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Classification of Psychotic Disorders from a Genetic Point of View

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Introductory

In musing upon my assignment for this Congress, I became aware of limitations that I must impose upon myself, inherent in the title of the address. First, the words " Psychotic Disorders " point to the fact that the whole province of Psychiatry is not included in its scope, and whilst it is pertinent to include with the psychoses, suicide, which is a not infrequent feature of the psychotic disorders, and the epilepsies, which commonly have a psychotic aspect, the large areas of the psychiatric field characterized as mental defect, psychoneurosis, psychosomatic conditions, psychopathic personalities, and sexual deviations (including homosexuality) are not relevant to to-day's talk. Nor is it my prerogative to treat of recent developments in the realm of chromosome anomalies, such as the trisomy underlying Mongolism, karyotypes and the sexing of cells. In the second place, the term " Classification " suggests to me that my task is to confine myself to the findings of genetic studies in our field of discourse and not stray into the tempting pastures of eugenics, or biochemical genetics with its rich promise of reversibility and cure by modern pharmaceutical means. Even now with our feet firmly on the ground of genetic fact, after this preliminary delimitation, we are not entirely free on the semantic side of things, for, if I mistake not, some appearance of ambiguity would seem to lurk in our title. Is its meaning that within the discipline of Psychiatry we are to attempt a classification of the psychoses from a genetic point of view, or, is it that as an exercise within the realm of Genetics we are seeking to classify the specific and non-specific hereditary mechanisms, which have been postulated as underlying different psychotic disorders? I incline to the view that both of these programmes are significant, and appropriate to the endeavour to which this paper is dedicated.

As a prolegomena to the first issue, namely, the legitimacy as a psychiatric ideology of marshalling clinical facts in terms of genetic classification, let us examine the vicissitudes of the notion of heredity as applied to mental disorders during the course of the past century. In this connection we should remember that it was only at the turn of the century that de Vries, Correns and Tschermak simultaneously rediscovered the work of Gregor Mendel, that on this score the notions of even Darwin and Galton on heredity were prescientific, and that accordingly we should regard with tolerant eye the crude hereditarian concepts prevalent among alienists, physicians and the common man during the latter part of the nineteenth century. How then may we characterize the views of heredity in mental disorders prevailing during that period? I think it a fair representation of the position to state that all mental disorders were regarded as hereditary, and *that* in a non-specific and undiffe-

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rentiated fashion. According to this view dementia praecox in parents could through the operation of heredity give rise to manic-depressive psychosis in children, to epilepsy in grandchildren, and alcoholism in great-grandchildren. As the notion of heredity presupposes the identity of the trait or disease transmitted as it appears in successive generations, the theorists of the late nineteenth century were forced to postulate a generalised " neuropathic taint " which could manifest in a variety of nosological forms, a position rendered untenable, as we shall see, by the specific mechanisms demonstrated by modern genetics as well as certain statistical considerations of contemporary psychology.

Early in the present century there was a reaction or over-reaction from the sweeping hereditarian claims in psychiatry of the century immediately preceding it. This reaction sprang from various sources. One might mention first a general origin, namely the common untutored human tendency to rebel against the idea of determinism in conduct, more particularly when, as in the concept of heredity, the determinism is not confined to one individual life, but is of a scope which extends from generation to generation. But there were far more specific sources of this reaction, having their roots in special ideologies and scientific disciplines. First among these was the march of scientific genetics itself which through its demonstration of specific genetic mechanisms and subtler formulations of nature nurture interrelationships, exploded the earlier cruder views. Indeed the need for intellectual restraint and humility induced by the vastness of the panorama of interacting and as yet largely unknown factors disclosed by the new science of Genetics led Hogben, as late as 1930, at the time that he was my teacher at the University of Capetown, to propound the view that if there are indeed genetic mechanisms underlying the psychoses, it would probably be generations before they were elucidated — a point of view, incidentally, which he, in true scientific spirit, reversed a decade later when substantial evidence disclosing a specific mechanism in one of our major psychoses came to light in the work of Franz J. Kallmann (1), presented at the Seventh International Congress of Genetics, at Edinburgh in 1939.

Over-reaction against hereditarian notions in Psychiatry came also from the specialized areas of the Psychoanalytic and Behavioristic schools. Certain extremists within the Psychoanalytic fold stressing the rôle of psychogenic factors in early life to the exclusion of the nativistic and instinctivistic aspects included by Freud, provided a mental climate hospitable to the environmentalistic reaction in Psychiatry. Similarly, Watson, founder of Bahaviorism, by his unsubstantiated claim to the effect that by differential conditioning ot two persons of comparable endowment he could produce a genius or an imbecile, fostered an environmentalistic, anti-hereditarian trend in our field.

Modern Studies in the Genetics of the Psychoses

The resulting slump in the stock of genetic ideas in Psychiatry might well have continued indefinitely had not substantial genetic studies in the field of our major psychoses, Schizophrenia and Manic-depressive Psychosis emanated from Franz J. Kallmann from the late thirties of this century on (2, 3, 8, 11), soon to be substantiated by Eliot Slater (9, 10). The findings of these and other important workers (4-7, 12-26) in the field of the genetics of the psychoses are reflected in Table I. The data presented are are all derived from studies based upon modern

Tab. I. 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			c. 15%			c. 15%	c. 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 & 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 ± 2.9%			19±5%		Autosomaldominant
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 single dominant
	Gibbs et al. (EEG)				25%	100%			Single dominant
8. Huntington's Chorea	Rosanoff & Handy				1 : 2	3 : 3			Autosomal dominant
	Haldane								Sex-linked modifiers

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methods of Human Genetics. These include, twin studies, family studies and twin-family studies of numerically adequate extent, which avoid or allow for selective factors in their methods of collection of subjects and employ specialized statistical techniques such as those involved in the calculation of expectancy figures. I do not propose entering into the rationale of twin, family and twin-family studies, nor into the details of these methods and techniques, which, in a specialized Congress of this kind I consider I am entitled to " take as read ".

I should however like to make the following comments in elaboration of the data reflected in Table I.

1. Manic-depressive Psychosis

The genetic mechanism is irregularly dominant with a high degree of penetrance, and with a pronounced tendency to a relatively mild symptomatology in the presence of stabilising constitutional modifiers. The diagnostic classification should be restricted to cases with acute, self-limited mood swings before the 5th decade of life and without progressive or residual personality disintegration before or after psychotic episodes. So diagnosed, the disease is correlated with a tendency to obesity, cardiovascular disorders, gout and diabetes and high resistance to tuberculosis, and is apparently based on a strictly specific genotype. This condition is genetically unrelated to reactive or neurotic depression, to menopausal and presenile depressions, or to other non-periodical forms of depressive behaviour in the involutional period. The dysfunction may be looked upon as one of regulatory instability, but present information about the biochemical constituent of the underlying genotype, as well as the range of its compensatory adaptiveness, is still far from complete.

2. Schizophrenia

The expectancy figures for schizophrenia in Kallmann's American study (1946) are as follows:

One-egg twins	86.2%	Half-siblings	7.1%
Two-egg twins	14.5%	Children	16.4%
Siblings	14.2%	General Population	0.85%

Inferences from these figures are:

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

2. With increasing degree of blood-relationship there is 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. Beside this the finding in the same study that the concordance of separated one-egg schizophrenic twins is 65.0% as compared with 71.0%, in those not so separated appears to imply relatively insignificant environmental factors in causation of the condition.

4. The essential similarity of the figure for siblings and two-egg twins (14.2% and 14.5%) is of intrinsic interest because of postulated lack of significant differences in average genetic equipment in these two categories. There is an obvious analogy here to the greater similarity of the environment shared by one-egg as compared with two-egg twins: in the present case there is a presumption that two-egg twins are on the average likely to share a more common environment that any two siblings taken at random, and yet here this environmental factor has exerted no effect on the comparative morbidities.

5. One additional statistic in relation to the question of dominance or recessiveness of the schizophrenic genotype is that in Kallmann's studies he has found a figure of 16.4% in children with one schizophrenic parent, and 68.1% with both parents schizophrenic. The most cogent view, according to Kallmann, is that the condition is determined by an autosomal and singlerecessive unit factor, the penetrance (70%) and phenotypical expressivity of which are limited by polygenic (non-specific) constitutional modifiers, measurably correlated with the compensatory capacities of the athletic or mesomorphic component of physique.

A close relationship between constitutional resistance to the schizophrenic genotype and graded resistance to pulmonary tuberculosis has been found. Only homozygous bearers of the specific (predisposing) genotype for schizophrenia are capable of reacting with a true schizophrenic psychosis. Other features emerging from an analysis of the detailed figures of Kallmann's work are reduced reproductivity rate, increased rate of consanguinity in the parents and transmission in the collateral line of descent. Schizoid personality traits may be found in homozygotes with very high resistance or in heterozygotes with relatively low resistance.

Of the other serious workers and thinkers in this field none are to be found who dispute the fact of heredity in schizophrenia and its great importance, but there are those who favour some other type or additional type of genetic mechanism. In Germany during the 1930s a simple dominant mode or inheritance was favoured and became the basis for eugenic sterilization laws. Lenz, Koller, Slater and Böök still support the dominance theory as covering some or all of the cases, on a strictly scientific basis.

Koller's argument cannot be presented here in detail, but it culminates in the contention that if the gene were recessive the incidence of schizophrenia should be lower in the children than in the sibs, whereas the reverse is the case. Slater likes this argument, inclines to the view that dominant as well as recessive forms exist, and adopts a view of genetic heterogeneity to explain the subgroups of schizophrenia which Kallmann deals with more effectively, in my opinion, in terms of the modifying effect of a polygenic resistance mechanism. Penrose's theory of a multifactorial genetic determination of the disease does not conflict formally with Kallmann's hypothesis of a specific single recessive predisposing mechanism plus a multifactorial constitutional resistance mechanism, for after all, " one plus many equals many ", but Kallmann's theory is so much richer in detailed content and in its fruitfulness as research hypothesis.

In bringing together findings in respect of manic depressive psychosis and schizophrenia, it is interesting to note the cumulative effect of the evidence of the specificity and distinctness of the two genotypes. In reviewing the work of Kallmann's department in 1952, Hurst (27) was able to report that among a total of 1,232 twin index cases no pair of one-egg twin partners was found whose clinical symptomatology warrants placing the two members of a pair into

different diagnostic categories. Recently published observations of 3 different workers-Elsässer (28), Slater (9) and Stenstedt (7) — point in the same direction.

The relative infrequency of manic-depressive psychosis in modern populations may be partly due to factors of selection which reduce the reproductive rate of the carriers without affecting the social level of their families (Kallmann, Stenstedt). At least there seems to be no tendency towards a social decline of the magnitude typical of schizophrenic family units.

3. Childhood Schizophrenia

In their paper antitled " Genetic Aspects of Pre-Adolescent Schizophrenia " Franz J. Kallmann and Bernard Roth provide the following conclusions from their study of 52 twins and 50 singletons under age 15 (quoted in part):

a) " These findings indicate an early effect in childhood schizophrenia of the same genotype (gene-specific deficiency state) assumed to be responsible for the basic symptoms of adult schizophrenia. The conclusion is supported by the observation that the psychoses in the co-twins of early schizophrenic cases occur sometimes before and sometimes after adolescence ".

b) " While the aetiological mechanism underlying the relatively infrequent activation of a schizophrenic psychosis before adolescence has not yet been adequately identified, it would seem to be connected with variable constellations of secondary factors lowering constitutional resistance ".

c) " Because of a dearth of statistically comparable data, it is difficult to appraise the part played by a poor home with disturbed intra-family relationships in the aetiology of childhood schizophrenia as compared with that of adult schizophrenia ".

4. Involutional Psychosis

According to Kallmann, the implication of comparative data " would seem to be that the principal genetic derivation of involutional psychosis is from an indirect relationship to the entity of schizophrenia, and not from a specific type of predisposition producing a particular impairment of the adjustive plasticity of aging persons ". The affiliation of involutional psychosis to schizophrenia, rather than to manic-depressive psychosis, under the heading of the affective psychoses, as is customary in the standard texts, is in line with recent studies on the pre-psychotic personality of this group, which reveal schizoid traits, including rigidity, rather than cyclothymic ones. This incidentally illustrates how genetic findings may enrich our clinical insights.

5. Senile and Pre-senile Psychoses

The severe maladjustment to aging resulting in the symptomatology of a senile psychosis would appear to depend on a combination of aetiological components, including age-susceptible personality traits, and declining adaptational plasticity and socio-economic security. From their relation to those gene-specific biochemical phenomena which control growth and decline, these may be expected to coexist more frequently in genetically alike persons (one-egg twins).

The genetic mechanism is in all probability polygenic in nature, despite Haldane's speculatively attractive attempt to assimilate it to the heterozygous state of phenylketonuria.

Of the presenile psychoses we shall confine ourselves to the brain atrophies of Pick and Alzheimer. The evidence from the investigation of the Sjögrens and Lindgren (1952) that makes it probable that polygenic or multifactorial inheritance operates in Alzheimer's Disease, fits in with the graded nature of the clinical picture in terms of varying degrees of dementia and of degenerative neuropathological changes. In Pick's Disease a dominant gene is almost certainly implicated. Grunthal's work (1930-1931) that had been suggestive of this was clinched by Sjögren (1952). In attempting to account for the preponderance of women in Pick's as well as Alzheimer's Disease, Sjögren rejected the hypothesis of sex-linked inheritance in favour of the thesis that either a reduced manifestation of the specific genetic factors in males is responsible, or an inhibiting gene on the X chromosome which prevents manifestation in men, but must be present in homozygous form before it can do so in women.

6. Suicide

In suicide, that final and irrevocable failure to adjust to life, there has been a widespread tendency to assume an inheritable type of unfitness in the general personality structure. This has not been borne out by the investigations of Kallmann and his co-workers. The first 27 sets of twin subjects were discordant as to suicide. In 1950 this run was broken by a pair of schizophrenic and overtly homosexual World War II veterans, who became concordant as to suicide, albeit at different ages, 25 and 29, and by different methods (drowning and gas). A single instance of this type in a sample of this size is clearly within the range of chance expectation. The general conclusion from this study of suicide in twins, as well as from another one by the same group in only children, is that there is no statistically valid support for the notion of hereditary or familial occurrence of suicide.

7. Epilepsy

In the field of epilepsy the evidence from various sources is conflicting. The presumption is that the tendency to seizures is a graded character — varying from the potentiality of all the human species (and indeed many sub-human organisms) to develop seizures under the influence of unusually potent stimuli such as that employed in electro-convulsive therapy, through the cases where rather special irritant agencies such as alcohol, fever or trauma are sufficient to elicit seizures, to the clinically recognised epileptics who have their seizures under the range of stimuli provided by the everyday environment. This would suggest the likelihood of a polygenic mechanism for any hereditary basis involved. The figures in Table I of Conrad provide substantial evidence for a genetic basis and are not incompatible with the polygenic hypothesis which is favoured by Kallmann. The figures of E. L. and F. A. Gibbs based not on a clinical but on an EEG criterion — dyshrythmia, are interpreted by them quite unexceptionably as favouring single dominance. The question is further beclouded by Alström's finding of an over-all incidence figure for children, parents and siblings of the same order as that characteristic of the general population concerned. These results would suggest either that in

general no genetic factor is discernible or that we have to do with a major dominant gene, of low penetrance due to powerful modifiers. Detailed scrutiny of the results reveals that in only about 1% of his 897 index cases — 11 probands belonging to 8 families — does the epilepsy appear to follow a single dominant course with high penetrance.

With a view to contributing to a solution of the discrepancy between the claim emphasizing the importance of heredity in Epilepsy, shared by Conrad and the Gibbses and Lennox, as against Alström's rare implication of the genetic factor in the condition, we have conducted a pilot study involving 46 epileptic index cases comprising Bantu patients attending the Meadowlands Clinic in the South-Western townships of the Johannesburg area (29). A special advantage of our clinical material from the point of view of a family study was the large size of the families in comparison with those characteristic of Whites. The average number of sibs per family in our sample was 5.8 with a range of from 1 to 16. Thirteen of our 46 families had at least one other close relation affected i.e. a figure of 28.3% in contrast to Alström's 0.8% (a difference significant at the 0.1 percent level). Our findings thus strongly support the protagonists (mentioned above) of the importance of hereditary factor in epilepsy.

On the side of detail it may be of interest to mention that of our 13 positive pedigrees 3 are suggestive of a highly penetrant single dominant mechanism, 1 of irregular dominance, and 9 are equally compatible with recessiveness or irregular dominance.

8. Huntington's Chorea

This, the first psychiatric condition to be recognised as hereditary in nature, is found in all parts of the world and affects Whites and non-Whites alike. It has been shown to be due to a single dominant gene of close on 100% penetrancy, for it rarely skips a generation. Rosanoff and Handy (1935) have recorded five pairs of twins from affected families. The three monozygotic pairs were concordant for the condition, whilst in the case of the two dizygotic pairs one was concordant and the other discordant. Haldane (1941) has advanced the thesis that there may be sex-linked modifiers which tend to raise the age of onset in males. Commenting on Bell's figures (1934) as to the differential distribution of affected progeny of affected fathers and mothers he finds that the difference is highly significant for the children of affected fathers. On the supposition that there are one or more sex-limited modifiers tending to lower the age of onset in males, it is clear that a man carrying such a modifier would be more likely than the average man carrying the main gene to develop the disease, and his sons would also on the average, develop it before his daughters. Both allelomorphs of the modifier must be fairly common, or alternatively there must be a number of not very rare dominant modifiers. They cannot have any conspicuous effect on normal people, but may have some. He goes on to speculate along the lines of Fisher's theory of dominance that in conditions like Huntington's Chorea, where modifiers are important, selection will cause them to spread. The present age of onset of this disease may merely mean that primitive men and women seldom lived much beyond forty, so postponement of onset beyond this age had no selective advantage. If the unfavourable modifiers are not disadvantageous, they will spread until the disease becomes one of old age. Then the gene frequency will be increased by mutation until unions of persons carrying it become fairly common. The homozygous form will be a severe and perhaps lethal disease, and then perhaps other modifiers will be selected.

Discussion of the Implications of These Studies

The above evidence would seem to supply ample justification for answering our first question as to the legitimacy of, from within Psychiatry, accepting specific genetically determined diseases or entities as a basis for classification of the psychoses. This amounts to a reinstatement of the nosological entities, so much despised by certain fashionable current psychiatric ideologies, notably Psychobiology and Psychoanalysis. Indeed it may be said that modern genetics corroborated by recent findings from factorial analysis psychology has ushered in an era of neo-Kraepelinism. With regard to the latter it may be in place to remind the audience that it was as the result of painstaking genius and an eye for unifying concepts that Kraepelin brought together or our two best known psychoses, Manic-depressive psychosis and Schizophrenia, from phases or syndromes whose relationship had hitherto been obscure. Factorial analysis studies by En Hsi Hsu (30) have moreover confirmed Kraepelin's clinical insights within this area. Furthermore, Eysenck's (31) more recent statistical analysis, in establishing neuroticism and psychoticism as separate dimensions, and not different degrees of the same dimension, is similarly in line with the ideology of discrete nosological entities in Psychiatry based on specific genetic mechanisms.

It may be asked to what extent this genetically-based classification of the psychoses is compatible with psychoanalytic methods of interpretation of the psychoses. As early as 1946 Kallmann argued that the two approaches are not mutually incompatible. The gist of his argument is that if Freudian psychodynamics are true of the normal person, they will appear, indeed they will be seen writ large, in the biologically handicapped organism of the schizophrenic. The rôle assigned to psychological factors in this view is, however, on the side of the content of symptomatology rather than in causation, which differentiates it radically from the psychoanalytic view in which a causal rôle of psychogenic factors is of the essence.

Passing on to the Psychobiology of Adolf Meyer, what is the standing of our genetically based classification of the psychoses in relation to this system? By clearer definition of a most important biological factor our genetic classification cannot but enrich a true Psychobiology. However, to what Psychobiology had come to mean in the Meyerian school, with its unwarranted rejection of nosological entities, and its soft-pedalling, in practice, of the biological side of the psychobiological partnership, the genetically based classificatory approach has supplied a double corrective.

Towards a Classification of Genetic Mechanisms

In conclusion with a view to systematizing the classification of the psychoses within the province of Genetics, I have brought together in Table II, under the headings of specified genetic mechanisms the psychoses in which there is substantial evidence of a genetic basis. Where the type of mechanism is in dispute I have assigned the condition to the mechanism which on the evidence, appears to me to have the strongest claim. The comments following it deal with dissentient opinions, modifications and elaborations.

In commenting on Table II only a few points need be made:

Tab. II. Classification of postulated Genetic mechanisms in the psychoses and associated conditions

I. Autosomal Single Dominant.
Huntington's Chorea.
Manic-depressive Psychosis.
Pick's Disease.
Epilepsy.

II. Autosomal Single Recessive.
Schizophrenia.

III. Polygenic or Multifactorial.
Alzheimer's Disease.
Senile Psychosis.

IV. No Genetic Mechanism Demonstrated.
Suicide.

1. Certain investigators, notably Slater and Koller, stress the existence of dominant as well as recessive forms of schizophrenia.

2. Kallmann, in some of his writings, inclines speculatively to a polygenic interpretation of epilepsy, on the basis that the proclivity to epileptic fits is a graded one, inasmuch as virtually all persons react with a seizure to the passage of an electric current through the brain as in electro-convulsive therapy, and others only have seizures under the influence of febrile conditions, drugs or alcohol, while yet others react in this way amidst the stimuli of everyday life. Moreover, epileptic seizures occur widely throughout the animal kingdom.

3. Modifiers are invoked by Haldane to explain certain apparently anomalous sex ratios in Huntington's Chorea.

4. The lack of demonstration of a genetic factor underlying suicide is quite understandable as we are certainly not here dealing with a nosological entity. This fact is an object lesson to to those sceptics who incline to the view that geneticists are biased in the direction of finding genetic mechanisms where none exist. For, in the case of suicide we have a category popularly regarded as undoubtedly hereditary in nature, and even a criterion for not marrying into the family concerned, where investigation by a leading geneticist fails to demonstrate a genetic mechanism.

Summary and Conclusions

This paper seeks, on the basis of modern studies in Human Genetics in the field of Psychiatry, to justify the classification of the vast majority of the psychoses on the basis of genetic determination, and from within the discipline of Genetics to classify the variety of genetic mechanisms involved. Within Psychiatry such an approach runs counter to such extremists of the Psychoanalytic School who admit only the existence of psychodynamic principles to the exclusion of constitutional factors, and the aberration of Meyerian Psychobiology which substitutes " reaction types " for nosological entities. Whilst the tenability of these positions are disproved from genetic and statistical psychological evidence, the potentially har-

monious relationship that may exist between a Genetic Classification of Psychotic Disorders and balanced and duly corrected Psychoanalytic and Psycobiological doctrines is explained. Finally, one may mention that omissions from our tables of the names of certain psychoses does not carry the implication that these are psychogenic in nature. Two categories cover and explain these omissions. First, there is the group in which exogenous physical agents such as toxins, infections, nutritional deficiency and trauma play a leading rôle. Even here the indi vidual variability in psychiatric reaction and symptomatology implies a genetic basis yet to be investigated by precise methods. Secondly there are psychotic conditions such as Paranoia in which no assessment as to the relative rôles of psychogenic and genetic factors can be made owing to the Iack of scientific genetic studies of sufficient extent.

In bringing my talk to a close, I should like to venture the statement that a genetic classification which covers the great majority of psychotic conditions has already been achieved, but that there are still others whose adequate scientific genetic investigation offers an exciting challenge.

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