The Relation of Genetics to Disease

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THE BREEDING of disease-resistant varieties of plants is one of the major triumphs of modern genetics. Could disease losses in livestock be reduced in much the same way that production is increased by breeding methods? Here is a cautious yet optimistic viewpoint on a question of great interest to agriculture.

THAT THERE IS an inherited resistance or susceptibility to diseases is by no means a new concept, but experimental evidence to substantiate the idea is relatively new. In the case of animal diseases, however, practically all the attention has been centered on the disease organisms themselves, the tissue changes brought about by their presence in the host, and therapeutic measures for control. Such studies have been remarkably fruitful in medical science, including veterinary medicine; the extensive use of vaccination as a means of avoiding disease is an example of the importance of the results. Nevertheless, during recent years there has been a growing interest in the natural resistance to disease shown by some individual animals. Interest has been stimulated primarily by advances in genetic knowledge, particularly in relation to physiological characteristics, and by the marked progress made by plant breeders in controlling plant diseases through the development of resistant strains.

The science of genetics seeks to explain the variations in characteristics shown by individuals connected by a common line of ancestry. If disease is defined as any abnormal condition of the body tissues, then inheritance may have a four-way relationship to it. There may be (1) specific inherited resistance to certain infectious diseases, (2) a connection between inherited vigor and resistance, (3) inherent variations in the disease organism itself, giving rise

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to strains differing in virulence, and (4) various specific abnormalities, many of them lethal. Many such abnormalities have been shown by experimental evidence to be inherited; in fact, there is much more information on this point than on the other three.

INHERITED RESISTANCE TO DISEASE

Specific inherited resistance to an infectious disease is perhaps best illustrated by Lambert's [2] experiments with White Leghorn chickens, the object of which was to determine whether continued selection for resistance to fowl typhoid would lower the death loss in the flock. The foundation stock consisted of 220 birds, all of which were given a massive dose of virulent fowl typhoid bacteria. Of this group 47.7 percent died. Among the survivors those showing the least severe clinical symptoms of fowl typhoid were saved as breeders to furnish the first selected generation of chicks. All chicks in this and the four succeeding generations, when 7 days old, were given injections intraperitoneally (into the abdominal lining) of a standard dose of the disease organism. The death losses resulting from these injections for five consecutive generations were 39.8, 29.3, 15.4, 15.0, and 9.4 percent. At the same time the losses in unselected control stock were 89.6, 93.2, 86.2, 86.4, and 85.0 percent. This remarkable difference was brought about by simple selection. It is also of interest that most of the mortality occurred sooner after inoculation in the control lot than in the selected group, indicating an even higher resistance in the latter than the figures for losses show. Following the five generations of selection, matings were made between males selected for resistance and unselected females, and also between selected females and unselected males. The results showed that the male as well as the female transmits resistance and that a passive transfer of immunity through the eggs probably is not involved. The death loss among the chicks from the resistant male × unselected female cross was 63.5 percent, while in the reciprocal group (unselected male × resistant female) it was 50.7 percent. These figures are intermediate between those for the selected and the control stocks.

A few other investigators have reported somewhat similar results for other diseases. Schott [3] was able in 6 years of selective breeding to reduce mortality from mouse typhoid from 82 to 24 percent. Roberts [4] developed a strain of chickens which showed only 35 percent mortality from pullorum injection, as compared with 73 percent in an unselected group. A recent case reported from the California Experiment Station concerns the discovery of some pigs that seem to be immune to repeated injections of the *Brucella* organism and to transmit the resistance to their offspring. Only a preliminary report has been made, and more breeding results are needed

[2] LAMBERT, W. V. NATURAL RESISTANCE TO DISEASE IN THE CHICKEN. Jour. Immunol. 23: 229–260, illus. 1932.

[3] SCHOTT, RALPH. THE INHERITANCE OF RESISTANCE TO SALMONELLA AERTRYCKE IN VARIOUS STRAINS OF MICE. Genetics 17: [203]–229, illus. 1932.

[4] ROBERTS, E. INHERITANCE OF RESISTANCE TO DISEASE IN ANIMALS. Internatl. Cong. Genetics Proc. 6 (2): 169–170. 1932.

before it will be known whether or not this is a case of a genetic factor giving practically complete resistance to a specific disease. It is to be hoped that the resistance of these pigs to *Brucella* will prove to be hereditary and that this finding can be used to advantage in combating brucellosis in swine. There have been reports in the past, however, of pigs immune to another disease, hog cholera, but no resistant strain has yet arisen from such animals, and it is entirely possible that such resistance may be due to acquired immunity or to some other factor that confused the genetic picture.

The cases cited show clearly that selective breeding can result in a marked decrease in death losses from certain diseases. If, for example, a loss of 85 to 90 birds out of every 100 can be cut down to 10, it would seem to be a matter of considerable economic importance. Why, then, has a system of selective breeding never been adopted in practice? The answer is probably to be found in the fact that resistance so secured is difficult and expensive to maintain. As Lambert's results show, a single outcross, bringing in other genetic factors, eliminates a large part of the resistance; then the process of selection, including tests with the disease organism, has to be repeated all over again in order to bring the stock back to a reasonably high degree of resistance. All this takes time and money. Unless the livestock industry can use such a system economically, it cannot be expected to find widespread application.

Theoretically, it would seem just as possible, through the application of genetic principles, to cut death losses from disease in half as it is to double egg production by breeding. The fact is, however, that in no single investigation of the possibility of breeding resistance to disease has the work been carried far enough to show how it might be given really practical application.

The plant breeder can hand the farmer seed from resistant plants, and the resulting plants will remain resistant in succeeding generations because their genetic purity is held relatively constant by self-fertilization, which is a natural process for many crop plants, including some of the grains. This the animal breeder cannot do. What can be done with animals is to approximate genetic stabilization through a less intense system of inbreeding than is possible with plants, but one sufficiently intense to fix any heredity for disease resistance that may now exist in a diluted form in animal populations. The problems of distributing resistant stocks to farmers and maintaining resistance afterward are bridges that must be crossed at a later time. The first step is for the experimenter to locate resistance and build up strains that breed reasonably true for this characteristic.

It can be said that such work has been begun only in a very minor way. The method of breeding used by most livestock breeders does not lead quickly to the formation of lines sufficiently inbred to mean much as far as the fixation of heredity for resistance to disease is concerned. Moreover, any selection that is practiced probably would be carried out in the absence of disease, because it is not to the advantage of the breeder to have disease in his herd. Thus any closely bred line developed under such conditions would not show

significant resistance to any disease except by pure chance. But it is very easy for the experimenter using modern medical and veterinary methods to infect animals with definite doses of disease organisms or agents and identify individuals possessing resistance. The fact that such procedure may work successfully is well illustrated by the recent report, mentioned earlier, by Cameron, Hughes, and Gregory, of the California station, on genetic resistance of swine to brucellosis. Apparently these workers have located an inbred strain in which some individuals possess resistance to this disease. Resistant × resistant matings have produced pigs showing either a complete immunity or a very high resistance. If this resistance persists through following generations, this inbred line will be the first brucellosis-resistant line of pigs to be developed and may furnish the starting point for controlling the disease by breeding methods.

VIGOR VERSUS RESISTANCE

The belief is fairly widespread that a vigorous individual is more resistant to infectious diseases than one less vigorous. It would be logical then to assume that inherited vigor would mean inherited resistance to disease. Whether this is true depends to a large extent on the definition of vigor.

The vigor of a family or line of animals is not inherited as a single unit but as a complex of several units which are largely independent of each other. This was shown by Wright [5] with guinea pigs. Long-continued inbreeding brought about a fixation of genetic factors affecting growth, body size, fertility, the occurrence of certain abnormalities, and resistance to tuberculosis. The differences in the closely inbred lines followed a pattern of independent assortment and fixation of heredity for these characteristics; resistance to tuberculosis, for example, did not show a tendency to be associated with any particular element of vigor. Possessing heredity for the elements of vigor is therefore no guaranty of heredity for disease resistance. Moreover, resistance to one disease does not necessarily have anything to do with resistance to another disease. A possibility coming out of the evidence on the lack of a relationship between resistance and inherited vigor is that heredity for vigor might be combined by suitable breeding methods with that for disease resistance; in other words, there is no reason why breeding cannot be used to raise the general levels of vigor and of resistance to disease at the same time.

CHANGES IN VIRULENCE OF DISEASE ORGANISMS

It is a matter of common knowledge that pathogenic organisms vary considerably in virulence, but not much is known about the causes of such variations. They may be due to the effects of a changing environment, or to some inherent change in the organism itself, or to both. The one thing certain is that there are changes.

[5] WRIGHT, SEWALL, and LEWIS, P. A. FACTORS IN THE RESISTANCE OF GUINEA PIGS TO TUBERCULOSIS, WITH ESPECIAL REGARD TO INBREEDING AND HEREDITY. Amer. Nat. 55 : 20–50, illus. 1921.

The fact that such changes occur introduces another complexity into the relation of genetics to disease. If the agent itself can mutate and hybridize, there is almost no end to the possible interactions between the host and the organism. What is interpreted to be an increased resistance might well result from a lower virulence, and vice versa. During the last 10 or 15 years there have been many reports on variability in pathogenic bacteria, but it is still not known whether genetics is playing a decisive role in bringing about such changes. Until new evidence is produced, speculation should be held to a minimum. The very important matter of a varying virulence should not, however, be overlooked; but nothing much can be done about it, nor can the facts be discovered, until the animals on which it is tested are stabilized genetically so that the results can be attributed to variations in the organism rather than in the host. Here is a relatively virgin field that is a challenge to research workers.

HEREDITARY DEFECTS IN FARM ANIMALS

Numerous physical variations that occur among animals should be mentioned here because of their relation to disease. Many of them can be classed as defects, and a high proportion are lethal—that is, they kill the animals inheriting them. In many cases the mode of inheritance of the defects has been worked out by actual breeding experiments.

No attempt will be made here to cite all the references to the scientific literature on the subject. Eaton [6] has published a summary report which includes about 150 literature citations, and the reader is referred to his paper for original sources of information.

CATTLE

Achondroplasia. Two types of achondroplasia have been reported, one of which seems to be a dominant and the other a recessive. The dominant form is the cause of the bulldog calves which occur in the Dexter breed and some African cattle. The affected calves have very short legs, a large rupture, and a much shortened bulldoglike head. The thyroid gland and kidneys are also markedly affected. Such fetuses are usually aborted during the fourth month of pregnancy. The recessive form, which occurs in Telemark and Holstein cattle, also results in a very short head, deformed jaws, and sometimes a cleft palate. Death occurs a few days after birth.

Acroteriasis congenita. Characterized by either the absence of all limbs or their development only to elbows and hocks, atrophy of the upper jaw, almost complete absence of the lower jaw, and a cleft palate. The affected calves either are still-born or die shortly after birth. Genetically the defect is a single-factor recessive.

Ankylosis. An ossification, or stiffening, of the joint of the lower jaw, which is shortened. It is reported to occur in Norwegian

[6] EATON, O. N. A SUMMARY OF LETHAL CHARACTERS IN ANIMALS AND MAN. Jour. Hered. 28: 320–326. 1937.

Lyngdal cattle. What is probably a related form in which there is ossification of all joints and a cleft palate occurs in some German cattle. Both are recessive.

Congenital dropsy.—Probably a single factor which results in an accumulation of water in the subcutaneous tissues (those immediately under the skin) and in the body cavities. Affected individual fetuses are frequently dropped 1 or 2 months prematurely.

Congenital ichthyosis.—A recessive factor that causes scaly and cracked skin. This factor may have some relation to the epitheliogenesis imperfecta (imperfect formation of skin) reported in Holstein-Friesian and Jersey cattle. Affected individuals have large hairless patches over the body and defective skin on the legs and the mucous membranes of the mouth and nostrils. The animals are born at term but die from septicemia (a general poisoning of the blood) soon afterward.

Hypotrichosis congenita.—A single-factor recessive which prevents hair development except on muzzle, eyelids, ears, pasterns, and top of tail. Affected calves die very soon after birth. It is reported to occur in Swedish Holsteins.

Impacted molars.—The premolars are impacted in the jaw, and the lower jaw, or mandible, is shortened. Affected calves are born at term but usually die during the first week. The defect is reported to occur among Milking Shorthorn cattle.

Muscle contracture.—A single-factor recessive causing a bending backward of the head, stiff neck, and rigid joints. It is reported to occur among Norwegian and Holstein cattle. A related form in Red Danish cattle makes the hind legs lame so the calf cannot stand. Such calves are born alive but soon die.

Short spine.—A single-factor recessive which occurs in Norwegian mountain cattle. The axial skeleton is much shortened, and the ribs and vertebrae are fused. Affected calves are usually still-born.

Some other lethal defects, such as mummification of fetuses and short limbs, have been reported, but there is some question as to whether they may not be only a phase of the action of one of the other factors already mentioned.

Horses

Atresia coli.—A single-factor recessive which results in death 3 or 4 days after birth. The ascending colon is greatly restricted or has a blind ending. Often the affected individual has a brain tumor.

Abnormal sex ratio.—A sex-linked recessive factor which kills about one-half of the male colts before birth.

Stiff forelegs.—Characterized by failure to stand and early death, probably due to hereditary factors. Matings between animals known to carry the defect produced 8 crippled to 18 normal foals.

Sheep

"*Amputated.*"—The absence of hoofs on all four feet. It has been reported to occur in Holland, but the mode of inheritance is unknown.

Earlessness and cleft palate.—A single-factor recessive which causes cleft palate, earlessness, short lower jaw, and tripartite claws. It has been reported to occur in Norwegian sheep.

Lethal gray.—A recessive factor reported in Turkana sheep in Rumania and in Karakul sheep in Russia. Homozygous gray lambs die.

Muscle contracture.—A recessive factor which makes leg joints stiff and neck crooked. Lambs are still-born. It is reported to occur in Welsh mountain sheep.

Paralysis.—A recessive factor which paralyzes the hind legs and causes death of the affected lamb a few days after birth.

Skeletal defects.—A single-factor recessive, reported to occur among sheep in Iceland, which produces a short body, large skull, short upper jaw, rigid fetlocks, and absence of wool from brisket to anus. The lambs are born alive but soon die.

Swine

Atresia ani.—Partial or complete closure of the anus of pigs. Affected animals die soon after birth. It has been reported in Europe and observed in the United States.

"*Catlin mark.*"—A single-factor recessive which causes an opening between the parietal (side) and frontal bones of the head. Death occurs within an hour after birth.

Cleft palate.—A recessive factor which gives various degrees of abnormal palate. Pigs die soon after birth owing to inability to nurse.

Fetal mortality.—A factor, probably recessive, which seems to be associated with inability to utilize certain vitamins and salts, causing death of fetuses.

Hypotrichosis.—The hereditary form of hairlessness in swine, which is not lethal as it is in cattle. The most common type of hairlessness in swine is due to an iodine deficiency and usually results in still-born pigs. The administration of iodine to the sow will prevent the occurrence of this type but has no effect on the hereditary form of hairlessness.

Muscle contracture.—A single-factor recessive which causes stiff front legs. Affected individuals are either still-born or die soon after birth.

Paralysis.—A single-factor recessive which produces complete paralysis of the hind legs.

Poultry

Abnormal upper mandible.—A recessive factor which reduces the maxillae (jawbones) and nasal bones and bends the beak to one side. Such chicks rarely hatch.

Chondrodystrophy.—Fetal deformation of bones and joints. Inheritance of this defect is complex and probably involves three recessive factors.

Congenital loco.—A single-factor recessive which results in bending

back the head and in inability to stand. Over three-fourths of the affected individuals die within a month after hatching.

Creeper.—A dominant factor which in homozygous condition causes death on the fourth day of incubation.

Dwarf.—A single-factor recessive which causes death when in homozygous combination.

Recessive white.—A recessive factor which may be sex-linked. The homozygous whites die.

Short legs.—A factor reported to occur in Dark Cornish fowl which when homozygous causes death near the end of the incubation period.

Sticky embryo.—A recessive factor which causes the presence in the egg of sticky liquids that prevent chicks from hatching.

Crested.—An inherited factor which causes extreme cerebral hernia in ducks. Affected individuals die when nearly ready to hatch.

There are some other conditions such as malposition of embryos and embryonic abnormalities of several types, which cause death before hatching, for which the inheritance has not yet been determined.

CONCLUSIONS

The preceding list of lethal defects includes those that have been studied sufficiently to determine that they are due to genetic factors. New cases are continually being brought to light as more attention is given to genetic investigations in livestock. For instance, a case of what appears to be inherited hemophilia (delayed clotting of blood) was observed in swine in 1940. This defect is due to a single autosomal recessive factor and thus differs from hemophilia in man, which is sex-linked in its inheritance,

There are some types of defects in small animals, such as guinea pigs and mice, which are known to have a hereditary basis, but which have not been studied in farm animals. An illustration is the well-known case of otocephaly in the guinea pig, which produces cyclopean monsters, with only one eye. The same kind of defect has been observed in cattle, sheep, swine, cats, dogs, and man. While its inheritance is very complex, enough is known to say that herd or flock sires producing it should be discarded.

Fortunately, the number of hereditary lethals occurring among breeds of livestock in the United States is not very great, nor do they appear very often in most stocks. Nevertheless, they are a big factor in some strains, and because most of them are recessive they can be spread far and wide without showing their presence. When lines of ancestry containing such a defect are brought together it may be expected that some of the offspring will show the character. When this occurs it is important to remember that both the sire and the dam carry the recessive genetic factor, and they and all their offspring should be eliminated from the breeding herd if it is desired to get rid of the trouble.