THE INHERITANCE OF RESISTANCE OR SUSCEPTIBILITY TO INFECTION.

by

J.W. McLean
Canterbury Agricultural College, Lincoln.

INTRODUCTION:

Since Biffin demonstrated in 1905 that resistance and susceptibility of wheat to yellow rust depended on the effects of a single gene pair, plant breeders have made valuable use of the innate disease resistance of certain varieties, by transferring it by appropriate crossings to modern, high quality plants not previously exhibiting this character. A consideration of the part played by heredity in the resistance and susceptibility of animals to infectious disease is a much more recent development. Nevertheless, something has been done, and it is my object in this paper to bring to your notice, with all due modesty, a brief, and, I fear, very imperfect outline of some of this work and perhaps to suggest how a consideration of its various aspects might help in the investigation of some of our disease problems.

It is proposed to deal with the subject under a series of headings in the form of interrogations.

1. Has genetic investigation been able to clarify the mode of inheritance of infectious disease diathesis in animals? This, I think, can be answered in the affirmative. That variations in disease diathesis do occur between species and even within species is well known, for example, domestic ruminants are immune to swine fever, horses are immune to contagious bovine pleuro pneumonia. Algerian sheep are said to be naturally immune to Anthrax and fowls are immune to tetanus. Viewed from an evolutionary point of view, this is to be expected, since the natural resistance of any animal host must be the result of progressive adaptations throughout a long series of ancestral forms to an environment of which a rich and varied bacterial flora forms an important constituent. From this point of view, also, it is only to be expected that variations in disease diathesis would be inherited.

   Most of the early experimental work arose from the observed differences in mortality rates between varieties of laboratory animals in spontaneous epidemics of bacterial septicaemia. Tyzzer (1917), for example, records the difference in reaction of Japanese waltzing mice and the common tame mouse to infection with B. piliformis. The entire stock of waltzing mice in his colony succumbed, while few of the common mice were affected. That this difference in susceptibility is hereditary is shown by the work of Gower and Schott (1933). They crossed the susceptible Japanese waltzing mice to resistant silver browns. The F.1 as a class was resistant. This on being back crossed to the two parental stocks gave results which suggested very strongly that a single major factor difference was responsible for the resistance of the common mouse strain and the susceptibility of the Japanese strain. Tests for linkage suggested that the genetic factor complex was not carried on the sex chromosoma or the chromosomes containing the loci of the dominant white spotting gene or the waltzing gene.

   Similar evidence of susceptibility and resistance to staphylococcus infection in Japanese and common white mice being due to a single gene pair is given by Hagedvorn and Hagedoorn (1920).

Proceeding now to the effect of selection, as an illustration of the effect of a high degree of selection continued over several generations, we may consider the results which Lambert (1932) obtained with the domestic fowl. He commenced with a flock of white leghorn chicks which he infected intra-peritonially with a standard dose of virulent fowl typhoid (B. gallinarum). The plan followed was one of selective breeding from survivors to infection. Not only were the selected parents in each generation survivors but they were also from families in which the percentage of survivors was high. In five generations he was able to reduce the mortality rate progressively from 48% to 9%, while in the controls (half white leghorn and half other breeds) it remained relatively constant around 90%. Reciprocal crosses between the two strains gave F.1 generations which were approximately intermediate.

Webster (1933) also has demonstrated the possibility of building up strains of mice both more resistant and more susceptible to B. enteritidis than normal controls. Reistance in these varieties was dominant to susceptibility and not linked with sex or colour. Back crosses of F.1 generations to each parent stock suggested the influence of one or two gene pairs. The question of specificity from an immurological point of view is one about which there has been considerable difference of opinion. Webster, in his early publications, put forward evidence which he claimed as showing that resistance was of a non-specific nature; that is, that mice having a resistance to one infective agent were not only resistant to unrelated bacterial infections, but also to the poisonous action of such substances as mercuric chloride and botulinus toxin. Later extensive work by Webster (1933) however, indicates that there is a considerable degree of specificity or, at least, a limitation of the range of infective diseases against which any group of genes is operative; and this range does not include such widely different causes of disease as bacteria viruses and chemical poisons. Whether this specificity corresponds in any way to that found in acquired immunity is a problem that awaits solution.

Very much more recent work by Webster (1939) shows quite clearly that resistance and susceptibility to mouse typhoid and St. Louis encephalites are inherited separated. By selection and inbreeding he was able to produce three strains of mice, one of which was bacteria and virus susceptible, a second which was bacteria susceptible and virus resistant and a third which was bacteria resistant and virus susceptible. The difference in susceptibility of the least susceptible and the least resistant lines was of the order of 95% mortalities as contrasted with 10%. Crossing highly susceptible with highly resistant lines and testing F.1, F.2 and backcross progeny, resulted in percentage mortalities in the neighbourhood of those expected on the basis of a single factor inheritance for resistance to each disease, resistance in each case being dominant.

Webster summarises the position by stating that resistance and susceptibility is inherited in some instances on a multiple and in others on a single factor basis, resistance being dominant more frequently than susceptibility; also that resistance to one infection generally proved to be independent of resistance to another; and further, that no anatomical or physical mechanism has thus far been proven casually related to resistance or susceptibility.

An important aspect from the practical viewpoint is stressed by Lambert (1939) who states that differences in resistance and susceptibility are relative rather than absolute, the degree of resistance depending upon such factors as genetic

constitution, virulence of the pathogen, the degree of infection, age, and various environmental factors such as diet and temperature. Work involving the study of the influence of some of these factors has led Webster to suggest modifications to the current theory of epidemics.

Let us pass now to a brief outline of the work on farm animals, where unfortunately, very little published evidence is available.

Horses: Significant group differences in resistance to infectious equine encephalomyelitis were observed by Lambert et alia (1939) in an epizootic occurring in 1938 in a stud of horses at the U.S. Range Livestock Experimental farm. A greater percentage of horses of Nonius (Hungarian) than of other breeding were affected in this outbreak.

	Nonius	Other Breeds
Yearlings	50%	11%
Foals	72%	10%

This is believed due to innate susceptibility of the nonius breed which is transmitted to crosses as a dominant. The Nonius stock, previous to its importation, was not subjected to any selection against the American-type encephalomyelitis virus; and this, the authors state, may be the cause of their increased susceptibility.

In cattle, White and Ibsen (1934) report what they believe to be an instance of inherited susceptibility to acute mastitis. Out of several hundred cows bred on the Experimental Station, only three showed evidence of virulent mastitis, and these were dam, daughter and granddaughter. The mammitis was so severe that the udders eventually became entirely non-functional. It is perhaps worth noting that in both the dam and the daughter separate quarters became affected in three successive lactations; also that the granddaughter's sire was the daighters half-brother on the sire's side. The author's main purpose was to call attention to the problem in the hope that data of a more critical nature would be accumulated by other workers.

This actually has been done by Ward (1938) whose data is derived from the mastitis records of nine dairy herds in the Waikato. The high correlation in incidence of severe udder infection between susceptible dams and their daughters is strong evidence that heritable characters play a part in susceptibility to infection.

Although not strictly within the subject matter of this paper, it is perhaps permissible to make passing reference to two recorded instances of evidence suggesting breed and individual differences in susceptibility to infestation with the stomach worm Ostertagia cercumcincta and probably to other strongylids, (stewart, Miller & Douglas, 1937), and (Gregory Miller & Stewart, 1940).

The first paper shows breed differences in susceptibility in the following ascending order, Romney, Rambouillet, Southdown, Shropshire and Hampshire, the three "down" breeds being on approximately the same level. Significant differences in resistance are also recorded within some of these breeds.

The second paper provides strong evidence of individual differences in susceptibility within a Hampshire flock, and furthermore, that these differences are hereditary. From these results the authors state that selection should effectively change the degree of resistance or susceptibility in populations of sheep. Although perhaps not very convincing, it does indicate differences.

Pigs: Amongst pig breeders there has long existed a belief that certain strains are more resistant to swine fever. Numerous attempts have been made both in American and Europe to establish disease resistant strains by selective breeding. Ossent (1932) attempted to combine in a new breed the good qualities of the improved types and the hardiness and resistance to swine fever of the wild pig. He claimed that, after ten years, about 95% of the wild-coloured progeny could be raised whilst the white animals suffered heavily from swine plague; the litter size and weight, however, were far below the average for improved breeds. The results of other works are far less encouraging. Smith (1938) in summarising the data states that a certain degree of resistance seems to be inherited, the mode of inheritance depending on multiple factors acting in a recessive manner; and that it appears unlikely that an absolute immunity to the disease exists in nature.

11. Has a knowledge of the mode of inheritance of infectious disease diathesis been helpful in animal breeding, - or can it be so?

As far as the breeding of experimental laboratory animals is concerned, I think this can be answered quietly in the affirmative. Thus far, its use is limited to these animals, because it is in them only that our knowledge - meagre though it is - is sufficient to be of some practical value.

In larger animals, our knowledge is even more fragmentary. Should genetic investigation however, be able to show that variations in disease resistance depend upon the action of at most, a few major genes, as has been demonstrated in mice, there may be some hope of its ultimate usefulness, at least with regard to some diseases. Furthermore, although it has been generally accepted that innate differences in susceptibility to infection do occur, the experimental demonstration of their existence and the fact that they may be concentrated by selective breeding are contributions of real value.

111. Is there information from abroad on the inheritance of disease resistance, which is directly applicable to infectious disease problems in New Zealand?

Without assuming a degree of complacency in excess of that usually attributed to New Zealanders in general, I think one can answer this in the negative. Two instances come to mind in this respect; firstly, the report on the possible inheritance of susceptibility to bovine mammitis, and secondly, that on the inheritance of susceptibility to Stomach-worm infestation in sheep. Work along these two lines is already proceeding in this country.

1V. Finally, are there problems of disease control in N.Z. a study of the genetic aspects of which might be expected to yield helpful information?

The answer, I think, is "yes", but in my opinion there are only certain kinds of disease in which a study of the inheritance of diathesis is likely to be of assistance. In this respect I should like to mention three important points.

The first is the nature of the infective agent. In some virus diseases such as Foot and Mouth disease and equine encephalomefelitis there are different strains of the same infective agent. It is possible that resistance to each strain of virus would be inherited separately.

The second is the effectiveness of other methods of control. In diseases such as canine Distemper, Bovine Tuberculosis, Footrot in sheep, and possibly Contagious Bovine Abortion, we

have now relatively effective means of control if we chose to use them.

The third point is the effectiveness of natural selection. It is difficult to imagine a more intensive selection towards resistant stock, if it exists, than occurs naturally by mortality in some diseases. In these we must of necessity breed from resistant animals.

There are, however, some diseases which, by their very nature, do not cause a high degree of natural selection in the host, and further, against which we have as yet few other effective means of control. This class comprises such diseases as the internal parasitic diseases of sheep, bovine mammitis, the septicaemias of pigs, avian coccidiosis, Pullorum disease and possibly contagious bovine abortion. It is in diseases of this type that an investigation of the possible inheritance of susceptibility or resistance might be expected to yield helpful information.

With the exception of these I believe there is little hope that selective breeding towards resistance to infection will yield results of material benefit. At present, the animal breeder is frequently faced with the difficulty of keeping alive sufficient animals on which to practice effective selection for those numerous characters which he now considers desirable. To add even one more may have the effect rather of delaying progress.

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