RECENT PROGRESS IN PSYCHIATRY

VOLUME THREE

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RECENT PROGRESS IN PSYCHIATRY

VOLUME 3

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INTRODUCTION

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SINCE the Second Volume of *Recent Progress in Psychiatry* was published in 1950, the spate of psychiatric literature has continued to increase but many of the papers published on psychiatry are of little value. This cannot be said of the ancillary subjects, and once again it is to these that we look for the foundations on which the theories and practice of treatment must be built. For some years it has become obvious that the basis of psychiatry is largely on physiology and biochemistry, together with a wide knowledge of the anatomy of the brain. The theory and application of the group of tranquillizing drugs is based on a knowledge of biochemistry and pharmacology. The time is not ripe yet to include a chapter on these drugs. They are at present the subject of wide misuse by the public, the general practitioner and the field of competitive sport. What the future will show remains to be seen. It is hoped to include chapters on tranquillizing drugs, psychiatric hospital management and epilepsy in the next volume. In addition to the time-honoured subjects, chapters have been included on child psychiatry, the neuropathology of oligophrenia, mental deficiency, alcohol and drug addiction, and crime.

Modern psychiatry is passing through a period of apparent change. The law relating to mental illness has come under considerable criticism, some of it from the unstable and hysterical. This has led to changes in administrative outlook which are certainly not always in the best interests of the patient, his relatives, or the public, but bolster up the ego of the inferiority unconscious psychiatrist. Amongst the inexperienced there is an impression that what they are doing has never been done before, and they either make no attempt to ascertain how much was done twenty and more years ago, or turn a deaf ear and a blind eye.

New journals of particular interest to us have appeared in the period under review—*Behavioral Science*, *Information and Control*, the *Journal of Psychosomatic Medicine*, the *Journal of Neurochemistry*, the *Journal of Mental Deficiency Research*, the *International Journal of Alcoholism*, the *International Journal of Social Psychiatry*, *Archives of Criminal Psychodynamics*, the *Journal of Analytical Psychology*, *la Revue de l'Alcoolisme*, *Nevrasse*, *Revista Brasileira de Saude Mental*, *Acta Neuropsiquiatrica Argentina*, and *la Infancia Anormal*.

The Journal Committee is most grateful to those men who have contributed the various chapters. In these days of intense competition and rivalry, it is often difficult to find time to go through a vast number of journals to make sure that nothing worthwhile has escaped notice.

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PSYCHIATRIC GENETICS

By VALERIE COWIE* and ELIOT SLATER
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I. MENTAL DEFICIENCY

INTRODUCTION

IN the field of genetics as applied to mental deficiency, the need for a broad approach is being fulfilled by workers who view the subject from many different angles. Conditions in which genetical factors are known to play a part are being studied from many aspects including biochemical, cytological and serological points of view. The effect has been to give genetics in this field a wider meaning and to open up new possibilities for extensive and rewarding research.

Professor Penrose has always worked towards establishing the study of mental defect as a biological science, and his recent book (Penrose, 1954b) emphasizes the necessity for a comprehensive approach to the subject using clear-cut methods.

In the Report of the Joint Expert Committee convened by the World Health Organization on the Mentally Subnormal Child (1954) genetics is cited as being one of the main fields in which research is needed. Stress is laid, however, on the necessity for collaboration between workers in different professions, as today what little research that is being done is for the most part being undertaken by individuals working largely in isolation from their colleagues in other professions. As a result of this, according to the Report, there is perhaps an over-emphasis on the genetic and other factors responsible for certain rare clinical conditions.

The importance of a broad approach to the study of the genetics of mental disorders is emphasized in a paper by Halperin and Guensberg (1951) who have criticized the tendency of some workers in this field to overlook the importance of environmental influences against which the gene or gene complex is active.

Roberts (1950) reviews modern genetic theory with respect to oligophrenia, drawing attention to the distinction made between major genes and polygenes. He points out that the polygenic determination of the genetic component in high-grade oligophrenia is consistent with the close fit of the Gaussian curve down to a level of roughly Binet I.Q. 50 or slightly less, and that low-grade oligophrenia represents a group of extremely diverse causation, depending, when genetic, upon single major genes or chromosome abnormalities. In a further review, Roberts (1952) shows that evidence is in general strongly in favour of this hypothesis and that

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sib regressions are of the expected order: the sib regression in the feeble-minded group is approximately 0·5, which is the value in the general population, and in the low-grade defectives' group is close to zero, the sibs of the low-grade defectives tending to fall into two classes—a small class of low-grade intellect like the subjects themselves, the majority being of relatively normal intelligence.

Böök (1953) in his genetic and neuropsychiatric survey of a North Swedish population, refers to this work of Roberts, but states that in conformity with Scandinavian usage he prefers to restrict the use of the term oligophrenia to individuals unable to attend ordinary schools even if instruction is given in special classes, which would mean a dividing line at an I.Q. of roughly 60–70.

Dahlberg (1951) discusses the many different criteria used for the classification of the mentally deficient. He prefers the criterion for feeble-mindedness already mentioned as being favoured by Böök (1953). Dahlberg finds the frequency of feeble-minded persons in Sweden to be about 0·5 per cent., a little higher in men than in women. This indicates an increase in the incidence of feeble-mindedness in Sweden, but Dahlberg considers it reasonable to suppose that this increase is due to progressively more efficient registration rather than lowered mental ability. He remarks upon the very low fertility of the feeble-minded, only 0·11 children per feeble-minded person being born, which is in agreement with the findings of Penrose (1950a) who estimates that there is a maximal fertility at some point between I.Q. 50 and I.Q. 100, i.e. at about I.Q. 90.

Penrose (1950a) believes that while there is sometimes a place for sterilization in the case of those who are unable to bear the burden of parenthood on account of their mental defect, the genetical constitution of future generations is not likely to be jeopardized by allowing fertile high-grade defectives to have offspring. On the other hand, enthusiasm in the United States of America for the sterilization of mental defectives as a measure of social hygiene and economy is reflected in papers by Woodside (1950), Butler (1951), and Harshman (1951), and by Gamble (1952), who believes that the eventual humanitarian and financial benefits from this procedure would be large. Von Schubert (1952) discusses the legal situation in Germany concerning sterilization. He points out that the law is ambiguous and that sterilization for purely eugenic reasons can be regarded as criminal assault, and feels that new and more precise legal regulations are urgently needed. Bonhoff (1953) has carried out a survey of persons sterilized for genetic reasons under the Third German Reich in Hamburg-Altona, and concludes that in the light of their present status of good social adaptation more than half of those in his material were sterilized without justification. This group contains an exceptionally high proportion of mental defectives sterilized before twenty-five years of age.

The kind of belief which fosters enthusiasm for sterilization of the mentally deficient on a large scale is the misconception that the majority of mental defectives are born of mentally deficient parents. Burt (1955)

gives statistics from his own survey of feeble-minded pupils attending London special schools to show that this is not the case. In barely 6 per cent. of the feeble-minded individuals was either of the parents known to be mentally deficient, but in another 38 per cent. one parent was definitely dull, and in the sibs mental defect was found in 11 per cent. of the cases.

An interesting study has been made by Malzberg (1953) who examined the number of admissions to schools for mental defectives in New York State, and concluded that it seems highly probable that mental defect is more prevalent among males than females. The serious limitations of the data are freely admitted by Malzberg, who points out that the nature of such admissions is highly selective, in the first instance on account of the higher infant mortality of males, and later on account of social factors. He is, therefore, rightly cautious in the interpretation of his results, but points out that it is important for the question to be answered satisfactorily, because differences in the sex frequency may be related to other aspects of mental deficiency including the genetic background.

During the past few years there has been growing concern about the possibility of change in genetic constitution through the agency of irradiation. Papers read at the Conference convened by the Institute of Biology and the Atomic Scientists' Association in 1950 are brought together in a volume edited by Haddow (1952). Although mental disorders are not specifically mentioned, attention is drawn to the dangers of irradiation in medicine and industry, which threaten to increase the number of mutant genes with possible far-reaching adverse effects on the fitness of the population. Muller (1950, 1955) discusses the part that may be played by irradiation in altering man's biological nature by increasing our load of mutations. He points out that unless more caution is exercised than at present the majority of the population may in each successive generation have its gonads exposed to enough irradiation to raise the mutation rate by a significant amount, and he draws attention to the urgent need for a modification in current attitudes and practices concerning the use of ionizing radiation and radioactive materials. The same warning is issued by Sturtevant (1954): every increase, however slight, in the amount of radioactive material dispersed about the earth will increase the harvest of defective individuals.

A comprehensive report has been made by the Medical Research Council (1956) on the hazards to man of nuclear and allied radiations. A large section is devoted to the genetic effects of radiation. With respect to mental diseases, it is pointed out that these constitute the most important single category in which hereditary causes are known to be important, and that there are grounds for believing that a doubling of the mutation rates of the genes concerned with their causation would, in one generation, increase the frequency of low-grade mental deficiency by 3 per cent., and of schizophrenia and manic-depressive illness by about 1 per cent. It is strongly recommended in this report that any source of ionizing radiation on however small a scale should never be used without adequate justification.

Immunological and Serological Work

Gluecksohn-Waelsch (1955) discusses genetic factors and the development of the nervous system with reference to experimental work on mice. She reports the production of neural abnormalities using immunological methods. Female mice, free of abnormality of the nervous system, were injected with emulsion of adult mouse brain and mated to normal males. Eight per cent. of 139 embryos obtained showed abnormalities of the nervous system. Gluecksohn-Waelsch refrains from speculation or any connexion between these results of active immunization of the mother and abnormal gene effects at this stage of her work. Genetically determined abnormalities of the nervous system including hydrocephalus are dealt with.

Immunological effects in the production of mental deficiency have been considered by Desclaux, Soulairac, and Morlon (1951) who found a greater number than expected of foeto-maternal incompatibilities in a group of mental defectives for the ABO and MN as well as the Rhesus factors. Their findings are not in accordance with those of most workers on this point. Results obtained by Zwerling, Gold, Jervis, and Ginsberg (1951) suggest that maternal isoimmunization with A, B, C, and E factors, in the absence of haemolytic disease of the newborn, plays no significant role in the aetiology of mental deficiency. The data suggest that isoimmunization with the D antigen may be responsible for a very small number of cases of mental deficiency, even when evidence of haemolytic disease is lacking, but this is not established statistically. Hackel (1954) has obtained results which suggest that in his material mother-child incompatibility with regard to the ABO and Rhesus antigens does not play a significant part in the aetiology of mental deficiency, and that while this does not preclude the possibility that maternal isoimmunization with any of the Rh factors may be responsible for some cases of mental deficiency, the evidence gathered in his study indicates that no general pattern of isoimmunization may be inferred. Pantin (1951) examined the Rhesus and ABO blood groups of a random sample of 370 certified mental defectives and their mothers in East Anglia, but found no support for the idea that immunization of the mother might explain some hitherto inexplicable cases of undifferentiated mental defect.

Antigenic incompatibility between mother and foetus has been suspected in mongolism, but Lang-Brown, Lawler, and Penrose (1953) conclude from a study of the blood groups of members of over 100 families containing at least one case of mongolian imbecility, that mongolism cannot be due to such incompatibility for any of the antigens studied, the blood being typed for A_1A_2BO, MNS, Rhesus, P, Lewis, and Kell factors.

The techniques of serology are of service in the field of mental defect not only in shedding light on antigenic incompatibility, but for linkage studies. Insufficient data often lead to inconclusive results in investigations into genetic linkages, but such data put on record will eventually be of great value for analysis of the collected material. Linkage

studies are important in helping to locate genes determining morbid conditions upon particular chromosomes. From a practical clinical viewpoint, when close linkages are eventually found they will help to throw light on the presence of mild cases or formes frustes of inherited diseases.

Mohr (1954) has found an indication of linkage between dystrophia myotonica and the Lewis and Lutheran blood groups. He also examined the blood from Danish families with Huntington's chorea, but was unable to detect linkages owing to the small size of the material. A large family containing cases of Huntington's chorea was studied by Leese, Pond, and Shields (1952) and data for linkage studies comprising blood-grouping and phenylthiocarbamide taste-testing was obtained, but again this was insufficient to establish any linkage relationships. Pleydell (1954, 1955) in a survey of Huntington's chorea in Northamptonshire has also put serological data on record.

Schut (1951) records a large American pedigree containing hereditary ataxia which appeared as a dominant trait in 45 members. An attempt was made to demonstrate autosomal linkage between this condition and four blood-groups and taste for phenylthiocarbamide, but results were inconclusive. No mental abnormalities were reported, but in view of the frequent association between hereditary ataxias and mental defect, this interesting pedigree was considered worth while mentioning.

Data obtained from families containing at least one case of phenylketonuria were shown by Penrose (1951b) to lead to inconclusive results when searching for linkage of phenylketonuria with ABO blood groups. There was no indication of linkage with the MN group.

Special Clinical Types

Rarely-described Syndromes

As regards special clinical types in mental deficiency, a very rare recessive syndrome has been described, the features of which consist of cerebellar ataxia, often with evidence of pyramidal involvement; oligophrenia; cataract; multiple minor skeletal anomalies; and in some cases, vascular hypertension. The manifestation of the components of the syndrome appear to be variable from patient to patient, and families with members showing a varying number of signs are reported. Sjögren (1950) has reported fourteen patients suffering from this syndrome belonging to six families after a search throughout Sweden. He has obtained a Mendelian ratio, which, in conjunction with a high frequency of consanguineous marriages, indicates that the inheritance is due to a single recessive gene. It is believed that his report was only the second time, after an observation nineteen years previously, that the syndrome had been put on record. Gursdorf, Hécaen, and Nau-Massonet (1952) report a French family showing components of the syndrome. Garland and Moorhouse (1953) report two new examples of the condition.

Sjögren and Larsson (1949) also made a very complete ascertainment

of all cases of microphthalmos and anophthalmos in Sweden, with or without coincident oligophrenia. They found 137 such cases, of which 58 were oligophrenic. Rubella in the mother could not have accounted for more than a very small proportion, but the genetical explanation is problematic.

A heredo-familial disorder believed to be hitherto undescribed has been recorded by Harvey, Haworth, and Lorber (1955). This consists of athetosis, hypotonia, absent tendon reflexes, extensor plantar responses, mental retardation, and periodic febrile attacks, occurring simultaneously in several members of the family described, with episodes of prolonged unconsciousness. Five children and their father were affected. It seemed likely that three of the children were approximately normal mentally and physically in early infancy, but deteriorated subsequent to the febrile illnesses. It was suggested that the febrile attacks may have been encephalomyelitis superimposed on an already abnormal and unusually susceptible nervous system.

Menkes, Hurst, and Craig (1954) have reported what they believe to be a new syndrome occurring in four sibs, all of whom developed cerebral symptoms of progressive severity, commencing within the first week of life, and terminating fatally within three months of their onset. A characteristic feature of the illness was the passage of urine with an odour strikingly similar to that of maple syrup. Biochemical investigations failed to reveal the cause of this smell, but in spite of lack of evidence the speculation was made that the substance might represent a degenerative product of an abnormal cerebral metabolic process.

Turpin, Duchène, and Delbarre (1948) have described a familial variety of profound mental retardation with disturbance of nitrogen metabolism and lesions of the fundus oculi, and with consanguinity. Ford *et al.* (1951) have described a familial degeneration of the cerebral grey matter with dementia and death in status epilepticus.

The Lipoidoses

Herndon (1954a) in a survey of the data available on the genetics of the lipoidoses concludes that gargoylism may be divided into two genetically distinct varieties, one due to an autosomal recessive gene, and the other to a sex-linked recessive gene, the sex-linked form being characterized by absence of corneal clouding, infrequent dwarfing and frequent deafness, while the other form is characterized by a high incidence of corneal clouding and dwarfing, deafness being rare. Millman and Whittick (1952) report an interesting pedigree exemplifying the first-mentioned type, in which five male cases of gargoylism without corneal opacity appear in three generations, and Cunningham (1954) has reported a family containing twelve cases, confirmed and presumed, of the same type, in three generations. Craig (1954) describes gargoylism with corneal opacity in a twin brother and sister, in whom it was considered that the condition was determined by an autosomal recessive gene.

MacGillivray (1952) expresses the view that gargoylism is more

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common than is indicated by the number of reported cases. He describes five cases, of whom one was the child of a cousin-marriage, whilst another had a family history of gargoylism on the mother's side.

Jervis (1950a) draws attention to the fact that partial manifestation of the condition of gargoylism may not be uncommon. He describes a series of ten cases of gargoylism, which include seven formes frustes. The diagnosis of the latter was based on association of mental defect with characteristic deformities of bone. In five of the formes frustes, enlargement of the liver added evidence in favour of gargoylism. Corneal opacities were conspicuously absent in all seven of the formes frustes. Pathological findings are described in this paper, the lesion consisting essentially of ubiquitous swelling of the nerve cells with a cytoplasmic deposit of a granular lipid material.

The degree of mental defect in gargoylism shows great variation, and not all cases are mentally deficient. Jackson (1951) describes a sibship of two sisters and a brother showing signs of gargoylism, including corneal clouding. The brother and one sister were of normal mentality and their physical signs were less marked than those of the third sib who was mentally defective. A male case of gargoylism showing osseous deformities, hepato- and splenomegaly and other signs is reported by Gilliland (1952) who records that he did reasonably well at school and subsequently was able to learn shorthand and typing. Two adult cases of gargoylism have been reported by Smith and his co-workers (1952). Neither of these was mentally defective, and one had completed studies in economics and accounting. The biochemical and histopathological findings in these cases support the belief that the disease is a dysmetabolism of a substance related to glycogen, and the absence of lipoid material in the livers of these patients was stressed.

Klein and Ktenidés (1954) have examined 64 sibships containing Tay-Sachs disease drawn from the literature between 1933 and 1954. The resulting genetic data were compared with those of Slome collected from 1881 to 1933, and an increase was found in the frequency of the non-consanguineous cases in Gentile families, which was considered possibly to be related to an increase of the incidence of the pathological gene in the general population. Alternatively, it could be due to a drop in inbreeding, during the period 1933 to 1954.

Cares (1951) has made a clinical and histopathological study of a case of juvenile amaurotic idiocy and has found pathological and histochemical features similar to those associated with alterations in the senile brain, and he suggests that juvenile amaurotic idiocy may throw light on the phenomenon of senile dementia, the handicaps of concomitant vascular, endocrine and nutritional deficiencies common in the late decades of life being absent in this juvenile condition. Löken and Cyvin (1954) have reported another case, a boy whose parents were first cousins, in which the clinical picture was that of juvenile amaurotic idiocy and the histological findings were those of Alzheimer's disease, the findings being a diffuse cortical atrophy with Alzheimer's fibrillary changes in the

ganglion cells and numerous senile plaques. No swollen nerve cells, as seen in lipoidosis, were found.

Cumings (1953) describes changes in the cerebral lipids in amaurotic family idiocy and in disseminated sclerosis. In five cases of amaurotic family idiocy increases of cerebroside and of neuraminic acid were found in the grey matter, and in two adult cases there was, as well, loss of all phospholipins. Decreased amounts of phospholipins, especially in the demyelinated areas, were found in two cases of disseminated sclerosis. Cumings calls for more extensive studies in the cerebral chemistry of all varieties of demyelination, with special reference to the enzymatic processes responsible for both myelination and demyelination. He considers that in this field there is considerable scope for investigations which might well reveal some of the answers to the problems associated with demyelinating diseases. It is in work of this kind that the biochemist and geneticist can collaborate most profitably. Already there is growing evidence of genetically determined enzyme dysfunction underlying such conditions as phenylketonuria. Such findings, it is hoped, will provide eventually a basis for prophylaxis and treatment.

A case of late amaurotic idiocy, which has rarely appeared in the literature, is described by Jervis (1950b), the patient showing progressive mental deterioration with generalized muscular spasticity, but without ocular manifestations. In the sibship, four, including the patient, out of twelve were similarly affected. Pathological examination showed ubiquitous neuronal lipidosis. It was thought that the condition was determined by a rare single autosomal recessive gene.

In this connexion a pedigree reported by van Bogaert (1953) is of interest. It is of a Jewish family containing cases of infantile amaurotic idiocy without the characteristic cherry-red spot, but with atypical changes in the retina.

A case has been reported by Klien (1954) in which ocular histopathological findings constituted a differential diagnostic problem between infantile amaurotic idiocy and the juvenile form. The age of onset, during the second year of life, was characteristic of neither type, but the diagnosis was finally made in favour of a delayed infantile amaurotic idiocy on account of the cerebral lesions typical of this condition. Klien presents this case as constituting a link between the infantile and juvenile types, in support of the recent trend of emphasis upon similarities rather than differences between them. As well as the histopathological and clinical findings, she takes as evidence of the atypical character of this case as one of infantile amaurotic idiocy the non-Jewish racial background. This is not a strong point in her argument on account of the growing number of recorded instances of non-Jewish cases (Klein and Ktenidés, 1954) and seems unnecessary in view of her findings.

A case of juvenile amaurotic idiocy is reported by Levy and Goodman (1952) in which features of gargoylism were also present, including bone deformities of the skull and universal lipoidosis of the nerve cells throughout the central nervous system. The case was classified as belonging to

"the syndrome of Juvenile Familial Amaurotic Idiocy associated with the Formes Frustes of Gargoylism". The patient's sister developed a condition which ran a similar course. A few cases previously reported in the literature of amaurotic idiocy associated wtih some manifestations of gargoylism are quoted, but it is hard to see that there is sufficient evidence for the coincidence of the features described to merit the designation of a syndrome, which would introduce genetical as well as other implications.

A case of Hallervorden-Spatz disease (slowly progressive muscular rigidity, extrapyramidal in type, extending over a period of years with mental deterioration and specific histo-pathological changes including characteristic hyperpigmentation of the pallidum and substantia nigra) associated with atypical amaurotic idiocy, is reported by Jervis (1952b). Both from a pathological and from a clinical point of view the patient was considered to show an intermediate form of infantile and juvenile types of amaurotic idiocy. Jervis goes on to discuss instances in medical literature of similar association between two distinct rare endogenous diseases of the brain, including the association of amaurotic idiocy with myoclonic epilepsy. He points out that since it is accepted that in many of these conditions genetic mechanisms play a significant aetiological role, the association of two diseases in the same patient is of considerable theoretical importance. He rightly criticizes the vagueness of speaking in these cases of "neuropathic diathesis" in the sense that impairment of germ-plasm, once established, is capable of a wide range of manifestations. Instead, he puts forward an interesting hypothesis, on the grounds that it would be difficult to interpret the association between the rare diseases as the result of the action of two independent genes present by chance in the same individual, on account of their rarity. He suggests that the presence of the two conditions is the pleiotropic expression, or plural manifestation, of one and the same gene; but as the frequency of the association of the two diseases is much lower than the incidence of each separate disease, Jervis postulates that the pleiotropic gene would be distinct from that responsible for the majority of cases of the separate disease.

The wide range of variations seen in amaurotic idiocy has been commented upon by van Bogaert and Klein (1955). They have studied eleven families presenting different forms of amaurotic idiocy which demonstrate the diversity of manifestation which can be encountered. They have shown how the genetic approach makes it possible to assemble clinical conditions which first seem to be heterogeneous owing to the number of ways in which a gene may express itself, in order to proceed to a more adequate nosological classification.

As regards gargoylism and infantile and juvenile amaurotic idiocy, Jervis (1952a) gives statistical evidence strongly indicating that these are due to rare recessive genes. In the same article, Jervis discusses briefly the mode of inheritance of mental deficiency and intellectual deterioration associated with other types of abnormal metabolism, namely, phenylketonuria, hepato-lenticular degeneration (Wilson's disease), galactosuria and glycogenosis (Gierke's disease), for which recessive genes are known

to be responsible in the first two conditions and are probably responsible for the last two. Jervis points out that the important genetic problem of detection of carriers awaits investigation, and that intensive biochemical study of the heterozygous state might be fruitful in this respect.

Phenylketonuria

Jervis (1954) in an excellent review of the subject of phenylketonuria summarizing the available information to date on clinical, pathological, biochemical, genetic, and therapeutic aspects of the condition, again provides strong evidence of its inheritance by a single recessive gene.

Pleiotropic effects, or multiple manifestations, of the homozygous phenylketonuric gene, including dilution of hair colour, head size, intelligence, and certain biochemical findings, are analysed quantitatively by Penrose (1951a) using a statistical method to show the degree of genotypical misclassification of phenylketonurics with a control population for each metrical character. It is indicated that attempts to separate major and minor genes are of doubtful value, since each gene can be shown to have both major and minor effects.

Keup (1955) describes a case of "facultative" phenylketonuria, in which only under certain forms of stress such as febrile conditions, or loading with albumin, mixtures of amino-acids or phenylalanine, was there elimination of phenylpyruvic acid in the urine. Pathological aminoaciduria, damage to the liver and elevation of the serum phenylalanine were not shown. The point is discussed as to how far the genetical statistics obtained so far may be in need of correction if, with the help of the test procedures described, such cases are to be found in numbers among mental defectives. Keup's findings may help in the elucidation of the phenomenon of apparently spontaneous phenylketonuric "intermittent excretors".

In view of the belief held by Penrose that heterozygotes for phenylketonuria may be prone to develop psychotic illnesses especially in the involutional period, a family reported by Bhaskaran (1952) may be of significance. In this sibship of nine, two are affected with phenylketonuria and three non-phenylketonurics suffered from affective psychotic illnesses with an onset at forty years of age or later. Three other sibs died in infancy. It is not known whether the psychotic sibs were, in fact, heterozygotes for phenylketonuria. Moreover, the psychotic state may have been inherited independently. It would, however, be worth while to record families containing phenylketonuria with reference to the incidence of psychoses to enable a statistical evaluation to be made.

Larson (1954) has estimated the gene-frequency for phenylketonuria as 1/200 in a South Swedish population, with a frequency of homozygotes with phenylketonuria at 1/40,000 and of heterozygotes at 1/100. As might be expected with a recessive trait, first-cousin marriages were high amongst the parents of the phenylketonurics, being 12·5 per cent. Larson remarks upon the occurrence of phenylketonuria in a man, never institutionalized, who was intellectually subnormal but the supporter of a family of five.

He draws attention to the observation by Cowie (1951) of a phenylketonuric boy of intelligence in the dull and backward range. Such findings are rare since the great majority of phenylketonurics are idiots or imbeciles.

Tuberose Sclerosis

Borberg (1951) has carried out careful clinical and genetic investigations into tuberose sclerosis and neurofibromatosis in Denmark. He considers the two conditions to be separate entities. His findings for the most part confirm the view that tuberose sclerosis follows a dominant mode of inheritance, and he considers there is strong evidence to believe that the remainder of his cases of tuberose sclerosis were of mutative origin. He believes that the genetical basis of neurofibromatosis is similar to that of tuberose sclerosis.

Kirman (1954) in a paper dealing with the treatment of tuberose sclerosis by deep irradiation puts forward evidence which supports a suggestion made by Penrose that tuberose sclerosis may be at least in part a reaction to a virus infection rather than being, as commonly suggested, wholly explicable as determined by a Mendelian dominant character, partially expressed.

Oxycephaly

Karabanow (1950) records a family in which furrowed scalp over the frontal region (cutis frontis gyrata) with oxycephaly appears in a family as an irregular dominant character. This family contains two affected males who are the surviving members of monozygotic triplets, the third member being stillborn. The anomaly of furrowed scalp in this family is not, however, associated with mental defect as is frequently the case. Karabanow discusses the inheritance of both oxycephaly and cutis frontis gyrata, and concludes that in both conditions there is a dominant mode of transmission with variable penetrance of the gene responsible. Polan and Butterworth (1953) review the subject of cutis verticis gyrata and report seven new cases. They are inclined to believe that the familial occurrence of the isolated condition, of which several cases are reported in the literature, has been probably a matter of coincidence, but in familial cases where it has been accompanied by other abnormalities of development, they consider it more likely that an hereditary factor has been at work. They do not discuss the genetics of the condition any further.

Franceschetti and Klein (1952) describe three cases of identical twins concordant for oxycephaly. One set of twins are those described by Karabanow (1950) showing oxycephaly associated with cutis frontis gyrata. The literature dealing with oxycephaly in monozygotic twins is reviewed, and Franceschetti and Klein conclude that the more rare occurrence of discordant oxycephaly in monozygotic twins must be interpreted as the result of an unstable gene of feeble penetrance. They consider that a recessive mode of inheritance is likely in oxycephaly, two cases in the literature being of consanguineous parentage. Concerning the association of oxycephaly with cutis frontis gyrata in one of the sets

of twins described, Franceschetti and Klein keep an open mind as to whether the combination is fortuitous or whether the two anomalies are related.

Moffie (1950) has described a family in which cases of oxycephaly were seen in four consecutive generations accompanied in some cases by syndactyly or by epilepsy or by paralysis of the ocular muscles. The pedigree shows the oxycephaly to follow apparently a dominant mode of inheritance in this family.

Kalischer-Sturge-Weber Syndrome

Kirman (1950) has reported the family history of a case of "naevoid amentia" (Kalischer-Sturge-Weber syndrome) with fits, paralysis or other neurological lesions present in other members of the family, none of whom showed definite evidence of naevus. These conditions may have been formes frustes of the complete syndrome. Kirman presents evidence in favour of the operation of a recessive hereditary factor.

Laurence-Moon-Biedl Syndrome

During the past five years numerous reports of familial or single cases showing all or some of the components of the Laurence-Moon-Biedl syndrome have appeared. A most comprehensive review of the literature on the condition, including a discussion of its heredo-familial aspects, has been given by Gualandi, Bernardoni, Bonati, and Govoni (1954), who report clinical and laboratory data on ten cases. Strong criticism is made by Keifer, Wortham, Zanartu, and Hamblen (1950) who describe the Laurence-Moon-Biedl syndrome as a "confused symptom complex" and recommend a more stringent application of diagnostic criteria in respect of the condition.

Work by Dr. Julia Bell (1956) on the Laurence-Moon-Biedl syndrome, which is still in preparation, will, it is hoped, shortly appear in the Treasury of Human Inheritance.

Spastic Diplegia

Böök (1953) in his survey of a North-Swedish population concluded that a group of individuals suffering from spastic diplegia associated with mental defect belonged to a specific clinical and genetic entity, caused by a simple recessive gene, which he called genetic spastic oligophrenia, and considered to represent another identified specific type of inherited mental defect, which may possibly be identical with that formerly described by Hanhart.

Karn and Allen (1953) and Allen (1955) have described cases of cerebral palsy occurring in a series of mentally defective twins, only one of the 11 pairs being concordant.

Specific Dyslexia

An excellent study of specific dyslexia ("congenital word blindness") has been reported by Hallgren (1950). The series includes 273 personally investigated cases, with 117 propositi. He could find no support for

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