GENETIC INDICATORS OF RESISTANCE TO DISEASE IN DOMESTIC ANIMALS

Indicadores genéticos de resistencia a las enfermedades en los animales domésticos

Indicateurs génétiques de résistance aux maladies chez les animaux domestiques

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The quest for indicators of performance in domestic animals is nothing new. In the first century A. D., COLUMELLA advised poultrymen to breed hens with five toes because (said he) such birds are better layers than those with the usual four toes. Ever since then, animal breeders have looked for some outward and visible sign of what performance they might expect from the animals under their care.

Over the years, a number of such indicators have been recognized, particularly those associated with faulty reproduction. Others, like that of COLUMELLA, have been imagined, and have persisted for centuries, but, when tested in the cold, critical light of controlled experimentation, have been found wanting. Only 40 years ago, PRAWOCHENSKI made exactly such tests of a belief then prevalent in Poland that the amount of milk and butterfat to be produced by a cow is indicated by the extent of colour in her muzzle, or of black pigment in her coat. It wasn't.

If we may consider as disease any condition that causes subnormal health, productivity, or reproduction, a number of genetic indicators of such disease are already known. Most of them are monogenic and recessive. Obviously, the genes causing such defects are genes for susceptibility to disease. Equally, the alleles of such genes, usually dominant, are indicators of resistance, *i. e.*, they induce normal anatomy, physiology and health.

COLOUR INDICATORS

Genetic susceptibility to disease is most easily recognized when it is associated with some colour. Familiar examples include the sterility long known in white

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heifers, low viability and digestive disorders in grey sheep, and the higher incidence of melanomata in grey horses. One such indicator recognized in recent years is the grey coat of the Collie, which apparently always foretells cyclic neutropenia and early death of dogs showing that recessive character (5). The dominant gene inducing the Heggedal mutant (dilution of melanin) in the mink is not only lethal to homozygotes but also causes disorders of the reproductive tract in many of the heterozygotes (24).

Limitations of time and space preclude any complete listing here of such indicators. Some have been discussed elsewhere (14). The first gene to be recognized as lethal has multiple pleiotropic effects and is an indicator of resistance to one disease and of susceptibility to another. It is the dominant gene A^y causing yellow coat in the mouse. Homozygous yellows die early in embryonic development. Heterozygous yellows, when compared with their non-yellow litter-mates, become slightly bigger and more obese. They are more resistant to spontaneous mammary carcinoma (21), but not to other neoplasms, and are more subject to diabetes (4).

In a broad definition of disease, all of the abnormalities mentioned thus far are diseases, but all are idiopathic, *i.e.*, not caused by infection or by other kinds of adverse environment.

Cancerous eyes in Hereford cattle.—One indicator of genetic resistance to an environmental stress is found in Hereford cattle. In that white-faced breed, carcinoma of the eye («cancer eye») is a common affliction in areas having intense sunlight, especially in animals over four years of age. There are genetic differences in such suceptibility to cancer of the eye, but, with onset of the condition so long delayed, breeding for resistance to it would be impracticable unless some indicator of that resistance could be recognized at a younger age.

Studies in Africa (3), Australia (10), and America (2) have revealed exactly such an indicator. A ring of pigment in the skin and hair around the eye provides almost complete protection. As such pigmentation is heritable, and can be recognized long before breeding age, it is a valuable indicator that should make breeding for resistance to cancerous eye comparatively simple.

Other indicators

Indicators other than colour include the rose comb of the fowl, which prevents fertility or greatly reduces it in homozygous males, but not in heterozygotes (7). The pea comb of the fowl increases susceptibility to breast blisters (12). Horned goats have fewer intersexes in their progeny than polled ones, and among homozygous polled bucks only about 20 % are fertile (26).

Infectious diseases

Resistance to infectious disease is more likely to be polygenic than attributable to a simple pair of alleles. It is greatly influenced by the severity of exposure to the pathogen (virulence, dosage) and of environmental stress. Genetic resistance can seldom be recognized without exposure to the infectious agent. Even then some kind of additional environmental stress may have to be added if the pro-

portion of the flock or herd showing symptoms is to be brought high enough to reveal genetic differences in resistance. Nevertheless, a survey made some years ago showed that, in domestic animals ranging from honey bees to horses, wherever genetic resistance had been adequately sought, it had been found (13).

Difficulties encountered in breeding for resistance to infectious diseases in domestic animals have been discussed elsewhere (15, 16, 17). For present purposes it should suffice to say only that one such difficulty is that stockmen and veterinarians naturally object to any deliberate exposure of their animals to disease, even to breed resistant stock.

That objection could be overcome if some genetic indicators of resistance could be found, so that the breeder could use them to raise resistance in flocks or herds never exposed. Some such indicators have been found, and it is to be hoped that future research will reveal more of them.

Resistance to mastitis in cattle.—Mastitis is probably still the most costly infection besetting dairy cattle. The ample evidence of genetic resistance to it has been reviewed earlier (13), and it was later pointed out that, by a single generation of mass selection on the dam's side only, the incidence of mastitis had been reduced by about one third (14). Since it is less prevalent in early lactations than in later ones, breeding for resistance by the usual procedure of progeny testing is likely to be a slow process.

Resistant cows can be readily identified by experimental infection (19, 23), but, since resistance tends to decline with successive lactations, those highly resistant cannot be recognized until they are five years of age, or older. Any indicator that would reveal resistant animals at younger ages would change that situation and make such breeding feasible.

The possibility that exactly such an indicator may be found is suggested by the finding that resistant cows differ from susceptible ones in the proportions of certain fatty acids in the sebum-like material from the teat canals. Resistance was associated with a higher proportion of myristic, palmitoleic and linoleic acids than in the teats of susceptible quarters. The latter showed significantly more palmitic acid than resistant ones (1).

Further study is necessary, but the fact that these differences could be recognized even in two-year-old heifers suggests that such an indicator might be used in young animals before lactation (and possibly even in bulls) to identify relatively resistant and susceptible animals. If so, breeding for resistance to mastitis would become simpler than breeding for more milk or butter fat.

In this connection, the findings of EDWARDS *et al.* (9) with monozygotic and dizygotic Ayrshire twins are of interest. They found that significant differences among comparable cows in the proportions of fatty acids in their milk were highly heritable. The possibility that such differences might serve as indicators of resistance and susceptibility to mastitis seems worthy of investigation.

Resistance to pullorum disease in the fowl.—In a long series of experiments which has been summarized elsewhere (13), it was found that resistance to *Salmonella pullorum* is greatest in chicks that have best control of their thermoregulatory mechanism. Such chicks can be identified (without being infected) by determining the rate at which they make the transition from their poikilothermic state (during incubation) to the homeothermic state of the 10-day chick.

That rate can be measured by the average temperature of the chick (on three days or more) during the first six days after hatching. By 10 days, when the range is 105°-107 °F, resistance is enhanced or assured.

After this indicator had been discovered, two separate lines of chicks were bred, one for early high temperature, the other for early low temperature. In the second generation, the average temperature in the high line was only 0.59 °F above that for the other. Nevertheless, when samples of both lines were inoculated with equal doses of *S. pullorum*, mortality to three weeks of age was consistently lower in the high-temperature line than in the other one. With the lightest dose, mortality in the former was only 8.6 %, against 40.7 % in the low-temperature line (18).

This is believed to be the first demonstration in animals that genetic resistance to some disease can be raised — without exposure to it — by selection for some indicator proven to be associated with resistance to that disease.

The mechanism of resistance to pullorum in this case is not the attainment of a thermal death point for the bacterium, but, rather, the capacity to make a quick febrile response to infection.

As pullorum disease can now be controlled by other means, the indicator thus sought and found effective is not needed for that particular disease. To what extent it might be useful in breeding for resistance to others remains to be determined.

Resistance to pneumococci in rabbits.—Closely related to the indicator just described is one found by LOCKE in rabbits (22). Those resistant to virulent pneumococci can be differentiated from susceptible ones by measuring the «warming time», *i. e.*, by first chilling the animals to body temperatures of about 95 °F and then determining the time required for a subsequent rise of three degrees. At each of three different dosages, rabbits previously found to have warming times below 35 minutes were more resistant than those requiring more than 45 minutes.

This indicator, like that for resistance to pullorum, suggests that superior control of the thermoregulatory mechanism may be essential for resistance to some bacterial infections. Together they provide a good lead in the quest for indicators.

Resistance to the «Chediak-Higashi» syndrome.—This disease, now known in man, in partially albinotic Hereford cattle, in Aleutian minks and (probably) in beige mice (20), is caused in all these species by a recessive gene in the homozygous state. Among its several manifestations is susceptibility to infections of various kinds (25). The dilution of pigments, which is always conspicous, is thus an indicator of susceptibility to infection, and the syndrome provides an unusual situation in which general susceptibility to infections of various kinds results from homozygosity for a single recessive gene.

Obviously the dominant allele at the same locus is an indicator of genetic resistance to the CHEDIAK-HIGASHI syndrome and to the assorted infections that go with it.

Resistance to neoplasms in the fowl.—Attempts to relate specific blood antigens to performance in domestic animals have not been conspicuously successful, but there is at least one case in which a blood group is an indicator of genetic resistance to disease. CRITTENDEN *et al.* have shown that embryos lacking the antigen R_1 are resistant to infection by viruses of sub-group B causing avian leukosis (8).

In striking contrast embryos that carry the dominant allele R^I are all susceptible. Further search for other similar relationships may be rewarding.

Discussion

It is possible that most indicators of resistance or susceptibility which can be readily seen, such as colours or anatomical features that differentiate breeds, have already been recognized. The quest for indicators not yet known will have to deal with variations in physiology, like those in proportions of fatty acids, control of body temperature, and blood antigens mentioned earlier. In other words, it will not be easy.

Chromosomal aberrations may be indicators, but those recognized thus far in domestic animals shed light on disorders of reproduction rather than on viability, or on resistance to infectious disease. Examples include the Kleinfelter syndrome in several species and the 1/29 translocation in cattle (11).

To those who ask for what diseases is genetic control desirable, the best answer may be that it should be tried with any disease for which other methods of control are inadequate or too costly. Some that come readily to mind are mastitis, rhinitis in swine, foot-and-mouth disease, and tick-borne diseases. Genetic resistance to all of these has been demonstrated. Furthermore, genetic resistance persists but the temporary cures by drugs and antibiotics do not.

As for procedures, the simplest way would seem to be to find how the most resistant animals differ from the most susceptible ones. The two kinds are easy to identify. Whenever disease strikes animals equally exposed, the most susceptible are those affected most severely, or earlier, or at younger ages (in populations of different ages). Those most resistant may show mild symptoms, or be entirely unaffected. Other things being equal, the cow that develops mastitis in her first lactation is susceptible; the one in the same herd still free of it at 10 years of age is resistant.

Put in another way, the search is first for the exceptional individuals, breeds or strains that thrive when others succumb, and then to find what they have got that susceptible animals have not. Examples are the cows that could not be infected with *Str. agalactiae* in 16 attempts to do so (23), and the amazing Honduran cow found able to keep free of ticks for nine months, in an environment infested with ticks, when 70 other cattle could not do so (27).

The search for such exceptional animals and study of them should reveal more genetic indicators of resistance to disease than those known to-day. Meanwhile, let us remember that, even when no indicator was known, and long before any other control became practicable, the feasibility of breeding strains of the fowl highly resistant to Marek's disease and to leukosis, and at the same time highly productive, was demonstrated (6).

SUMMARY

Familiar genetic indicators of disease include white coat in heifers (frequent sterility), grey fleece in sheep (fatal digestive disorders), and grey colour in the Collie (lethal cyclic neutropenia). The yellow mouse is resistant to one disease

and susceptible to another. Dilution of melanin in the CHEDIAK-HIGASHI syndrome foretells susceptibility to various infections. Animals lacking any of these indicators of susceptibility automatically carry indicators of resistance.

A genetic indicator of polygenic resistance to a disease caused by environmental stress is the ring of colour around the eyes of Hereford calves. It protects them from developing cancerous eyes in later life.

An indicator of genetic resistance to a specific bacterial infection (pullorum disease in chicks) was used to breed resistant stock in birds never exposed to the pathogen. The desirability of similarly breeding animals resistant to other diseases is considered, especially for diseases not otherwise adequately controlled.

RESUMEN

Los indicadores genéticos comunes comprenden la capa blanca en las terneras (frecuentemente esterilidad), la lana gris en las ovejas (alteraciones digestivas mortales) y el pelo gris en la raza Collie (neutropenia cíclica mortal). El ratón amarillo es susceptible a una enfermedad y resistente a otra. La dilución de la melanina en el síndrome de CHEDIAK-HIGASHI presagia la susceptibilidad a diversas infecciones. Los animales en los que faltan algunos de estos indicadores de susceptibilidad son portadores automáticamente de indicadores de resistencia.

Un indicador genético de la resistencia poligénica a una enfermedad causada por las tensiones en el medio ambiente es el anillo de color (ojalado) alrededor de los ojos de los terneros de raza Hereford. Les protege contra el cáncer del ojo más adelante en su vida.

Un indicador de resistencia genética a una infección bacteriana (pullorum en los pollitos) fue utilizada para la producción de estirpes resistentes a la enfermedad, que no quedaron jamás expuestos al agente patológico. Se considera la conveniencia de producir análogamente animales resistentes a otras enfermedades, en particular a las que no pueden controlarse con eficacia.

RESUME

Des indicateurs génétiques communs, comprennent robe blanche chez les génisses (frequemment stérilité), laine grise chez le mouton (désordes digestifs mortels) et robe grise chez le chien de race Collie (neutropènie cyclique mortelle). La souris jaune est susceptible à une maladie et resistant à une autre. La dilution de la mélanine dans le syndrome de CHEDIAK-HIGASHI présage la susceptibilité à des infections variées. Les animaux manquant certain de ces indicateurs de susceptibilité portent automatiquement des indicateurs de résistance.

Un indicateur génétique de la résistance polygénique à une maladie causée par les tensions du milieu est l'anneau de couleur autour des yeux des veaux de race Hereford. Il les protége contre le cancer de l'oeil plus tard dans leur vie.

Un indicateur de resistance génétique à une infection bactérienne spécifique (pullorum chez les poulets) fut utilisé pour la production de souches resistantes à la maladie, qui ne furent jamais exposées a l'agent pathologique. L'attrait de reproduire, semblablement, des animaux résistants à d'autres maladies est considéré, particulièrement pour les maladies qui autrement ne sont pas controllées éfficacement.

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