INVESTIGATION OF DISEASE RESISTANCE AND THE MATHEMATICAL PROBLEM OF PATTERNS

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Immunology, a well-established and highly fruitful discipline, is concerned primarily with the investigation of acquired or induced resistance or immunity to infectious diseases. We are concerned here primarily with the investigation of disease resistances which lie outside this major interest of immunologists. These have received relatively little attention.

What, for example, is the basis for the observation that some individuals are immune to an infectious disease from birth to death or that some can be carriers of an infectious disease without ever having suffered from it? Still more important to our discussion is the apparent fact that each individual in a population has a peculiar assortment of susceptibilities and resistances to all types of noninfective diseases.

The fact that people are unequally affected when there is an infectious epidemic might possibly be explained on the basis of some previously acquired immunity on the part of some of the individuals. But this inequality of response is observed also when noninfective diseases are concerned. When pellagra-producing diets are consumed in a community only certain individuals are severely affected; when polished rice is the basic food of all, only selected individuals exhibit acute beriberi. In regions where endemic goiter is prevalent, only susceptible individuals exhibit the diseased condition. Only certain individuals have specific tendencies toward gout or arthritis or diabetes, hyperinsulinism, hypo- or hyperthyroidism, coronary disease, nephritis, Addison's disease, duodenal ulcers, or any one of a host of other diseases. Other individuals appear to exhibit specific resistance toward any one (or more) of these diseases.

Innate immunity with respect to leukemia, mammary cancer, stomach cancer, etc., also appears to exist in some individuals who are free from these diseases throughout life, living in the same environment as those who are afflicted. Many medical and public health authorities are loath to admit the existence of potent genetic factors in cancer because such admission appears to pronounce doom for a percentage of the population. Failure to admit does not change the facts, however, and failure to face them realistically retards the arrival of the day when cancers can be prevented by critical and intelligent alteration of the environment.

This problem has come to the fore in recent years when it has become reasonably evident that heavy smoking is a potent factor in the production of lung cancers, that is, of the squamous-cell type. According to the best evidence, however, only about one heavy smoker in ten actually suffers from this type of lung cancer. Among women, the incidence is estimated to be somewhat lower. It is becoming increasingly evident that some substantial percentage of the population is relatively immune to this type of lung cancer; these are not liable to contract it even as a result of heavy smoking. Wouldn't the tobacco companies like to know who these invulnerable individuals are and why?

The recognition of innate resistance factors does not conflict with the probability that heavy smoking is an important precipitating factor; neither does it conflict with the growing probability that virus-like agents are involved in all cancers. It seems most likely on the basis of available evidence that only vulnerable individuals suffer from lung cancer and that these are most likely to suffer when heavy smoking allows the cancer-producing agents (possibly carcinogens and eventually virus-like agents) to function.

Another area in which I am fully convinced that similar resistances and susceptibilities exist is that of mental disease. If mental disease has a biochemical basis (on this point, doubts grow less and less), then it is reasonable to conclude, because of the known relationships between biochemistry and genetics, that genetically-induced metabolic tendencies play an important part in determining who will and who will not be afflicted with mental disease—as well as the type of impairment.[1] This does not deny the importance of environmental factors any more than recognizing variable susceptibilities to lung cancer denies the importance of heavy smoking or the role of virus-like agents in the production of this disease. Again in the case of mental diseases, there is a tendency to think that if we admit that hereditary factors predispose toward them, this is equivalent to concluding that mental disease is inevitable in certain individuals. This is very far from the truth. There is a real and substantial hope that recognizing the roots of mental disease—in those who are vulnerable—will prepare us to prevent its occurrence.

Ignoring the innate susceptibilities which exist in every population—or at least failing to explore them adequately—has been, in my opinion, a serious block to progress in the control of many noninfectious diseases—nutritional, metabolic, degenerative—including mental disease, alcoholism, addictions of other kinds, and a host of disorders in the mental realm which are not regarded as frank mental disease. If the vulnerable individuals in many areas could be spotted in advance, the disorders might be prevented with comparative ease.

In our laboratories, attempts have been made to find biochemical earmarks which may indicate vulnerability to alcoholism. Some progress has been made since the last report[2] but we have encountered a new obstacle in the fact that for certain items with which we are concerned there appear to be inter-ethnic differences (highly significant statistically) which probably make some of the prospective earmarks applicable only to the ethnic group within which they have been observed.

A most crucial lack in connection with the investigation of innate resistances and susceptibilities in general is the lack of straightforward and entirely suitable mathematical techniques for dealing with patterns effectively.

There exists in each individual because of his distinctive anatomical, physiological, neurological, biochemical, and psychological inheritance a host of innate, measurable factors.[3] Individually, each of these items yields, when applied to a population, a distribution curve. Collectively, these items constitute a *pattern* which is distinctive and different for each individual and which cannot be handled by traditional statistical methods.

Among the numerous measurable items, some are presumably pertinent to one's resistance to a specific disease, e.g., leukemia, and others would be meaningless in this connection but may be highly pertinent to one's resistance to another disease such as arthritis.

In the exploration of the factors which enter into the make-up of one's pattern it is essential that we distinguish between those measurements which correspond to innate factors and those which are transitory and insignificant from the standpoint of inborn characteristics. Though little attention has been directed toward this problem, the difficulties it offers are not insurmountable.

It is also necessary in the exploration of the numerous measurable items to select those which are pertinent to any specific disease susceptibility under investigation. This selection enters into the problem of patterns.

Difficulties of mathematical treatment arise not in connection with individual items but with patterns. For these there are no averages, norms, standard deviations, or distribution curves in the usual sense. Various mathematical techniques have been used to compare these patterns involving psychological data[4] but none fully fills the need. To test out the value of these and other techniques[5] requires that they be applied to the less nebulous data obtainable from anatomical, physiological, and biochemical measurements.

I am not, of course, in a position to speak for mathematicians or to keep abreast of most recent developments, but it does appear that there is a growing mathematical interest in patterns (often for reasons quite independent of our particular application) and that we may hope for significant progress, particularly with the growing availability of magnificent computers capable of carrying out complicated operations with great rapidity.

The lack of the development of suitable mathematical techniques, readily available to biological and medical scientists, has been and continues to be a strong deterrent to the collection of necessary data. These data must be extensive with respect to each individual studied and are both expensive and laborious to collect, and the inclination to collect will not be strong as long as doubt remains as to how the data can effectively be treated mathematically once it is collected.

The potentiality exists for the complete exploration of the innate susceptibilities to every disease and to identify in advance those individuals who are vulnerable to each. Recognition of vulnerability and the factors which enter into it should go a long way in the direction of effective control.

While it is logical that susceptibility to each disease be studied as a separate problem, the techniques for such study are undeveloped, and advancement with respect to any disease will throw much light not only on related diseases but upon the whole strategy of discovering susceptibilities.

This largely unexplored problem of disease susceptibility is such an extensive one that no individual investigator nor any ordinary team of investigators can do more than scratch the surface. It is a problem requiring large and sustained support. The Congress of the United States has been and continues to be generous with funds to support research in the field of health. It seems obvious to the writer that some substantial part of these funds should be channeled into the investigation of the disease susceptibility of individual people—about which we know so little. We need to remind ourselves that individual people are the only kind that exist. Some of the funds devoted to disease susceptibility should be used if necessary to stimulate mathematicians to develop whatever tools may be necessary.

[1] Williams, R. J., "The Biological Approach to the Study of Personality," (Presented to Berkeley Conference on Personality Development in Childhood, University of California, May 5, 1960).

[2] Williams, R. J., R. B. Pelton, H. M. Hakkinen, and L. L. Rogers, "Identification of Blood Characteristics Common to Alcoholic Males," these PROCEEDINGS, **44,** 216–222 (1958).

[3] Williams, R. J., *Biochemical Individuality* (New York: John Wiley & Sons, 1956).

[4] Cronbach, L. J., and G. C. Gleser, "Assessing Similarity Between Profiles," *Psych. Bulletin*, **50,** 456–473 (1953).

[5] Williams, R. J., "Etiological Research in the Light of the Facts of Individuality," *Texas Rpts. Biol. and Med.*, **18,** 168–185 (1960).

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*EFFECT OF SURFACE TENSION ON THE KELVIN-HELMHOLTZ INSTABILITY OF TWO ROTATING FLUIDS**

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1. *Introduction.*—The Kelvin-Helmholtz instability arises when two uniform fluids, separated by a horizontal boundary, are in relative horizontal motion. Without surface tension this streaming is unstable no matter how small the velocity difference between the layers may be. It was shown already by Kelvin[1] that surface tension will suppress the instability if the difference in velocity is sufficiently small.

The effect of uniform rotation about the vertical axis on the development of the Kelvin-Helmholtz instability has been treated by Chandrasekhar.[2, 3] He found that rotation does not stabilize the motion for any difference in the velocities in the absence of surface tension. We shall show that in a rotating system surface tension fails to stabilize the motion for any difference of velocities and any angular velocity of rotation. The exact effect of surface tension is discussed.

2. *The Characteristic Equation.*—Let two uniform fluids of densities ρ_1 and ρ_2 be separated by a horizontal boundary at $z = 0$.—Let the density, ρ_2, of the upper fluid be less than the density, ρ_1, of the lower fluid so that in the absence of streaming, the arrangement is a stable one. We shall further suppose that the two fluids are streaming with the constant velocities, U_1 and U_2, and that the fluids are in uniform rotation about the vertical z-axis with an angular velocity Ω. Forces at the interface $z = 0$ arise from surface tension T.

As a result of a disturbance, let the components of the velocity in the perturbed state be $U + u$, v, w. Analyzing the disturbance into normal modes, we seek solutions whose dependence on x, y, and t is given by

$$\exp i(k_x x + k_y y + nt). \tag{1}$$

Chandrasekhar[4] has shown that the characteristic equation for this arrangement is given by

$$\alpha (n + k_x U_1)^2 \left[1 - \frac{4\Omega^2}{(n + k_x U_1)^2}\right]^{1/2} + \alpha_2 (n + k_x U_2)^2 \left[1 - \frac{4\Omega^2}{(n + k_x U_2)^2}\right]^{1/2} = gk\left\{(\alpha_1 - \alpha_2) + \frac{k^2 T}{g(\rho_1 + \rho_2)}\right\} \tag{2}$$