GENETICS IN RELATION TO PSYCHIATRY AND NEUROLOGY*

LEWIS A. HURST, B.A., B.SC., M.B., CH.B., PH.D. (CAPE TOWN), M.D. (PRETORIA), *Professor of Psychological Medicine, University of the Witwatersrand, Johannesburg*

The notion of heredity in psychiatry has undergone many changes during the last hundred years. In the closing decades of the 19th century it was the predominant trend to consider all mental disorder and defect as hereditary in an undiscriminating, non-specific manner. With the development of scientific genetics at the beginning of the twentieth century there came a reaction against these crude views from within the science itself. This reaction was encouraged by the prevailing opinion of the age, and reflected in the ideologies of many followers of Freud and in Watson's Behaviorism.

Psychiatric genetics became established on a firm scientific foundation at the beginning of the fourth decade of this century, through the systematic and extensive family and twin studies in schizophrenia, by Kallmann[1, 2] and Slater.[3] From this time on the more discriminating view developed that where psychiatric deviations are hereditary, they are so in a specific way: Schizophrenia can through inheritance give rise only to schizophrenia ; manic depressive psychosis only to manic depressive psychosis, and epilepsy only to epilepsy.

Methodological advances in two other branches of genetics have widened the applicability of the science to psychiatric conditions and brought revolutionary new insights.

Cytogenetics

The first of these is in the field of cytogenetics. The discovery of new techniques for the study of the number and characteristics of chromosomes, coupled with the discovery in 1956 by Tjio and Levan,[4] that the normal chromosome complement in man is 46 and not 48, as had been accepted for many decades, has focused attention on the chromosomes themselves in the origin of disease. Hence the extensive development, almost overnight, of karyotyping. This has already provided a rich harvest in the realm of psychiatry, for not only has Down's syndrome, or mongolism, yielded its secret to this technique, but other forms of mental defect, with and without congenital bodily deformity, have received fundamental clarification on the basis of chromosome abnormality. The very tangibility of these findings brought conviction of the importance of genetics in psychiatry to those whose psychogenic orientation, or inability to grasp the remote intricacies of gene action, has rendered them unsympathetic to genetic interpretations.

The Chemical Sector

The second methodological advance lies in the chemical sector. Goldschmidt's studies on developmental genetics[5] converging on Garrod's demonstration of inborn errors of metabolism[6] have established the chemical nature of gene action. This concept achieved greater specificity in the notion of enzyme blocks. Now the cornerstone to the edifice has been added in the studies of the structure and function of DNA and RNA, resulting in the hypothesis of the genetic code.[7] According to this a pathogenic mutation, for example schizophrenia, may result from a misprint in the code in the form of a misplaced nucleotide in the chain, which transmits incorrect information to RNA, with resultant disturbances in protein synthesis. This, in the view of three groups of workers,[8-13] features prominently among the chemical disturbances in this disease.

Applications in Psychiatry

From these preliminary generalizations, we turn to more detailed applications in different areas of the psychiatric field in the following order: mental defect, the psychoses, the psychoneuroses, epilepsy and the neurological disorders.

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MENTAL DEFECT

The sphere of mental defect provides particularly fine examples of the two new methodologies, chemical and chromosomal, to which we shall now refer.

1. Chemical Aberrations

Garrod's concept of inborn errors of metabolism, enunciated in 1902,[14] bore fruit in the domain of mental defect in 1934, when Fölling[15] drew attention to the association of phenylketones in the urine and mental retardation. To date, some 3·5% of mental defectives have been shown to have an underlying biochemical abnormality. These may be broadly divided into errors of carbohydrate, lipid, and protein metabolism. The aminoacidurias are the common factors in most diseases of protein metabolism, and classification is in terms of blood amino-acid level and chromatographic pattern. An outline of these main facts is embodied in Tables I and II.

TABLE I. FAMILIAL METABOLIC DISEASES ASSOCIATED WITH MENTAL DEFECT

Diseases of Carbohydrate Metabolism
- Galactosaemia
- Sucrosuria
- Glycogen-storage disease
- Gargoylism (mucopolysaccharide storage)

Diseases of Lipid Metabolism
- *Progressive leukoencephalopathies*:
  - Schilder's disease
  - Pelizaeus-Merzbacher
- *Progressive lipidoses of gray matter*:
  - Gaucher
  - Tay-Sachs
  - Niemann-Pick

Diseases of Protein Metabolism (Aminoacidurias)
- Phenylketonuria
- Hartnup disease
- Cystinuria
- Argininosuccinaciduria (Allan-Dent)
- Cystathioninuria
- Maple-syrup urine disease
- Oasthouse urine disease

Other Diseases
- Goitrous cretinism
- Wilson's disease
- Congenital renal tubular acidosis
- Pyridoxine dependency

TABLE II. THE AMINOACIDURIAS

1. The Blood Levels

Syndromes with Levels Above Normal (Overflow Aminoaciduria)
- Phenylketonuria
- Maple-syrup urine disease
- Glycinuria

Syndromes with Abnormal Blood Amino Acids (Dent's No-threshold Types)
- Argininosuccinaciduria (Allan-Dent Disease)
- Cystathioninuria

Syndromes with Normal Levels (Deficiency of Tubular Reabsorption)
- Wilson's disease
- Galactosaemia
- Cystinuria
- Hartnup disease
- de Toni-Fanconi syndrome
- Oasthouse Disease

2. Chromatographic Pattern of Aminoaciduria

Generalized Aminoaciduria
- Wilson's disease
- Galactosaemia
- De Toni-Fanconi syndrome

Single Aminoaciduria
- Phenylketonuria
- Allan-Dent disease
- Galactosaemia

Multiple but Patterned Aminoaciduria
- Maple-syrup urine disease
- Hartnup disease
- Cystinuria
- Oasthouse disease

Phenylketonuria, which may be classified as a single overflow aminoaciduria, has become the paradigm of the chemical mode of action of single gene effects and enzyme blocks.

The complex of biochemical events disclosed in this condition is as follows: phenylalanine hydroxylase, an enzyme concerned in the conversion of the essential amino acid, phenylalanine, to tyrosine, is at fault; consequently,

(*a*) There is an accumulation of phenylalanine in the blood and CSF and overflow in the urine.

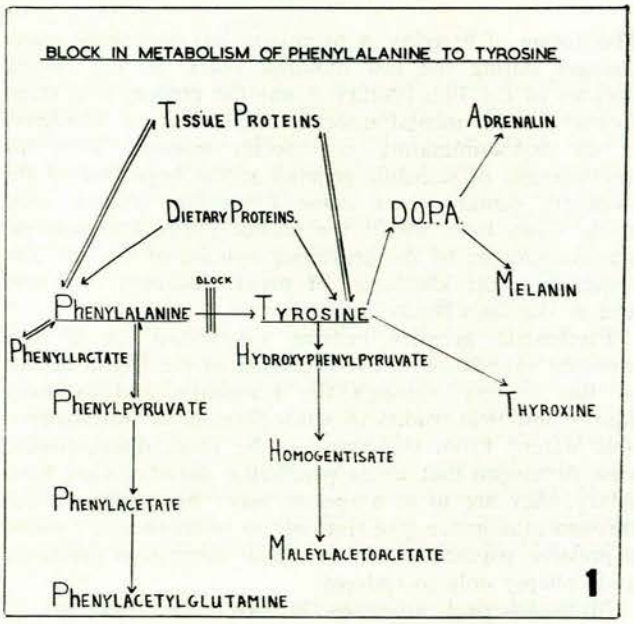

Fig. 1. Chemistry in phenylketonuria.

(*b*) Phenylpuruvic and phenyllactic acids and phenylacetyl-glutanine are therefore in excess, and, since the renal threshold is low, are excreted in the urine.

(*c*) The administration of the excess phenylalanine to normal people, produces a rise in the blood-tyrosine levels, but none follows in phenylketonurics.

The matter has often been raised of how directly or

completely the mental retardation in phenylketonuria is related to failure of conversion of phenylalanine to tyrosine. Confirmation of the central aetiological role of this mechanism comes from two sources.[16, 17] Treatment that commenced early (in which dietary phenylalanine was maintained at a bare minimum) gave indications of the prevention of mental retardation.

A test for the detection of carriers in this disease, based on the plasma phenylalanine levels at 1, 2 and 4 hours after a standard test dose of laevo-phenylalanine has been evolved.[18]

2. Chromosomal Aberrations

Our remarks will be confined very largely to Down's syndrome, or mongolism, the condition in which the new chromosome work won its spurs, with some slight reference to other conditions.

1. Down's syndrome or mongolism. Lejeune *et al.*[19] and Jacobs *et al.*[20] showed independently that in mongolism a trisomy of chromosome number 21 exists—this chromosome is present in triplicate instead of in duplicate. The two mechanisms postulated as bringing this about are non-disjunction and translocation. The usual process is non-disjunction during meiosis, where two homologous number 21 chromosomes, instead of separating and each migrating to its own pole, stick together and move to the same daughter cell. Much rarer is non-disjunction occurring during mitosis, resulting in normal trisomy 21 mosaicism, as described by Clarke *et al.*[21] Clinically, only certain mongoloid features appear in these cases.

Translocation involves breakage of non-homologous chromosomes (one of which is number 21) and an exchange of fragments between them—a reciprocal translocation as described by Polani *et al.*,[22] and more commonly seen in cases born to young mothers.

2. Other forms of mental defect. A survey by Maclean *et al.*[23] of 4,514 mental defectives, discloses a significant association between oligophrenia and an increased complement of X chromosomes in both phenotypic males and females. Trisomy 22 has been reported in connection with the Sturge-Weber syndrome,[25] but has not been confirmed.[25]

3. Polygenic mechanism. Despite the special interest attaching to chemical and chromosomal aberrations in mental defect, it is probable that the great majority of mental defectives, especially those of higher grade, represent the tail end of the normal curve of distribution of intelligence and are accounted for on the basis of a pylogenic mechanism.

THE PSYCHOSES

In the field of the psychoses we shall take schizophrenia as our example and present the salient findings in the other conditions in tabular form.

A. Schizophrenia

Kallmann's main studies in the genetics of schizophrenia[1, 26] are exceptionally fine examples of the family and twin-family methods of human genetics. We cite some of the salient expectancy figures from the latter study, based on a series of over 600 twin pairs and their relatives, collected and analyzed along the lines of critical statistical requirements:

One-egg twins	86·2%
Two-egg twins	14·5%
Siblings	14·2%
Half-siblings	7·1%
Children	16·4%
General population	0·85%

Inferences from these figures are:

1. The morbidity figures for all degrees of blood-relationship are much higher than in the general population—even in half-siblings the incidence is 8 times greater.

2. With an increasing degree of blood-relationship there is an increasing degree of morbidity—from 7·1% in half-siblings and 14·2% in full siblings to 86·2% in one-egg twins.

3. The concordance rate for one-egg twins is very high (86·2%) and is approximately 6 times the figure for two-egg twins. Besides this, the finding in another part of the study, that the concordance of separated one-egg schizophrenia twins is slightly lower than for non-separated, one-egg twins (65% as compared with 71%), implies relatively insignificant environmental factors in the causation of the condition.

4. The essential similarity of the figures for siblings and two-egg twins (14·2% and 14·5%) is of interest, because of the lack of significant differences in average genetic equipment postulated for these two categories of blood-relationship. There is the further point that there is an obvious analogy here to the greater similarity of the environment shared by one-egg twins as compared with two-egg twins. In the present case there is a presumption that the two-egg twins are on an average likely to share a more common environment than any two siblings taken at random, and yet, here this environmental factor has exerted no effect on the comparative morbidities.

One additional statistic of relevance to the dominance or recessiveness of the schizophrenic genotype is that in Kallmann's studies he has found an expectancy figure of 16·4% in children with one schizophrenic parent, and 68·1% in children with both parents schizophrenic. The hypothesis best fitting this finding is that the condition is determined by an autosomal and single recessive gene of about 70% penetrancy.

Recent Trends in the Genetics of Schizophrenia

Two recent trends in Professor Kallmann's Department of Medical Genetics (Columbia University) worth reporting are the following, constituting chapters 6 and 7, respectively, in *Expanding Goals of Genetics in Psychiatry*:[27]

(*a*) *Mating and fertility trends.** Under the design of this study, a random sample of schizophrenic patients admitted to New York State mental hospitals during the three-year period 1934 - 1936 is compared with a like sample admitted in 1954 - 1956. The most significant finding, reviewed in a preliminary communication on 1,552 cases, or one-third of the proposed final sample, is that of relatively greater increases in marriage and total reproduction among schizophrenics than in the general population in this era of improved therapy and socialization of schizophrenic mental hospital patients. The implications of this for the health of future generations calls for careful appraisal by geneticists and psychiatrists alike.

*Authors: L. E. Kimling, Ph.D. and C. Goldfarb, M.D.

TABLE III. GENETIC CLASSIFICATION OF PSYCHOTIC AND ASSOCIATED CONDITIONS

Psychiatric condition	*Investigator*	*General population*	*Half-sibs*	*Sibs*	*Two-egg twins*	*One-egg twins*	*Parents*	*Children*	*Postulated genetic mechanism*
1. Manic-depressive psychosis	Kallmann	0·4%	16·7%	23%	26·3%	95·7%	23·4%		Autosomal irregular dominant
	Luxemburger			12·7%	1 : 16	31 : 33		24·4%	
	Rosanoff				11 : 67	16 : 23			
	Stenstedt			15%			15%	15%	
2. Schizophrenia	Kallmann	0·85%	7·1%	14·2%	14·5%	86·2%	9·3%	16·4%	Autosomal recessive: 70% penetrance
	Slater				14·0%	76·0%			Recessive and dominant cases
3. Childhood schizophrenia	Kallmann and Roth			12·2%	17·1%	70·6%	12·5%		As in adult form
4. Involutional psychosis	Kallmann	1·0%	4·5%	6·0%	6·0%	60·9%	6·4%		Heterozygous carriers of schizophrenic genotype
5a. Senile psychosis	Kallmann	less than 1·0%		6·5%	8·0%	42·8%	3·4%		Gene-specific biochemical factors plus adaptive personality traits
b. Presenile psychosis									
Pick's disease	Sjögren	0·1%		6·8 ± 3·9%			19 ± 5%		Autosomal dominant
Alzheimer's disease	Sjögren			3·8 ± 2·1%			10 ± 4%		Polygenic
6. Suicide	Kallmann *et al.*				1 : 28				None demonstrated
7. Epilepsy	Conrad			4·0%	4·3%	86%			Polygenic (Kallmann)
	Alström			1·5%			1·5%	3·5%	Not genetic except rarely dominant
	Gibbs *et al.* (EEG)				25%	100%			Single dominant
8. Huntington's chorea	Rosanoff and Handy				1 : 2	3 : 3			Autosomal dominant
	Haldane								Sex-linked modifiers

(*b*) *Deafness and schizophrenia: Interrelation of communication stress, maturation and schizophrenic risk.** While Diane Sank has worked extensively on the genetics of early total deafness as such, the other workers named have devoted themselves more specifically to the theme indicated in the title. On the basis of their statewide survey, they conclude that the severe and varied stresses associated with early total deafness apparently do little to increase the chance of developing the clinical symptoms of schizophrenia, whereas sibship consanguinity to a schizophrenic person results in a marked increase in schizophrenic morbidity risk.

A living monument to this 7-year intensive research programme (recently embodied in a monograph),[28] is the Schizophrenic Deafness Unit, which is now a going concern at Rockland State Hospital, New York.

Another significant recent work in the realm of population genetics is that of Gaston Garrone.[29] This work confirms the conclusions of Kallmann's studies and includes the genetic homogeneity of schizophrenia regarding its clinical sub-groups, and a simple recessive mode of inheritance with a homozygous penetrance of 67%. The crude incidence of schizophrenia in the Geneva population is estimated at 1%, the morbidity risk at 2·4%, and the prevalence of the schizophrenia gene at 19%.

Then there is the paper of Prof. E. Essen-Möller,[30] in which he demonstrates that the doubled frequency of affected mothers, as compared to fathers, in the ancestry of schizophrenics, is not to be interpreted as supporting a psychogenetic view of schizophrenia, but that it relates in terms of statistical bias to the fraction of the risk period in the two sexes, between the time of entering systematic observation and the birth of probands. This explanation fits in with the observation that among children those descended from male probands become schizophrenic quite as often as those descended from female probands.

Chromosomal Studies in Schizophrenia

Raphael and Shaw[33] point out that within the past 3 years, the causes of an increasing number of clinical disorders have been elucidated by the study of human chromosomes. It is understandable and desirable, therefore, that schizophrenics should be studied from this point of view, in spite of the strong evidence that we are here dealing with a single autosomal gene effect. The following are brief reports on 3 papers:

1. Money and Hirsch,[31] in a survey of 784 female and 916 male mentally defective patients, found 3 triplo-X and 2 XXY patients. Two of these patients were schizophrenic, and their pedigrees were traced as far as possible. The authors, while concluding that schizophrenia, when coexistent with mental deficiency in the triplo-X syndrome, could not be ascribed to the tripling of the X chromosome, surmise that 'perhaps there is a *closer genetic linkage* between schizophrenia and mental deficiency than can so far be demonstrated'.

2. Tedeschi and Freeman,[32] in a study of sex chromosomes in male schizophrenics, while finding in 2 cases a count of sex chromatin cells far above the expected frequency in the normal male (but lower than in the normal female), demonstrated a frequency of positive sex chromatin 'not too dissimilar from that found by others in normal and mentally defective males', in the series as a whole.

3. Raphael and Shaw[33] describe chromosome studies of 10 adult schizophrenics (5 men and 5 women), followed by a more extensive series of 100 male and 100 female patients, and presents in compendious form 27 sex chromatin surveys (3 on newborn infants, 18 on mental defectives and 6 on schizophrenics).

The authors conclude that one Klinefelter and one triplo-X syndrome in their series of 210 patients, suggest that specific abnormalities of sex chromosomes are more frequent among schizophrenics than in the general population. With regard to the sex chromatin studies they comment that, while the difference between the mental defectives and the newborn is statistically significant, in schizophrenia the numbers are as yet insufficient to confirm a trend.

Summarizing my own impression of these studies, it may be said that to date *chromosomal anomalies have been demonstrated in only a very small minority of schizophrenics.*

B. Other Psychoses

A compendious view of the status of research findings in the other psychoses is presented in Table III, in which the expectancy figures in the general population and stated categories of blood-relationship are set out. The matter is further schematized in Table IV, in which genetically determined psychiatric conditions are classified in terms of the genetic mechanism involved.

TABLE IV. CLASSIFICATION OF POSTULATED GENETIC MECHANISMS IN THE PSYCHOSES AND ASSOCIATED CONDITIONS

1. *Autosomal single dominant*
   Huntington's chorea.
   Manic-depressive psychosis.
   Pick's disease.
   Epilepsy.
2. *Autosomal single recessive*
   Schizophrenia.
3. *Polygenic or multifactorial*
   Alzheimer's disease.
   Senile psychosis.
4. *No genetic mechanism demonstrated*
   Suicide.

PSYCHONEUROSES AND ANXIETY

Although genetic evidence confirms the clinical impression that genetic factors have relatively little influence in the psychoneuroses compared with the constitutional psychoses

*Authors: F. J. Kallmann, M.D., K. Z. Altshuber, M.D., B. Sarlin, M.D., J. D. Rainer, M.D., W. E. Deming, Ph.D. and Diane Sank, Ph.D.

(schizophrenia and manic-depressive psychosis), they are nevertheless not outside the purview of genetics.

Thus, Eysenck[34] has, by methods of factorial analysis, provided proof that neuroticism and psychoticism are different dimensions of personality. Moreover, on the basis of a study of 25 one-egg and 25 two-egg twin pairs Eysenck and Prell[35] classified 'the neurotic personality factor' as a biological and largely gene-specific entity, estimating the genetic contribution to this neurotic unit-predisposition at 80%.

Anxiety, that frequent concomitant of neurosis, is brought together with psychoneurosis by Cattell and Scheier[36] for critical statistical scrutiny, and both items are enriched by their treatment. Not only do these authors confirm Eysenck's finding that neuroticism and psychoticism are separate dimensions, but they establish the multifactor nature of neurosis on the basis of the method of multivariate analysis. In contrast to neurosis, both the trait- and the type-definition attach the clinical concept of anxiety to a single second-order factor. The main first-order components of this factor are ergic tension, ego-weakness, guilt-proneness, low self-sentiment strength, and protension of suspiciousness—and on these components a valuable clinical test of anxiety has been devised. The general point that their analyses has established is that anxiety is part, but not all, of neurosis, which is a broader and more complex concept.

Moving from the general psychological dimension 'neuroticism' to clinically overt psychoneurosis we have to consider Slater's earlier work in which he tends to assimilate neurotic and psychopathic reactions in terms of their common feature of graded adjustment to stress. Genetically he considers that his figures suggest the hypothesis of non-specific polygenic deficiencies in relation to stress. Moreover, in the neuroses he found the form of symptoms less closely related to the form of stress than to the basic personality. In his 1961 Maudsley Lecture[37] he reviews his own data on twins as well as those of Ljungberg,[38] illustrating the heterogeneity of the 'hysteria' group, and dethroning it from the status of a nosological entity.

EPILEPSY

In contrast to the unequivocal findings, relating to specific, unit-factor, genetic mechanisms in the major psychoses, schizophrenia and manic depressive psychosis, extensive work in the sphere of epilepsy has not resulted in the same clear-cut conclusions. In fact, the findings of certain substantial studies are in such striking conflict that we are faced with the serious problem of how to reconcile them.

Work stressing the importance of the genetic factor, comes from two sources:

a. In Conrad's comprehensive pioneer study of idiopathic epileptics,[39] the expectancy rates were 4·0% for siblings, 4·3% for two-egg twins, and 86·0% for one-egg twins.

b. Lennox and the Gibbses,[40-42] employing dysrhythmia in the EEG as their criterion of epilepsy, found 100% concordance for one-egg twins, and 25% concordance for the two-egg variety—the ideal figure for a fully penetrant, single, dominant gene.

In striking contrast to this came the publication of work by Alström[43] in 1950, based on the study of epileptic patients and their families admitted during the years 1925 - 1940 to a university clinic for neurology in Sweden at the Serefiner Hospital. Salient findings of this study were as follows:

Firstly, the expectancy figures for parents (1·3±0·27%), for siblings (1·5±0·25%), and for children (3·0±0·93%) were not significantly higher than those in the general population.

Secondly, families with epilepsy in members other than in the index case, were lacking in the majority (i.e. 92%) of cases.

Thirdly, among the 16 pairs of twins of this study, 2 of which were monozygotic, there was not a single case of concordance as to epilepsy. All this notwithstanding, examination of individual pedigrees in Alström's series discloses, according to his own submission, a single-factor genetic mechanism in approximately 1% of cases—11 index cases belonging to 8 families in his sample of 897 index cases and their families. This is compatible with the type of genetic mechanism postulated by the Gibbses as being operative throughout their series, instead of in only 1%.

With a view to finding further evidence towards settling the dispute, Hurst, Reef and Sachs[44] undertook a study at the Meadowlands Clinic (1959 - 1961), where the clinical material had the special advantage for genetic study of large sibship size (average 5·8, range 1 - 16).

The preliminary pilot study produced evidence along the following two lines:

1. The percentage of families showing one or more members exhibiting epilepsy in addition to the index case, for comparison with Alström's low figure cited above.
2. The types of genetic mechanism exhibited in the pedigrees making up the material.

With regard to the *first point*, there is an incidence of 13 out of 46 families, i.e. a figure of 28·3%, in contrast to Alström's 0·8%—a difference significant at the 0·1% level. This strongly supports the views of Conrad, Lennox and the Gibbses in the dispute.

Turning to *the second point*, analyses of the 13 positive pedigrees (of the 46) show that 3 are suggestive of a penetrant single dominant mechanism, 1 of irregular dominance, while the remaining 9 are equally compatible with recessiveness—or irregular dominance. A portion at least, therefore, of these results is in line with the thesis of *single dominance* of Lennox and the Gibbses.

Metrakos[45] offers a solution which resolves the problem in a most ingenious fashion. On the basis of the EEGs of the parents and siblings of 211 probands and 112 controls, he claims that epilepsy of the centrencephalic type may be explained on the basis of a *single-dominant* gene showing a variable penetrance with age—such that the penetrance is *low at birth, rises rapidly* to almost complete penetrance during the age range 4 to 16 years, and *declines gradually* to almost zero penetrance after the age of 40.

NEUROLOGICAL DISORDERS

We should like to commence this section by indicating general perspectives derived from the application of genetic principles and insights to neurology. Firstly, the fundamental aetiology of a long list of neurological conditions has been established by demonstrating them as being caused by single-dominant, single-recessive or sex-linked genetic mechanisms. Secondly, examining the constellation and varying prominence of the signs and symptoms in stated neurological syndromes in the light of the genetic concepts of penetrance and expressivity, makes these more understandable, and shows that cases with only a fraction of the total symptomatology, are classifiable with the more fully-fledged syndrome, the missing features being explicable in terms of deficient expressivity. And, finally, the now fully recognized fact of the chemical basis of all single-factor genetic mechanisms, such as underlie a long list of neurological disorders, has brought a *reasonable hope of reversibility and cure* in an area hitherto regarded as chronic and without hope.

We refer here to two reviews of this field. The first is the *1953 Proceedings of the Association for Research in Nervous and Mental Disease*.[46] The main contributions were those on muscular dystrophies, neural atrophies, the hereditary ataxias, the lipidoses, and migraine.

The more current review of Haberlandt and Glanville appearing in the work *Expanding Goals of Genetics in Psychiatry*,[27] already referred to, will be discussed in some detail: After surveying the question of hereditary myopathies in animals, the authors turn to the genetics of muscular dystrophies in man.

MUSCULAR DYSTROPHIES

Among the pure muscular dystrophies, 4 genetic types were distinguished by them:

(*a*) *Duchenne.* Sex-linked, occurring exclusively in males.
(*b*) *Facioscapulohumeral.* Autosomal dominant.
(*c*) *Limb-girdle.* Autosomal recessive form including most 'sporadic' cases, without known affected relatives.
(*d*) *Limb-girdle.* Aetiologically undetermined. They may represent occasional pathological expression in the heterozygote, or may be phenocopies without a simple genetic aetiology.

There is now little doubt that there is a form of dystrophy, which is clinically indistinguishable from the Duchenne type, but which can affect both boys and girls. The importance of distinguishing this type from the sex-linked form, from a eugenic point of view, is stressed by the authors of the review.

The prevalence, mutation and fertility rates for the 4 genetically determined forms of muscular dystrophy, vary considerably. The *prevalence* of the types in the order mentioned, are 66 living cases per million *males*, 2 living cases per million, 12 living cases per million, and 8 living cases per million respectively. The corresponding *fertility* rates are 4% of normal for group (*a*), nearly normal for group (*b*), and 25% of normal for groups (*c*) and (*d*). *The mutation rates* have been estimated at 89 per million gametes for group (*a*), 50 per million gametes for group (*b*) and 31 per million loci for group (*c*).

On the *chemical* side of the serum enzymes with a known tendency to increased activity in neuromuscular disease, aldolase has been found to be particularly increased in dystrophic patients. Other enzymes in this category are phosphohexose isomerase, lactic dehydrogenase, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase. Increased aldolase activity seems most pronounced in rapidly progressing forms, especially in the early phases of Duchenne dystrophy, and may precede the onset of clinical symptoms. It has been suggested that excess enzyme may leak into the serum from the muscles, owing to an abnormal permeability of cell walls. The potentially greater value of creatine phosphokinase, because of its more important role in muscular contraction in both clinical diagnosis and the identification of carriers, has been broached by Okinara, Dreyfus and others.

Other Myopathies

Apart from these classic inherited muscular dystrophies, several other related conditions can be distinguished both genetically and histologically. Since a striated muscle has many enzymatic functions, it presents multiple possibilities for genetically determined dysfunctions. In this sphere recent work has been done on McArdle's syndrome and muscle core disease, both of which, unlike dystrophy, are not related to primary defects in the muscle nucleus, but to defects in the mitochondrial enzymes and the structure of the myofibrils respectively. In McArdle's syndrome (myophosphorylase deficiency glycogenosis), which is inherited as an autosomal recessive, excessive amounts of glycogen are deposited in the muscles, presenting clinically as weakness, pain, and stiffness after exercise. This results from deficiency in myophosphorylase. The enzyme appears to be completely inactive in the homozygote. In muscle core disease we have to do with a congenital non-progressive myopathy, inherited as an autosomal dominant, in which, as yet, no biochemical basis has been determined. And finally, in this category, there is the recent study on congenital myotonia by Becker, which showed a fairly even distribution of the condition throughout Germany. Familial cases could be distinguished from sporadic ones, showed an earlier onset (before the age of 10), and were equally distributed between a dominant mode of inheritance with no difference between the sexes and a recessive one with excess of males.

There has been much recent work on the neuropathies and other neurological syndromes in the fields of dystonia musculorum deformans, multiple sclerosis, syringomyelia, tuberous sclerosis, and Charcot's disease, but to save space, we limit ourselves to two conditions in which there has been an advance into the biochemical genetics of the conditions—familial periodic paralysis and Wilson's disease (hepato-lenticular degeneration).

In familial periodic paralysis, where an autosomal dominant mode of inheritance has been established, attacks may occur spontaneously or may follow the administration of salt-retaining adrenocortical steroids. While an increase in serum aldosterone and 17-ketosteroids tends to precede the attack, the serum-potassium level is found to be decreased during the paralysis. The condition may, therefore, be connected with defective permeability of the muscle membrane, resulting in an abnormal Na/K balance 'triggering' hypersecretion of aldosterone; conversely, it may well be that an increase of aldosterone induces the observed electrolyte imbalance. A genetically *distinct* but clinically *similar* variant is adynamia episodica hereditaria, also inherited as an autosomal dominant. The main differences consist of an increased serum-potassium level during attacks, EMG abnormalities, and provocation of the episodes by hunger or KCl administration.

Turning from the review of Glanville and Haberlandt, we direct our attention to the especially effective studies, genetic and chemical, of Wilson's disease, that have been undertaken by Bearn[47] and his associates of the Rockefeller Institute. Bearn postulates a single recessive gene mechanism. But differences in age at disease onset, consanguinity, fertility and variance in serum copper and ceruloplasmin levels, noticed between cases of eastern European and Mediterranean origin, led him to suggest a modifying gene in the former group, or alternatively, the presence of more than one allele at the Wilson's locus.

Evidence is as yet insufficient whether ceruloplasmin is the primary gene product of Wilson's disease—the incorporation of copper into ceruloplasmin may be of more importance than the synthesis of ceruloplasmin itself.

On the hypothesis of two different alleles, the common allele is associated with a decreased serum ceruloplasmin, whereas the less common allelomorph is associated with a normal or near normal level of ceruloplasmin synthesis. Heterozygotes may similarly show marked depression of ceruloplasmin and serum copper levels, but vary from marked depression to relatively normal values in others. Furthermore, a diminished serum ceruloplasmin level in a heterozygous parent is apparently not associated with earlier age of onset in affected offspring. Radioactive data provide the insight that, although total ceruloplasmin levels may be normal in both patients and heterozygotes, abnormalities in the rate of synthesis may be present.

The question of the *normality of the structure* of the ceruloplasmin molecule in Wilson's disease came under investigation by means of the techniques of chromatography and immunophoresis in 1959. In 1961 Poulik and Bearn[48] were in a position to comment on the heterogeneity of ceruloplasmin. They reported that, in line with the increasing awareness of the heterogeneity of serum proteins previously regarded as homogeneous, particularly the haptoglobins and transferrins, Morell and Scheinberg have demonstrated the existence of polymeric forms of ceruloplasmin, possessing different electrophoretic mobilities in the starch gel system. They further suggest the possibility that these differences may be genetically based, as suggested by the studies of McAlister *et al.* and of Parker and Bearn. (A family study, extending over 4 generations, showed that a fastly migrating band segregated as a dominant character.) In one preparation, 7 distinct ceruloplasmin bands were observed. Bearn has also shown that the lability of ceruloplasmin with regard to its oxidase activity is related to a particular part of the molecule.

SOUTH AFRICAN STUDIES IN PSYCHIATRIC AND NEUROLOGICAL GENETICS

The work by Drs. Geoffrey Dean and H. D. Barnes on porphyria is well known, and Dr. Dean is also at present engaged on a study of multiple sclerosis. We have already dealt with our own study on epilepsy at Meadowlands. Other work of our Unit may be summarized as follows:

(*a*) *Genetic Counselling*

This has been conducted on a variety of medical and psychiatric problems. Over the past two years an average of 10 people per month have sought advice at our centre.[53]

(*b*) *Cytogenetics*

(*i*) *Mentally defective population* (Witrand Institution, Potchefstroom). Dr. I. Anderson[49] has taken buccal smears from 1,662 patients—one of the largest surveys in the literature. Ten anomalies in sex-chromatin were detected —5 females and 5 males. The chromosome culture studies were done by Dr. Clive Wallace and the 4 triplo-X or superfemales found are probably the first cases reported in South Africa. Drs. Anderson, Goeller and Wallace employed a rapid nuclear sexing technique, which has enabled them to do some 2,000 smears during 6 week-ends.

(*ii*) *New form of autosomal aneuploidy*. Anderson and Wallace[50] have described a new form of autosomal aneuploidy in the Witrand population. In essence they report a female with the clinical features of the 13 - 15 trisomy, in whom they found a 15 - 4 translocation chromosome and a modal count of 45. They introduce the concept of partial monosomy to account for this syndrome.

(*iii*) *Normal karyotypes* have been demonstrated at Witrand by the abovenamed in a case of Sturge-Weber syndrome,[51] one of pseudoxanthoma elasticum, and another of mental defect with multiple congenital defects.

(*iv*) *In a survey of 80 cases of Down's syndrome* (*mongolism*) at Witrand, Anderson and Goeller found a *cardiac abnormality rate* of approximately 40%. They have circularized parents in an endeavour to seek a possible relationship to such factors as parental age, exposure to X-rays and drugs.

(*c*) *Biochemical Genetics*

A survey of phenylketonurics at Witrand by Anderson,[52] not yet completed, has as special objective the assessment of blood relations using the L-phenylalanine load tests.

(*d*) *Population Genetics*

A preliminary survey of the 'genetic isolate' in 'Die Hel' (Gamkaskloof) conducted by Anderson in January 1963[52] has dispelled the popular impression of excessive inbreeding and mental degeneration there.

Klintworth's report[54] has established the presence of Huntington's chorea in 16 South African families. In the White population it was found in 5 Afrikaner families, probably belonging to one large family. In addition there were 4 English families, some of Austrian and German origin, and 2 Jewish families, in which the possibility of a non-Jewish ancestor could not be excluded. In one Bantu family, the purity of which has not been established, the typical clinical features of the condition were seen by Dr. H. Reef in 2 siblings, who had a similarly affected parent.

The attitudes towards Huntington's chorea in affected South African families are highly diversified. In some instances the majority of family members knew that their family was afflicted with this illness, but they were inclined to regard themselves as immune from risk, since several of the other members of the family had already been affected. Others refused to accept the hereditary nature of the condition and not uncommonly have as many as 10 children. In at least 2 families, the spouses *were fully aware of the hereditability* of the disease, but kept the information from their children for fear of upsetting them. Such an attitude may account for the fact that, in certain instances, patients seem genuinely unaware of the existence of the disease in their families. In a few families younger members decided to repudiate the family connection to the extent of changing their names. Suicide has also followed the discovery of a long-concealed family history. In a minority of cases family limitation has been practised to a varying degree.

CONCLUSION

I should like to say a word about the psychiatric dimension in genetic counselling. In the first place, there is a special feeling attached to counselling in the psychiatric sphere, originating from the terrors of ancient psychiatric practice and its cruelties in mediaeval times, and from the vividly recalled abuses introduced in the name of eugenics in the thirties.

This underlines the need for scientific counselling, which realizes the specific difference in the genetic mechanisms underlying schizophrenia and manic-depressive psychosis, and which should be reflected in the counsel given. Secondly, as stressed by Kallmann and Rainer,[55] there is a psychological dimension in all genetic counselling, whether it concerns psychiatric conditions or diseases and defects falling within any area of medicine. This renders psychiatric training an additional qualification in the genetic counsellor. Obviously, in a sphere of such profound significance to the client, he comes to the counsellor with a load of anxiety, often only partially recognized by himself, and this anxiety is a vital part of the situation to be handled by the counsellor.

In this context the question, whether giving the empiric risk figure to the client is the whole duty of the counsellor or whether indeed it is his duty at all has been discussed. It is questionable in the first place how meaningful such a statement is to any but a critical mind, trained in statistical theory, and how traumatic it might be in certain instances to any type of mind. A conclusion that would seem apposite is that genetic counselling is a synthetic art to which the counsellor should bring scientific genetic knowledge, psychological insight and, if possible, a medical and psychiatric orientation.

I might also give a perspective and a vista for the future and raise the curtain a little on the basic work being done at the chemical level. This work on the enzyme blocks which underlie individual psychiatric and neurological disorders, gives hope of fundamental pharmacological cure. However, the question of when in the next few decades the break-through will occur, is a matter for conjecture. Studies involving psychotropic drugs and psychopharmacological agents, as well as direct neurochemical investigation, have suggested a number of clues which require further elucidation and synthesis.

Success has already been achieved in phenylketonuria along the lines indicated, and this may serve as the model for what is envisaged in psychiatric diseases of single gene aetiology, notably schizophrenia and manic-depressive psychosis. We may recall the leads that appeared in this field in recent years—derailed metabolism of adrenalin ;[56, 57] anomalies in serotonin production ;[58, 59] abnormal serum protein, or substance attached to it ;[8-11] denaturation of protein through disordered nucleotide sequences in the DNA code ;[60, 61] special amine appearing in the urine -3,4-dimethoxy-phenylethylamine ;[62] shifting of carbohydrate into the shunt less effective for energy liberation ;[63, 64]

exploration of other areas of carbohydrate metabolism;[65] electrolyte imbalance and the possible role of glutathione and electrondonation,[60, 66] and the metabolism of haem.[67] Another line of approach was suggested by Hurst,[68] namely, attempting a link-up with the underlying gene-determined enzyme block in manic-depressive psychosis and schizophrenia, by tracing back the precursors of substances in the phenotype (e.g. noradrenaline and serotonin) influenced by effective neuropharmacological agents. The antidepressants (with the special advantage of 2 converging chemical paths in the case of MAO-inhibitors and imipramine), and high-dosage insulin and high-dosage tranquillizer therapy in schizophrenia furnish such experiments.

Finally, I should like to underline the reciprocal relationship obtaining between genetic counselling and fundamental cure directed at the genetically determined enzyme block underlying the psychiatric disorder concerned. With the establishment of the latter, namely, a specific gene-centred, fundamental cure, the need for the former (genetic counselling) disappears. A word of caution is necessary, however, for even when a specific break-through for one of the psychiatric disorders occurs, the therapeutic chemical may require a long period of refinement before it is effective *in vivo*, and even then the sufferer may be condemned to life-long use of the medicament.

This is the discrimination with which we must temper our enthusiasm in this era with its breath-taking possibilities, stemming from the splendid paradox of modern biochemical genetics—that the hereditary nature of a condition actually opens the way to its fundamental pharmacological cure by pinpointing the genetically determined biochemical anomaly underlying it.

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