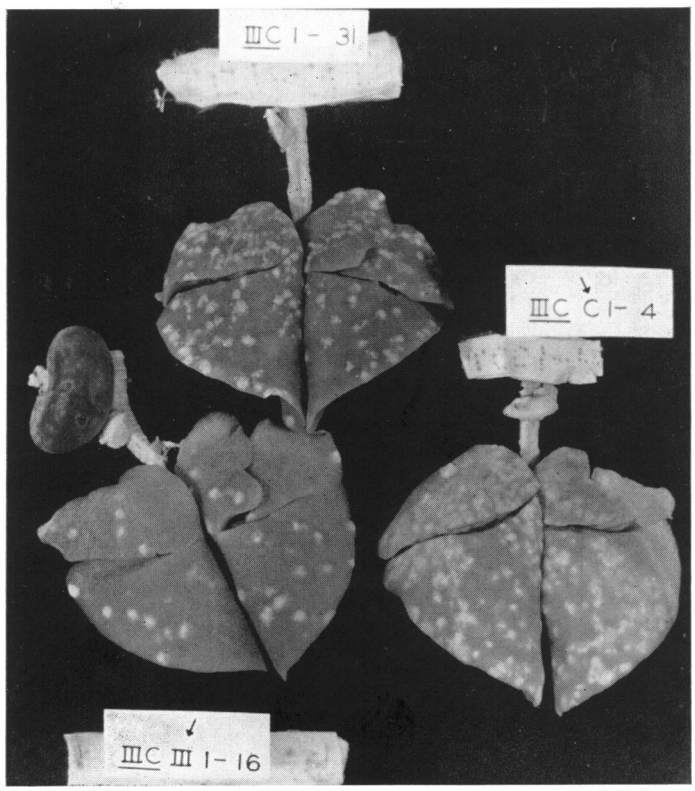

FIG. 2. The lungs of an F_1 hybrid, IIIC 1-31, of a back-cross of the F_1 hybrid to a resistant ancestor, IIICIII 1–16, and of a back-cross of the F_1 hybrid to a susceptible ancestor, IIICC 1–4, 4 weeks after the simultaneous exposure to an estimated number of 75,028, 79,171 and 63,521 tubercle bacilli, respectively. 497 tubercles were found in the F_1 hybrid; 142 tubercles were counted in the F_1 hybrid back-crossed to the resistant ancestor; and 772 tubercles were estimated to be present in the F_1 hybrid back-crossed to the susceptible ancestor. The ratio between the number of bacilli inhaled and the number of tubercles generated was 131 for the F_1 hybrid, 557 for the back-cross to the resistant ancestor and 82 for the back-cross to the susceptible ancestor.

practically identical to that of the highly resistant parent race III. The log of the mean number of bacilli required to generate a primary pulmonary focus in this cross was 2.8 ± 0.08 and an arithmetic mean of 620 ± 110 which is essentially the same as these values for race III, namely, 2.8 ± 0.11 and 640 ± 170. Obviously the difference between these figures is not significant. Furthermore, the range of individual variation in resistance in this back-cross

IIIC X III is also essentially the same as the range in the parent race III, log 1.9 to 3.6 in IIIC X III and 1.9 to 3.6 in race III. The relative resistance of the F_1 hybrid and the two back-crosses is illustrated in Fig. 2. Since the back-cross IIIC X III is of the same resistance as the original resistant race III ancestors, it would follow that the resistance of this back-cross is significantly different from that of races C, IIIC and IIIC X C as in case of race III. This was found to be the case.

It is imperative to state that exactly the same relationships held between the relative resistance of these races, the F_1 hybrids and the back-crosses, when all the data were evaluated in their originally observed arithmetic terms.

Thus the back-cross of IIIC to the resistant ancestor III is as resistant as the original race III. However, the back-cross of the same hybrid IIIC to the susceptible ancestor C is much more resistant than the original race C. For the mean resistance of IIIC X C is significantly much higher than that of the C race. These data would suggest that not only are the determinants for resistance multiple, but also that the factors for resistance are either more dominant in the phenotype than determinants for susceptibility, or that susceptible individuals lack certain qualities which resistant animals possess. These results do not prove either of these concepts. If this apparent phenotypic dominance of resistance holds in man, it is understandable why the mortality from tuberculosis may slowly diminish during the course of generations in an actively interbreeding society of heterogeneous native resistance apart from the forces of natural selection and hygienic measures taken. No light is shed by these observations on the number or dominance of the genes concerned with the inheritance of resistance, except that they are multiple and additive in nature. Whether a deeper understanding of the mode of inheritance of resistance in tuberculosis can be obtained from ascertaining the resistance of larger numbers of individuals of the various crosses presented thus far and from the F_2 generation of the IIIC hybrid is uncertain.

SUMMARY

An analysis of the pathogenesis of tuberculosis induced in inbred rabbit races of different genetic resistance to the disease by various methods of inoculation of bovine, human and attenuated tubercle bacilli has demonstrated that native resistance to tuberculosis in the rabbit is determined by the innate varying capacity of the phagocytes that ingest the microorganism to inhibit their intracellular multiplication, initially, and by their varying inborn aptitudes to develop rapidly and effectively an increased power to destroy the microorganism after the onset of the infection. The resistance acquired by a given race during the course of a given infection or after a certain immunization is greater in the natively resistant than in the natively susceptible strains.

High native resistance is often but not always associated with a low connective tissue permeability, and, more commonly, with a high level of develop-

ment of allergic sensitivity and antibodies. Estrogen, by reducing the connective tissue and vascular permeability, retards the dissemination of the disease and prolongs its course. Gonadotropin enhances the spread of the disease and shortens its duration by increasing connective tissue and vascular permeability. Neither hormone influences the growth and destruction of tubercle bacilli in the tissues, antibody production or the essential nature of the development of allergic sensitivity.

There is an incomplete parallelism between native resistance and adrenocortical function as indicated by its mass in relation to body weight. Cortisone in pharmacologic doses reduces the innate capacity of the phagocytes to destroy the ingested bacilli. It suppresses nonspecific and allergic inflammation as a result of the protective effect exercised by the hormone on the capillary walls against agents which increase their permeability. Cortisone tends to temporarily localize the disease at the portal of entry because the hormone suppresses inflammation and consequently reduces the cellular and humoral bridges between the focus and the rest of the body. Withdrawal of the hormone greatly accentuates the inflammation and the bacilli, accumulated in the foci as a result of a paralysis of the cellular digestive capacities by cortisone, now spread widely in the tissues and may cause a fatal issue in an animal which without this usually arrests the disease. Minimal doses of ACTH increased the resistance of rabbits with low native adrenal function but had no effect on a race with natively large adrenal cortices.

The most accurate, quantitative and rapid method of ascertaining native resistance, thus far, is the one of exposing animals to the quantitative inhalation of human type tubercle bacilli, to which this species is relatively resistant, and of determining the number of grossly visible primary pulmonary tubercles generated in them 4 to 5 weeks after this infection. The greater the native resistance, the fewer are the tubercles formed after the inhalation of a given number of microorganisms.

By the use of this method, the determinants of native resistance were found to be multiple, complex and additive in nature. The resistance of the F_1 hybrids of a natively highly resistant and highly susceptible race was intermediate between that of each parent race. The back-cross of the F_1 hybrid generation to the resistant ancestors yielded a strain which was of the same degree of high resistance as the original resistant race. The back-cross of the F_1 hybrids to the susceptible ancestors was significantly more resistant than the original susceptible ancestors. Phenotypic dominance of resistance over susceptibility is a possible, but not the only, interpretation of the observations. The implication of these data for the epidemiology of human tuberculosis is briefly discussed.

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4. The Bearing of Mouse Genetics on Our Understanding of Human Cancer[1]

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THE problems involved in our understanding of the cause, origin and development of cancer are basically problems in biology. The study of neoplasia concerns living cells and the factors acting through the physiology of the living

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