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THE GENETICS OF SCHIZOPHRENIA

Like the majority of common diseases, schizophrenia is of multifactorial origin with environmental and hereditary factors interacting closely in its causation. Until recently the attention of most investigators has been concentrated on possible environmental influence, but despite their endeavours a clear picture of the schizophrenia-producing environment has not yet emerged. Lately, increased attention has been paid to the genetic factors and some progress has been made in this direction.

The best evidence for a genetic component in the aetiology of schizophrenia comes from the study of twins. If one of a pair of genetically identical (monozygous) twins has schizophrenia, there is about an 80% chance that his twin will—sooner or later—also develop the disease. On the other hand, if one of a pair of unidentical (dizygous) twins is schizophrenic, the chances are only 15% or less that his twin will also be affected. These data are derived from the extensive investigations of Kallman in New York and have been confirmed by similar studies in Europe and Japan.[1] Among the cases described, there are several in which the role of heredity has most impressively been demonstrated. For example, Craike and Slater[2] have recorded the case of histories of identical twin sisters whose mother died when they were 9 months old. One sister was first brought up in the home of her violent, drunken father and then in a children's home. The other sister was brought up in the home of an affectionate aunt. The sisters did not meet until they were 24 years old, and then only briefly and irregularly. Yet, despite their totally different upbringing, both developed schizophrenia.

Among the relatives of schizophrenics, the chance of developing the disease decreases as the degree of relationship to the patient decreases. Among the sibs of patients it is 14%; in their half-sibs it is 7%; in first cousins it is about 4%; and so on.[3] In the general population the incidence is about 1%, and—with few exceptions—the incidence in different social and racial groups is approximately the same.

If it is accepted that heredity plays an important part in the development of schizophrenia, two questions must immediately be asked: what is the nature of the genetic defect; and what is the genetic mechanism involved? A great deal of speculation and research has been provoked by these two questions.

As far as the first question is concerned, a clearly-defined biochemical lesion has not yet been demonstrated, but several pieces of evidence suggest that such a lesion does exist. The experimental use of certain psychotomimetic agents such as mescaline has facilitated the research. When given to normal people, mescaline produces an acute schizophrenia-like illness. Mescaline is structurally related to adrenaline, and Osmond and Smythies[4] have suggested that in schizophrenia, the metabolism of adrenaline is disturbed. In stress situations there is an increased production of adrenaline; in schizophrenics, some of this may be methylated to dimethoxyphenylethanolamine (DMP), which is closely related to mescaline and may produce similar psychotic effects. This theory is attractively simple but, in fact, disturbed adrenaline metabolism has not yet been demonstrated in schizophrenics. However, in 1962 Friedhoff and Van Winkle,[5] of New York University, reported the identification of 3, 4-dimethoxyphenylethylamine in the urine of schizophrenics. This substance, like DMP, is closely related to mescaline and may be an abnormal adrenaline metabolite. It was found in the urine of 15 out of 19 schizophrenics, but in none of the 14 control specimens. The identification was made with a chromatographic technique, which isolated the abnormal substance as a pink spot. The 'pink spot' test achieved a certain degree of notoriety as a result of some rather sensational reports in the popular press last year.

This observation by Friedhoff and Van Winkle is of great interest because it may point to a specific biochemical defect in schizophrenia. So far, the observation has been made on a rather small series of patients and has yet to be confirmed by other workers. The results of a large-scale search for the urinary 'pink spot' in schizophrenics and their relatives and in controls are eagerly awaited.

The second question to be answered concerns the genetic mechanism in schizophrenia. Again, only tentative conclusions can be reached. Böök[6] and Slater,[7] after reviewing the available data, postulated that the inheritance of schizophrenia is dependent on a single dominant gene with 25% penetrance. Whether the effect of the gene is manifest or not will depend on social, cultural and physical factors in the environment, and perhaps on the influence of other minor genes.

But if schizophrenia is dependent on a single gene for its transmission, why does the disease persist with such a frequency throughout the world? Schizophrenics have many obvious reproductive disadvantages: high suicide rate, frequent and early hospitalization, inability to marry, etc. One would expect that such a harmful gene would die out rapidly; yet it persists with a frequency as high as 1%. This is a much greater frequency than can be accounted for by fresh mutations. The only reasonable explanation is that carriers of the schizophrenia gene must enjoy some substantial advantage which balances their more obvious disadvantages. The position must be similar to that of the gene for sickle-cell anaemia which has persisted at very high frequency in various parts of the world because those who carry it have a greatly increased resistance to malaria.

What biological advantage do schizophrenics possess? Clarke[8] has suggested that schizophrenics have an

increased resistance to certain physical stresses. Some psychiatrists have the impression that schizophrenics can withstand traumatic shock better than most, but there is no adequate data to support this. However, it has been shown that schizophrenics are less susceptible to allergens; for instance, intradermal injections of histamine produce smaller wheals in schizophrenics than in controls.[9] This phenomenon correlates with the observation that schizophrenics have fewer mast cells in their skin than controls, and this may represent an inherent biological advantage.

Sir Julian Huxley *et al.*[10] have recently taken up Clarke's suggestion with enthusiasm. They believe that schizophrenics also show greatly enhanced resistance to such diverse stresses as visceral perforation, burns, insulin, thyroxin, arthritis, pain and many infections (except tuberculosis). They quote a suggestion of Slater's that in historic times, schizophrenics were more able to withstand the epidemics of smallpox and bubonic plague. They may also be more likely to survive the simpler infectious diseases of childhood.

Much of this, of course, is just speculation. However, it does serve to indicate some of the thought processes and research programmes which may lead to a better understanding of the nature of schizophrenia and its cause.

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KONGRES OOR GESONDHEIDSVOORLIGTING

Niemand kan daaraan twyfel dat mediese aangeleenthede van enige aard vandag groot nuuswaarde het nie. Die samelewing is oor die algemeen baie beter ingelig oor haas alle sake as wat die geval 'n geslag of wat gelede was, en dit geld veral ook mediese sake. Daarom het elke koerant en elke tydskrif sy mediese medewerker.

Nogtans is daar 'n groot leemte op hierdie gebied. Omdat dit ongelukkig vandag die geval is dat so 'n groot deel van die pers in 'n groot mate ingestel is op die aanbied van sensasionele berigte, is die inligting wat die publiek bereik nie altyd betroubaar nie. Berigte wat sonder twyfel òf skadelik is òf onvervulbare hoop en verwagtings wek, bereik die publiek gedurig.

Daar is dus aan die eenkant die pers se neiging tot ondiskriminerende beriggewing. Maar aan die anderkant is ons as dokters ook aanspreeklik vir die verspreiding van verwarrende berigte—omdat daar nog in so 'n groot mate verskil van mening bestaan oor baie sake. Dink byvoorbeeld aan die uiteenlopende en dus verwarrende menings wat dokters en groepe dokters gereeld uitspreek oor die vraagstuk van die oorsaaklike verband tussen rook en longkanker.

Omdat daar 'n behoefte bestaan aan gesonde en betroubare gesondheidsvoorligting, het die Noord-Transvaalse Tak van die Mediese Vereniging nou besluit om in Mei 1966 'n kongres oor gesondheidsvoorligting in Pretoria te organiseer. Hierdie hele saak sal dan op 'n deurdringende en verantwoordelike manier ondersoek word, en die moontlikhede van hoe om aktiewe inligtingskanale tussen die lede van die mediese professie en van die algemene publiek te bewerkstellig, sal dan bespreek word. Die Noord-Transvaalse Tak van die Mediese Vereniging voel dat hier 'n belangrike saak is wat op die basis van spanwerk aangepak behoort te word. Die volledige program van die kongres sal hopelik binne die volgende paar maande voltooi word, en ons sal dit dan ter inligting van al ons lede publiseer.

CALCITONIN AGAIN

An editorial article published in the *Journal* of 28 March 1964, discussed the logical discovery by Copp and his colleagues[1,2] in Vancouver of a new hormone which, in opposition to the previously known parathyroid hormone, rapidly depressed the level of calcium in the plasma. This was believed to be a second calcium-regulating substance derived from the parathyroid glands.

More recent work from Hammersmith[3] has confirmed the existence of this new hormone, calcitonin, but, at least in goats, appears to have excluded the parathyroids as its source. Further, Hirsch *et al.*[4] have extracted a potent plasma-calcium-lowering agent from rat thyroid glands and named it 'thyro-calcitonin'. This thyroid substance has been purified at Hammersmith[5] and Harvard,[6] and shown to be a polypeptide and to be obtainable from the thyroid glands of several mammalian species.

Present evidence, then, points to the thyroid gland as the source of calcitonin, but its mode of action and its importance in homeostasis is still entirely conjectural. It appears to lower the plasma phosphate[7] as well as calcium and to be active in nephrectomized animals,[6] suggesting the possibility that it promotes the accretion of calcium phosphate in the skeleton.

The value of a rapid control of the plasma calcium level is understandable—the action of parathyroid hormone in raising the plasma calcium is comparatively slow. The reason for a thyroidal origin of this hormone is not at all clear, nor is it known why totally thyroidectomized individuals do not develop high plasma calcium levels, nor what possible connection, if any, it may have to thyroxin, or to its synthesis.

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