Over the Medical Horizon

Genetic constitution of host and pathogen in relation to disease

John W. Gowen, B.S., M.S., Ph.D.*

MEN MIGHT quarrel over what is meant by horizons in medicine. I mean by horizon the time at which an idea, proved true and beneficial to the health of mankind, which in the breadth of its effects on the multiplicites of sickness alters our whole disease concept and is of such scope that its deliniation may occupy lesser mortals for years, centuries, yes, even millennia. Medicine has had few horizons and the dawning has often been long in coming to the whole earth.

The first great horizon is found in the earliest medical book which has survived for our reading, the Smith Surgical Papyrus, possibly the product of the hand of the man, Imhotep, later deified by the Greeks as the God of Medicine, Aesculapius. In this book disease is viewed as a rational process, not due to supernatural causes beyond the realm of man to understand and treat. A beginning of disease understanding was made but was long a-dawning, for the 2500 years between the Egyptian surgeon and the Hippocratic Corpus, was filled by star divination and astrologers whose pulp journals still have a place on our own newstands.

Second Horizon

The Hippocratic Corpus set forth a second horizon. Sickness could be broken into parts and these parts separated, classified and recognized by their characteristic symptoms. The working out of these disease syndromes occupies us today even though 2500 years have lapsed.

Whispers that disease often had its origin in minute, invisible, organisms living in the bodies of their host, were recorded in some of the earliest Egyptian and Biblical writings, were first clarified by Fracastorius in his sixteenth century writings on syphilis and given a true dawn a century ago by Pasteur and Koch in the formulation of the germ concept of disease. New vistas were opened—a disease could be regulated by controlling a particular pathogen.

Early Immunization

That pathogen and host develop reaction systems which may generate chemical bodies capable of immunizing the host or of being reacted upon by other drugs is an idea whose origin is lost in the heritage of our folklore. Specific drugs and vitamins were used in the earliest times of record, i.e. castor oil, oil of fish livers. Paracelsus emphasized the study of chemistry. The Chinese were practicing active immunization for small pox while the Incas were using cinchona bark for malaria. But the real dawning came in our century when the work of Bordet and Ehrlich opened to us the realization of the possibilities of specific chemical therapy in disease.

The thought that heredity has a relation to disease appears early, is lost and re-discovered in the writings of men who have tried to place medicine on a rational basis, but the significance of the heredity of host or pathogen to medicine is yet under our horizon. It is true that the Talmud recognized haemophilia as a cause for
omitting circumcision more than a millennium ago; that many pathological conditions have been pedigreed for over 500 years; that the understanding of modern heredity has been ours over the last half century in which breeders of plants have made great progress in controlling disease through genetic means. But it is also true that the importance of the genetic constitution of man or economic animals to disease prognosis is scarcely recognized, and the genetic constitution of the pathogen so little considered as to be almost dismissed. Yet should either of these genotypes be faulty, disease would not result or its syndrome would be greatly modified.

**Experimental Studies**

I shall draw on experiments conducted at Iowa State College to illustrate the extensive and inclusive effect of the genetic constitution of host or pathogen on disease and disease resistance. These experiments are in the nature of model experiments on small animals with which you are all familiar in your studies to establish principles of clinical disease, histological pathology or serum fixation.

Mice are susceptible to a typhoid-like disease caused by *Salmonella typhimurium*. The severity of the disease depends upon the dose of organisms which the mouse receives at its initial contact. For random bred mice at a constant dosage the death rate often ranges well over 90 percent. But random bred mice are a heterogeneous lot so far as their inheritance for any characters, disease resistance included, are concerned. Schott performed an experiment to isolate this heterogeneous inheritance into reasonably pure breeding lines some of which were resistant, some of which were susceptible to mouse typhoid. The initial population of mice with which he started had a mortality of 82 percent. Selecting from survivors and inbreeding these, the first generation progeny had a mortality, under the same conditions with the same organism and dose, of 64 percent. Repeating this genetic procedure, a second generation had a mortality of 46 percent; the third generation of 40 percent; the fourth generation of 36 percent; the fifth of 33 percent and the sixth of 24 percent. The steady reduction of these death rates as the genetic technique of isolating the resistance was continued shows the importance of the genetic constitution of the host to this disease resistance. In the subsequent years in which these experiments have been continued the dose of organisms has been raised from 50,000 to 200,000 while the death rate has now gone down to less than 8 percent.

At the same time susceptible lines were established through a similar technique. The death rate of the susceptible lines under the same dosage is almost uniformly 100 percent. For a dosage about 0.0002 of that of the resistant lines, the susceptible lines still die out almost completely.

A comparable experiment was performed by Lambert in which he separated a highly susceptible flock of White Leghorn chickens into lines. This experiment has much the same history as that of the mice. In six generations mortalities for fowl typhoid, *Shigella gallinarum*, were reduced to about 10 percent in the lines selected for resistance as against something over 85 percent for the lines with which he started.

**Results Universal**

The results obtained with mouse typhoid and chicken typhoid have proven to be well nigh universal in subsequent tests on other types of pathogens, including other bacteria, protozoa, viruses and even such large many celled pathogens as helminths. Within any host the variation from mortality to morbidity to immunity for a given disease appears as a consequence of the genetic constitution of the individuals composing the groups tested.

The inheritance of resistance or susceptibility behaves like other inherited characters with which we are familiar. By continuing the genetic technique which Schott had found adequate to establish resistant and susceptible lines, Hetzer was able to increase the resistance of the resistant strains to a still further degree. At
that time the average survival of the resistant mice had reached 84 percent for the standard dose of 200,000 organisms. Reciprocal crosses were made between resistant and susceptible strains. Where resistant males were used the survival value was about 89 percent. Where susceptible males were used it was about 79 percent. The results of these crosses are adequate proof that resistance is due to the inheritance received by the hybrids rather than to either passive immunity or active immunity transmitted to the progeny through one or both of the parents carrying the organisms for the disease. However, since this point is of considerable importance a critical test was made by Gowen, Schott. The progeny of the susceptible stock and of the F1 cross between the resistant and susceptible strains were derived from a single mother as members of the same litter by double fertilization. Progeny derived from susceptible sperm fertilizing susceptible eggs show practically no survival when inoculated whereas those from resistant sperm fertilizing susceptible eggs have a survival value corresponding to the corresponding Fl's tested by Hetzer and Schott.

Genetic Background

The genetic mechanism is further established by crossing the F1 individuals back to either the resistant or susceptible males or females. These crosses show the segregation of the genetic factors for resistance in the F1 animals in the same manner as segregation occurs for any other genetic character of like complexity. The results also show no linkage between the sex or color genes for albinism, silver, or agouti.

The physical mechanism on which this resistance or susceptibility to mouse typhoid is based is being studied. In an investigation designed to examine the part played by the circulating blood cells, Gowen and Calhoun have shown that the genetic techniques used in forming our mouse strains have fixed the numbers of both erythrocytes and leucocytes. As might be expected the fixation of the erythrocytes shows little relation to typhoid susceptibility or resistance. On the other hand the fixation of the numbers of leucocytes shows a very high correlation with the susceptibility or resistance of the particular strain. Of the circulating cells the leucocytes appear to have direct importance to the genetic susceptibility or resistance to disease.

The percentages of the different types of cells which compose the leucocytes are more variable, the breeding techniques having had little effect in fixing the different types. These facts suggest that inheritance affects the numbers of the leucocytes, but environmental conditions may cause the primitive cell to develop into any one of the several types of leucocytes.

Genetic Constitution Altered

With host resistance isolated into six different lines, each having a characteristic level of susceptibility or resistance to the disease, the question arose—is it possible to alter the genetic constitution of the pathogen causing the disease in the same manner as the genetic constitution of the host has been altered? This question has been studied in our laboratory utilizing pathogens of mice, the domestic fowl and corn. Results of these investigations are concordant in showing that it is possible to alter the genetic constitution for virulence in these bacteria.

In mice, Zelle repeatedly subjected the mouse typhoid organisms to the environment of either susceptible mice or resistant mice instead of the culture media on which they are ordinarily carried. He observed that sporadically organisms were recovered from a single mouse in the experiment which had markedly different virulence from that of the culture introduced. These changes were generally not found in cultures from the mouse's own brothers and sisters. The change was limited to a single mouse at any one time. Furthermore these virulence changes occurred at random throughout the pedigree history of the organism. Once the change was noticed a subsequent change was seldom observed in that strain in the limited time covered by the experiment.

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His ability to recognize these conditions promptly and to take the necessary measures for their suppression enables him to discharge his responsibilities in the manner expected by an enlightened citizenry. The role of the veterinary practitioner in our program of public health is significant and his contributions should be recognized and appreciated more widely.

As veterinarians we must take cognizance of the fact that gains made in suppressing infectious and parasitic diseases can be maintained and strengthened only by constant vigilance. The veterinarian and the physician must be mindful that the agents of disease recognize none of the rules of decent conduct but are always ready to attack when the circumstances are propitious. The task of controlling infectious diseases when once begun must be continued indefinitely. Old diseases may seem to disappear, yet they are only quiescent. New diseases are being recognized constantly. If our watchfulness and diligence are lessened through a false sense of security or indifference, infectious diseases are likely to get out of control, often with disastrous results.

Still No Utopia

Although the attack on the complex problems of disease is becoming more militant and intensified with each passing year, the final goal, that Utopia where disease has been banished, is probably not possible for man to achieve. Many infectious or parasitic diseases, however, can be controlled by reducing the possibilities for their transmission and by utilizing the agents and knowledge that research has provided for their prevention and treatment. To continue the attack and to maintain the objectives gained are important parts of every veterinarian's responsibility. In the conquest of disease the veterinarian has established a record of splendid achievement. In the field of medicine in which he is qualified he has contributed substantially.

The increasing awareness of the general public to matters concerning health emphasizes the opportunities and responsibilities for adequately trained veterinarians who can properly assume their share of the task of making the United States a nation in which bovine tuberculosis will have disappeared, undulant fever will have ceased to exist and rabies will no longer cast the tragic shadow of death over the lives of children. America is health-conscious as never before and the opportunities for veterinarians to contribute to the health of the nation are unlimited.

MEDICAL HORIZONS

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The extensive experiments agree with the concept of sudden mutation causing a sudden change in virulence of a particular bacterium. When once this mutation has occurred the strain derived from this mutated bacterium holds the new level of virulence established by the mutation. The lethal capacities attained by different mutations are different. We now have several of these strains in the laboratory. Some are far more virulent than we have had in the past. Other mutations are nearly avirulent forms of Salmonella typhimurium. Yet in each instance the mutants retain the characteristics of the species in sugar fermentation, growth characters and serum reactions. Similar experiments with the fowl typhoid organism, Shigella gallinarum, show the same results.

In corn wilt we have been able to extend the study of bacterial variation in virulence through the use of radiant energy. Mutants thus caused often markedly differ in their virulence from that of their parent strain. In some the virulence increases; in others it decreases.

These results show the interlocking of genetic constitutions of the host and the pathogen in the production of the abnormal state which we call a disease. There is no reason to suppose that these experiments are peculiar to the mouse typhoid, fowl typhoid or the bacterial wilt of corn. Are the experiments herein so hastily portrayed giving us a prevue of a new horizon in the march toward disease control?