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President's Address

Twins and Genetic Studies of Man

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The International Society for Twin Studies is a unique organization. It is unique in the status of members composing the Society. In addition to specialists of science and medicine we have non-specialist members including twins and their families, all enjoying excellent collaboration in undertaking research and related activities of common interest. This kind of collaboration is very important for academic societies, particularly for those devoting themselves to the studies of man. We aim at a better understanding of man; our purpose is to learn more about ourselves. This activity is not a monopoly of specialists. Our achievements should also be shared by lay people. ISTS can serve as a model for academic societies aiming at the studies of man. Science has the solid ground of logos. At the same time, we realize that the accomplishments of highly specialized science should be reevaluated in the light of human values. I am inclined to believe that our task is to integrate the logos of scientists and ethos of the public into one.

The purpose of twin studies is two-fold; studying multiple birth phenomena *per se*, and making inquiry into the genetic and environmental sources of human variation. The latter task was initiated by a number of pioneers in the early twentieth century. At that time, however, genetic studies of man including twin studies remained largely descriptive. We could not, and still cannot, perform genetic experiments on human individuals and populations, and the methodology available was limited to observation of a character presented in pedigree members and twins. However, despite the limitation of methodology, classical pedigree analysis has permitted us to accumulate a large amount of data on normal hereditary traits and genetic diseases, or more precisely, simple Mendelian characters.

Conventionally we categorize human genetic diseases and disorders into three groups. *First*, the simple Mendelian group which includes thousands of known hereditary diseases. The etiology is gene mutation, and the diseases in this category are transmitted following the Mendelian mode of inheritance. Ultimately the number of genes, or more exactly, the number of gene loci responsible for the etiology of the diseases may amount to anything from fifty up to one hundred thousand. The prevalence rate in the

newborn population of those affected with, or predisposed to, one of the diseases is estimated to be between 0.5 and 1 per cent. The frequency of any one disease is therefore very low, in the magnitude of one in ten every hundred thousand.

In the 1950s there was a breakthrough in human genetics. Due to advances in the study of the chromosome, a new research field of human cytogenetics developed. Many types of chromosome anomalies were found, and it became clear that these were, in fact, responsible for causing of a number of congenital anomalies. Surveys on the frequency of chromosome anomalies showed the prevalence rate among the newborn to be about 0.6 per cent. We categorize these chromosome anomalies as the *second* group of genetic diseases and disorders.

Soon after, yet another new field emerged, somatic cell genetics. By introducing the new methodology of cell fusion it became possible to perform test-tube analysis of gene-carrying chromosomes; marked development is the assignment of genes to specific chromosomes or chromosome regions. Thus, the early limitation of methodology in human genetics was largely removed, and these new fields paved the way for the introduction of molecular biology to the genetic studies of man.

During the last four decades revolutionary progress was made in the realm of life science, which was mainly due to the amazing advances of molecular and cell biology. Worth noticing is the fact that progress in this area of science made us realize that the basic elements and functions of life on the earth are common to all, from man down to microorganisms. As a student of human genetics, I closely observed the progress of molecular biology and its application to the genetic studies of man. It became clear that in a number of simple Mendelian diseases the etiology is in the structural anomaly of genes. Making exact diagnosis became possible, even before the manifestation of diseases, in an increasing number of instances. A Human Genome Project has been initated in several countries. This aims at disclosure of the entire human genetic makeup, or more precisely, the DNA base sequence of the human genome. The project will, provided it is appropriately conducted, clearly improve human welfare by throwing light on a number of diseases and disorders, of which the pathological mechanism is still largely speculative. It is anticipated that the Project will eventually lead to the discovery of means for the prevention and therapy of a number of human diseases and disorders.

Despite amazing progress in new areas of human genetics which disclosed the gene and chromosome anomalies in a number of genetic diseases and congenital anomalies, there still exists a large group of diseases and disorders of questionable etiology. These constitute the *third* group which are sometimes called common familial diseases. Empirically it is known that some common diseases aggregate in certain families. Hypertension, bronchial asthma, diabetes mellitus, schizophrenia and manic depressive psychosis are among the examples. It has been suggested that a genetic factor or factors contribute to the etiology of these diseases, although the pattern of transmission does not follow Mendel's law of inheritance. This has been puzzling to researchers, leading some to deny the role of genetic factors and to insist that the familial aggregation was due to common environmental factors shared by family members. Here we see a typical nature-nurture controversy on human characters.

In efforts to solve the problem on the etiology of this group of diseases, twin study has contributed greatly since the early days of genetic studies of man. It has been repeatedly shown that for most of the common diseases so far studied, the concordance rate

in monozygotic (MZ) twins is higher than that in dizygotic (DZ) twins. This finding strongly suggests the significance of a genotypic contribution to the etiology. Still, MZ concordance rates are invariably less than a hundred per cent, which also clearly indicates the significance of environmental factors to the etiology.

In the early years, pioneers in human genetic research tended to divide human characters into hereditary traits and acquired characters, irrespective of normal or abnormal traits. Then, twin data on the concordance of diseases showed that the naive dichotomy of heredity vs environment is dificult to perceive. Indication was that genotype and environment both contribute to the etiology of a given disease. This produced another puzzle for the early researchers. It was then postulated that genotype and environment play their roles *separately* in causing a disease, or more generally, in the regulation of a human character. In other words, the concept of the relative powers of nature and nurture revived. The issue is now settled in yet another way. The progress of genetic studies permits us to conclude that genotype and environment are not variables entirely independent from each other. Their interaction is crucial, and this also applies to the evolution of complicated human characters.

One of the predominant genetic hypotheses, incorporating both genotypic and environmental etiology in common familial diseases, claims a contribution of multiple gene loci, ie, that genes on the loci function collectively to determine the susceptibility to a disease, in conjunction with the effects of environmental factors. For this reason the diseases of this group are sometimes called multifactorial diseases. However, except in a few instances, we must not forget that genes involved in such diseases are yet to be identified. Research strategy in this area is now being formulated little by little.

I have in the past been engaged in the study of twins with these kinds of diseases, particularly neurological and mental disorders. I feel that advanced methodology in twin studies is a powerful tool in the search for the etiology of these diseases, possibly leading to the identification of the genetic and environmental factors responsible.

On some occasions it has been shown how methodology improves the diagnostic tools in these common familial diseases. In this respect, starting with the sample individuation of affected cases, which should be as unbiased as possible, the twin register offers a great advantage. If applied in a wider perspective, the more representative the cohort and follow-up studies are, the greater the contribution to the future studies of many human diseases.

Routine twin research procedure is to see concordance and discordance of a disease in MZ and DZ twins. Here however, we often encounter a difficulty to adhere to the rigid concordance-discordance dichotomy. In a followup study of chronic epilepsy [1] it was found that among 26 MZ twin pairs about 30 per cent of cotwins were similarly affected. However, more than 40 per cent of the cotwins had only transient seizures or manifested EEGs typical to epilepsy but were free from clinical symptoms. In a longitudinal followup study of twins with schizophrenia the final conclusion was that in 58 MZ cotwins more than 20% presented abortive symptoms such as transient psychotic episodes, or peculiar chronic neurotic symptoms, or both [2]. These pairs were designated incomplete concordant. The symptoms illustrated a resemblance to those of schizophrenia, but criteria did not establish the diagnosis of schizophrenia in the cotwins. It was of particular interest to note that despite the presence of the symptoms they had adapted to society in a normal manner though with a peculiar formality. It must be added that

in the course of the followup study some other MZ cotwins with abortive symptoms developed typical schizophrenia. A somewhat similar abortive manifestation was observed in another study of MZ cotwins of index cases with typical chronic obsessive-compulsive neurosis [3].

In these incomplete concordant MZ pairs we can find clues to help understand the evolution process of the disease by analyzing the differences in symptoms between MZ index twins and their cotwins and observing the course and outcome of the abortive symptoms. I think this methodology can be applied to the study of other diseases, the pathogenic mechanisms of which are still unknown.

A most exciting undertaking in twin studies is the search for environmental factors contributing to the etiology of a disease. For this purpose, we analyse the differences in past histories of MZ twin partners discordant for the disease. Likewise, by analysing histories of incomplete concordant MZ twins, with a marked difference in symptoms, we turn to search for unfavorable environmental factors responsible for the more severe symptoms of the disease. In the study of chronic epilepsy [1] it was indicated that birth injury was responsible for its etiology. A history of birth injury was found in half of the 18 MZ index cases discordant or concordant with a marked difference of symptoms, while the births of the cotwins were uneventful. The majority of other index cases in this group had a history of either infectious disease of the brain or head trauma. Similar analysis was made in the study of schizophrenia [4]. Contributing factors found were: smaller birthweight than cotwins; introverted, unsociable, hypersensitive and obsessive personality traits before the onset of the disease; the presence of psychogenic factors, and having remained unmarried longer than their cotwins.

In these studies the information was obtained retrospectively, thus it is possible to cast doubts on its reliability. If prospective cohort study is made possible, it may give a firm basis to the above conclusions. This kind of study eventually paves the way for the prevention of diseases in genetically predisposed individuals, by reinforcing favorable environmental factors thereby suppressing the expression of abnormal genotype, and by introducing means to avoid the unfavorable ones responsible for the development of the diseases. In the future, errors of the genotype may be corrected by gene therapy in certain diseases, provided the safety of the therapy is guaranteed and ethical principles are established, but this is not the subject of present-day medical treatment.

Twin studies enable us to approach the question of genetic heterogeneity of a disease or a symptom complex. Suppose that a disease or a symptom complex of unknown etiology like schizophrenia is composed of different etiological entities; a genotype-dependent entity and an environment-dependent one. Theoretically it is possible to identify these entities in concordant and discordant MZ twin index cases, respectively. This method has been applied in a couple of studies in neurology and psychiatry, where the classification of diseases has been the subject of long-standing dispute. Applying this method to the study of chronic epilepsy [1] we classified three etiological groups: hereditary, exogenous, and an intermediate group. In the last group, both genotype and environmental factors were seen to contribute to the etiology. We also applied this method to the study of schizophrenia [4]. Briefly, three etiological groups were designated: the chronic progressive type, the relapsing type, and the chronic mild or transient type. The first two were predominantly found in concordant MZ twins, and the third type in discordant index cases. The outcome was most favorable in the third type, while patients

of the first type often developed severe personality deterioration. In the second type, social adaptation was almost normal with intervals of relapses which characterizes the course of this type of schizophrenia.

The results of past twin study on common familial diseases implies future developments in medical research. One will be the identification of genes and their products involved in the etiology of a variety of diseases. I think, however, this may not be productive if genetic heterogeneity is overlooked and if we simply attempt to look for genes and gene products in a group of patients with a symptom complex collectively diagnosed, as has been the case in biochemical studies of schizophrenia.

In the study of another group of chronic diseases twin study will prove to be a useful methodology. These diseases are often familial, and the incidence rate is very low. Their etiology is obscure and therapy is unavailable, hence they are designated as intractable diseases or "nambyo" in Japan. Because of the low incidence rate of these diseases, it is certainly instrumental to avail of twin register coupled with follow-up cohort study in these cases.

We are aware that the twin study method has been extensively applied to the study of human behavior. Elaborated analytical techniques have been devised and valuable data accumulated. Forty years ago, co-workers of our twin research panel started a series of psychological experiments [5]. The experiments were very simple. For example, the number of eye-blinks was counted while twins were given a psychological test. In another experiment twins were asked to listen carefully to a narrated story and as the story finished they were asked to evaluate its time lapse subjectively. These experiments attempted to uncover genotypically-regulated innate behavioral patterns by administering test situations which enabled the subjects to behave uninfluenced neither by external stimuli or by fixed standards of behavior, nor by conscious or voluntary control. In this way, extremely high correlations (around 0.8 to 0.9) were shown in MZ twins. An interesting point was that the high correlation in the number of blinks completely disappeared on administration of test situations where voluntary control exercised its due function to adapt to the milieu by modifying the pattern of innate behavior. Here, we first looked for variables illustrating high MZ twin correlations, instead of availing of ready-prepared experiments to assemble data. We then attempted to scrutinize the behavioral structure, instead of looking for variables underlying the data assembled. In other words, the starting point was simply a search for behavioral characteristics concordant in MZ twins. This research strategy takes the opposite direction to the conventional twin study method, and I think this reverse method will be useful in the future study of complex human characters.

In an attempt to look for a physiological basis in the innate and apparently genotypically regulated behavior, we compared EEGs of the left and right sides of the brain in MZ twins. A range of frequency of EEG called beta waves was sampled and measured, and indicated a higher heritability index in the right than in the left side [6]. Interpretation of the result was as follows. In most individuals the left hemisphere of the brain is dominant over the right and actively processes nervous impulses. Beta waves reflect active functioning of the brain like calculations. In the dominant left hemisphere nervous activity as reflected in beta waves is more dependent on stimuli coming from inside and outside the brain, therefore the adaptive activity becomes more evident than innate activity. In the non-dominant right hemisphere of the brain , activity is more indepen-

dent from these stimuli, thus innate activity is more evident than adaptive activity. The conclusion was later confirmed by two twin studies [6,7]; one which focused on left and right ear hearing ability, and the other on the shifting of the center point of body gravity in relation to bodyweight placed on the left or right foot.

I hope it may not be an overstatement to say that twin study has proved to be in the past, and will continue to be in the future, a powerful instrument in the search for genetic and environmental sources of variation in the complexity of human functions and structure, irrespective of the normal or abnormal, qualitative or quantitive components. It is not necessary to mention that there are still large, untouched areas of complex human variations to be researched and to which twin studies will continue to contribute in answering the call, by providing objective evidence rather than adhering to banal nature-nuture controversy.

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