SOME AETIOLOGICAL PROBLEMS IN MENTAL DEFICIENCY*

BY

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Though many classifications of the subject exist, mental deficiency may conveniently be considered in two groups—minor (high-grade) and severe (low-grade) mental defect. This simple division corresponds, though not exactly, with that proposed by Lewis (1933) and restated by Bourne (1957). Lewis regarded some cases of mental defect as pathological and some as subcultural. The subcultural cases coincide mainly with those of minor degrees of intellectual defect. This thesis, as presented by Penrose (1954a), assumes that some defectives are such because of pathological lesions, and others because of biological variation. In fact, if the biological variation is of such a degree as to produce seriously impaired intelligence, which does not permit the individual to cope with his environment, then the condition must be regarded as pathological. Similarly, it seems reasonable to suppose that many of the pathological lesions responsible for cases of mental defect are one of the means whereby biological variation operates.

There is no agreed definition of what constitutes high-grade, or minor, mental defect. Definitions based on intelligence quotient are of little value, as the Scottish Council for Research in Education (1949) showed that 3% of the population score less than an I.Q. of 70 on a standard test, equivalent to one and a half millions in a population of fifty millions. Definitions based on legal recognition or ascertainment as mental defectives are of even less value, as O'Connor and Tizard (1956) have shown that the average I.Q. of the feeble-minded admitted to mental deficiency institutions is in the region of 70. It seems clear that psychological, educational, and social factors operate in a much more direct manner in producing the problem of minor mental defect. None the less, it should not be assumed that gross pathological lesions are encountered only in idiots and imbeciles and that they are not responsible for numerous cases of minor mental defect. In fact, all the diseases and factors operating in the production of gross mental deficiency may operate in a "diluted" form to produce minor degrees of mental defect. We will quote some examples of this process before going on to the main theme.

High-grade (Minor) Mental Defect Associated with Distinct Syndromes

A case of phenylketonuria with intelligence within the normal range was reported by Cowie (1951). The intelligence quotient varied from 76 to 97 on different tests. This boy went to a special school, and now, at the age of 16 years, scores 94 on the Terman-Merrill scale and is expected to take up a skilled trade. The excretion of phenylpyruvic acid in the urine, the blood level of phenylalanine, and the excretion of 5-hydroxy-

indole-acetic acid, whilst being in the lower range of the phenylketonuric distribution, are very much higher than normal (Cowie and Brandon, 1958). Phenylketonuria is usually ascribed to a single recessive genetic factor, but it is obvious from the wide spread of intelligence among different cases, varying from extreme idiocy to the normal range, that modifying factors must be taken into consideration. These modifying factors may be genetic or environmental and may either enhance or partially suppress the ill effect of the specific factor for phenylketonuria.

Wright and Tarjan (1957), in a survey, found that three subjects, or 1% of all those considered, had an intelligence quotient above 70. Coates *et al.* (1957) report the case of a child with phenylketonuria with an intelligence quotient of 103. Serotonin levels in this case were within the normal range, thus adding force to the suggestion made by Pare *et al.* (1957) that it is the low level of this compound in the disease which is critical for mental capacity. If the claims made by Woolf *et al.* (1958) and by many other workers regarding the value of a low phenylalanine diet in phenylketonuria are substantiated, this will demonstrate the importance of environmental factors in the modification of the disease. The importance of the cultural factor in mental retardation of all types is illustrated by the fact that in Cowie's case the Terman-Merrill quotient on first testing was 52, gradually rising in the circumstances of the special school to 94 over a period of nine years.

Phenylketonuria may be taken as an example of a genetically determined form of specific defect, the effect of which on mentality may range from idiocy to average intelligence. Damage due to rhesus blood-group incompatibility illustrates a similar phenomenon produced by an environmental factor. One of our series of 44 children, initially regarded as mentally defective and subsequently found to be educable (Craib and Woodward, 1958), was suffering from the after-effects of kernicterus. He did not have the advantage of exchange transfusion, this technique not having been developed at the time of his birth, and was markedly ataxic and deaf. His intelligence quotient on the Drever-Collins scale was 61, and he was transferred to a school for the deaf, where he did well.

Again, when an attempt was made to assess nine cases of kernicterus (Crome *et al.*, 1955) on whichever formal test seemed most appropriate, the result was the following quotients: 7, 8, 8, 15, 27, 33, 34, 61, 64. This series of I.Q.s is artificially cut short by the fact that the nine patients were all ascertained defectives and could be supplemented and continued into the normal range by consideration of lesser degrees of post-kernicteric disability. Gerver and Day (1950) found that, on average, a group of children who had apparently recovered completely after icterus gravis neonatorum were a little less intelligent than their unaffected siblings. Kernicterus also provides a good example of the effect of an appropriate environment, with special training for deafness and athetosis, in modifying the degree of disability.

As further illustrations of this phenomenon of "shading off" of the effects of specific pathological lesions into the general community, two other conditions will be mentioned—tuberous sclerosis and the Sturge-Weber syndrome. Tuberous sclerosis (in its fully developed form) is a well-recognized cause of gross

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mental defect. It is also well known that minor forms of the condition occur. Most cases are attributed to new mutations, but some are thought to be transmitted directly through individuals having the minor forms. Of 13 cases at the Fountain Hospital, 11 showed no record of any other member of the family being affected. The mothers of the remaining two patients had a minor form of the disease. Both mothers showed the facial rash of adenoma sebaceum, and one of them had an epileptic cousin and a father who died of a brain tumour. She was a laboratory assistant in a paint factory prior to her marriage and cared for her home and children very adequately. The other affected mother was in a backward class in an ordinary school and was semi-literate: she did canteen work and successfully managed her home. These two parents were at no time regarded as mentally defective, and were accepted as ordinary members of the community.

In the Sturge-Weber syndrome a facial naevus is associated with angiomatous malformation of the meninges of unknown origin. In its fully developed form gross mental defect results, but one of us (B.H.K.) saw the case of a cook with the facial naevus and epilepsy who had a minor form of the syndrome, which did not prevent her being successful at her profession and acquiring a diploma. Such minor cases of this syndrome are well known.

It is impossible at present to make any accurate assessment of the extent to which such diluted pathological factors are responsible for educational subnormality, though it seems certain that in many instances the social milieu and educational opportunity are factors of greater importance. Even in gross defect it is possible to make a precise diagnosis of the nature of the disease process in only a minority of cases. In these less severe cases the problem is even more difficult. The following brief survey of clinical and necropsy findings in educational subnormal children may throw some light on the incidence of overt pathology in this group.

Clinical and Necropsy Findings in Educationally Subnormal Children

Clinical Findings

The clinical findings in Craib and Woodward's series of 44 educationally subnormal children are set out in Table I. Although at one time all were looked upon as mentally defective, these children were subsequently accepted into school for education: their formal intelligence quotients ranged from 49 to 102. These findings stress the importance of gross clinical and physical factors in the production of mental retardation of this degree. Eight children had a clinically diagnosed syndrome, which was in itself sufficient to account for the backwardness. Another eight had findings strongly suggestive of an encephalopathy. In 14 cases defects of hearing or vision seemed to be contributory factors,

TABLE I.—Clinical Findings in 44 Educationally Subnormal Children

Group A.	With clinical diagnosis, 8 (meningococcal meningitis, 1; tuberculous meningitis, 1; meningovascular syphilis, 1; maternal rubella, 1; rhesus incompatibility, 1; microcephaly, 1; "subthyroid," 1; schizophrenia, 1).
Group B.	With evidence of encephalopathy, 8 (cerebral palsy: ataxia, 1; epilepsy, 3; infantile convulsions, 3; slight hydrocephalus, 1).
Group C.	With sensory defect, 14 (blind, 8 (corneal opacity, 1; cataract, 2; vitreous opacity, 1; choroiditis, 1; optic atrophy, 2; coloboma, 1; deaf, 6).
Group D.	With somatic defect, 2 (cleft-palate, 1; double thumbs, 1).
Group E.	Without clinical diagnosis or gross physical signs, 12.

while two others had somatic evidence of embryopathy. Each child appears only once in the table, though many of them had more than one clinical finding. Thus 32 of the 44 children (73%) had some evidence of clinical abnormality which could account, at least partially, for the degree of mental retardation. Experience of necropsy findings in comparable cases suggests that this clinical evidence underestimates the true incidence of brain lesions. It is not, however, intended to convey the impression that the degree of backwardness is solely dependent on such physical factors as brain morphology or to underestimate the very great part played in this matter by social circumstances. Some indication of the importance of education in this group was provided by a study undertaken by one of us (Kirman, 1958). Craib and Woodward's study showed in particular that, in their group, social circumstances were more important than low intelligence *per se* in determining successful social adaptation.

Necropsy Findings

It is natural to turn to post-mortem studies for a better understanding of the role of physical factors in producing educational subnormality. However, the expectation of life in this group is relatively good and therefore anatomical studies are few. Crome (1957) found that of 200 brains of mental defectives which he studied, only three approached the normal, but most of the 200 were from idiots and imbeciles. The findings in 12 cases above the imbecile range are shown in Table II (Crome, to be published).

TABLE II

Mongolism	1	Ventricular dilatation, marked	1
Laurence-Moon-Biedl syndrome	1	moderate	1
Hydrocephalus	1	Small corpus callosum?	1
Microcephaly, slight	1	Dysgenesis?	1
Astrocytoma	1	Nothing abnormal found	3

In concluding these observations on the upper ranges of mental subnormality, it is worth re-emphasizing that, perhaps particularly at this level, the development of the individual is a product of his structure and physiology on the one hand, and of his environment on the other, and that neither should be viewed in isolation.

Aetiology of Low-grade (Severe) Mental Defect

As mentioned above, it is possible in nearly all idiots and imbeciles to find changes in the brain after death. In addition, marked disturbance of function may occur, as in phenylketonuria, with very little obvious brain abnormality. Clinically, however, evidence of encephalopathy is not so readily available, hence the numerous attempts which have been made to divide off a "non-pathological" or "residual" or "garden" group of defectives. With improvement of diagnostic facilities, recognition of fresh syndromes and other developments, this residual group tends to become smaller. Table III illustrates the problem by reference to 200 consecutive admissions to the Fountain Hospital, mainly idiot and imbecile children under the age of 5 years.

It will be seen that even if cases in which the aetiology is known (Group A) are added to those in which it is reasonably certain (Group B), only 13.5% of the total are accounted for. The factors mentioned in Group C are much more difficult to assess—namely, birth trauma, a family history of neuropsychiatric abnormality, and a clinical diagnosis of mongolism or

reduced capacity for the uptake of vitamin A. These workers propose that the blood of pregnant women should be examined for the vitamin-A content.

In order to test adequately the tentative hypothesis outlined above, several tasks should be undertaken. The survey of the biochemical characteristics of mongolism at the Fountain Hospital should be continued and supplemented. This should be linked with a more extensive study of the metabolism of pregnant women, with particular reference to the deviations found in mongolism. Particularly valuable would be studies on the effect of ageing on metabolism in pregnancy, and also studies in which mothers who have had a child with mongolism were compared with women, matched for age and parity, who have not. If such a study were to furnish evidence of a correctable anomaly in the metabolism of the mothers of "mongols" then we would be well on the way to the possibility of prevention.

Other Clinical Groupings

Whilst the group of idiots and imbeciles with a known aetiology make up only a small proportion of the total, Table IV demonstrates that the majority, on clinical examination and history-taking, show some evidence of physical abnormality, a finding which is very much reinforced by post-mortem studies. Only 21% of the

TABLE IV.—*Clinical Findings in 154 Idiots and Imbeciles (Mongolism Excluded)*

<i>Skull</i>	68 (44%)	<i>Cerebral palsy</i>	57 (36%)
<i>Microcephaly*</i> ..	32	<i>Spastic diplegia</i>	30
<i>Hydrocephalus</i> ..	8	<i>Hemiplegia</i>	10
<i>Plagiocephaly</i> ..	28	<i>Ataxia</i>	9
		<i>Athetosis</i>	8
<i>Epilepsy†</i>	41 (27%)	<i>Psychotic</i>	3 (2%)
<i>Eyes</i>	69 (45%)	<i>Some other physical anomalies</i> 27 (18%)	
<i>Strabismus</i>	59	<i>Spina bifida occulta</i> ..	11
<i>Nystagmus</i>	24	<i>Deformed feet</i>	5
<i>Blind</i>	18	<i>Meningocele</i>	3
<i>Optic atrophy</i> ..	12	<i>Polydactyly</i>	2
<i>Ptosis</i>	2	<i>Congenital dislocation</i>	
<i>Cataract</i>	2	<i>of hips</i>	2
<i>Retrolental fibroplasia</i>	2	<i>Deformed ears</i>	2
<i>Buphthalmia</i>	1	<i>Congenital abnormality</i>	
<i>Microphthalmia</i> ..	1	<i>of heart</i>	2
<i>Macular coloboma</i> ..	1	<i>Pyloric stenosis</i>	2
<i>Interstitial keratitis</i>	1	<i>Recto-vulval fistula</i> ..	1
		<i>Bifid uterus</i>	1
<i>No clinical symptoms apart from mental defect</i>			
(Other than strabismus, spina bifida occulta, deformity of feet, or pyloric stenosis)			32 (21%)

cases had no physical signs, excluding minor abnormalities such as strabismus, spina bifida occulta, etc. To put the matter another way, if we leave on one side the cases of mongolism and those which fall into some definite aetiological category, we are left with approximately two-thirds of all idiots and imbeciles in whom there is no substantial clue as to aetiology. On the other hand, we know that nearly all these children have some gross encephalopathy. It seems likely that with the course of time further specific syndromes will be discovered which will account for some fraction of this total, and that some of these will prove to be inborn errors of metabolism transmissible on classical Mendelian lines. However, it seems unlikely that more than a small fraction will be accounted for in this way. Attention must also be paid to the environment, particularly to the maternal environment, as in the case of mongolism.

* Defined as more than 3 standard deviations below mean for age and sex, for head circumference.

† Fits observed in Fountain Hospital only.

At the moment surprisingly little is known about the optimum maternal environment for the development of the foetus. Sufficient information is available from animal work to show the complexity of the problem. Thus Millen and Woollam (1957), who had earlier demonstrated that hydrocephalus could be produced by shortage of vitamin A, have demonstrated that an excess of this vitamin also causes abnormalities of the nervous system, an action which is facilitated by the administration of cortisone. Some indication of the extreme variability of the maternal environment from one expectant woman to another is shown by the work of Baker *et al.* (1958), who found a constant tendency to depletion of the maternal store of folic acid and vitamin B₁₂ at parturition. The most striking finding, however, was the very wide range in values for these substances both in the mothers during pregnancy and in the infants at birth, the figures varying by a factor of 10 in the case of vitamin B₁₂ and as much as a hundredfold for folic acid. It is difficult to believe that all these figures fall within the optimum or desirable range.

It also seems likely that results of investigation of other essential dietary constituents would be similar. If this is so, then it is possible to form a very general hypothesis that the state of nutrition, health, and well-being of the mother during and before the pregnancy is of great importance in connexion with the subsequent mental development of the child. Because of the complexity of the problem, the less-sophisticated type of social investigation is unlikely to be very helpful in this matter beyond establishing what is well known—namely, the association between reduced intelligence test performance and large families or the concentration of children with a low level of performance in poor areas or in the Registrar-General's Classes IV and V. In the past there has been a tendency to explain these findings somewhat glibly on the assumption that such groupings are inherently less well endowed. Attention should, however, be given to the alternative possibility that poor performance is a direct result of poor living conditions, these conditions operating both after and before birth.

Table V shows the time at which the factors producing mental deficiency are determined in relation to the life history of the patient. Penrose (1954b) has

TABLE V.—*Stages at Which Factors Producing Mental Deficiency are Determined*

- Before conception.* Mainly genetic factors, but maternal ill-health may be determined at this stage.
- During pregnancy.* Maternal environment; disease; malnutrition; or other impairment of reproductive capacity as in rhesus incompatibility or difficult birth.
- After birth.* External environment; disease; injury; and unfavourable social, emotional, and educational circumstances.

used a similar arrangement, but for our present purpose a division into three stages is sufficient. Referring to some of the conditions which we have considered, phenylketonuria would fall into stage A, being determined before conception; a number of cerebral malformations with no known genetic basis such as hydrocephalus would fit into stage B, being decided during pregnancy; while meningitis would fit into stage C as a post-natal factor. Mongolism would, on the hypothesis outlined above, depend on factors determined in both stages A and B, while blood-group incompatibility may be mainly ascribed to stage B, though both the other stages are also important here—stage A since the maternal sensitivity is determined prior

to the conception, and stage C because the extent of neonatal jaundice is modified by external factors like exchange transfusion. Since the development of the human mind is a continuous process to which all three stages make their contribution, it is evident that in the final analysis each will modify the outcome in any given case of mental defect. We can merely express an opinion on which of these stages in the history of the individual is of decisive importance in order to focus attention on that stage when seeking preventive measures.

Summary

Aetiological problems are considered in high-grade (feeble-minded and educationally subnormal) and low-grade (idiot and imbecile) mental defectives. Psychological, educational, and social factors are generally of greater aetiological significance in the former group and gross brain pathology more often operative in the latter. However, such brain pathology, in "diluted" form, also produces minor degrees of mental defect, while environmental influences have a bearing on severe defect. This is illustrated with reference to phenylketonuria, kernicterus, tuberous sclerosis, and the Sturge-Weber syndrome.

Of 44 educationally subnormal children, 32 (73%) had clinical abnormalities which could at least partially account for, or be related to, their mental retardation. In another 12 high-grade patients who came to necropsy, only 3 had no gross pathological lesions in the brain.

Nearly all low-grade mental defectives show brain abnormalities at necropsy. The cause of these is elucidated in a small minority only. In 200 consecutive hospital admissions of low-grade cases, a known cause operated in 19 (9.5%) and a probable cause in another 8 (4%). Other factors were implicated in 111 (55.5%) and none in the remaining 62 (31%).

Of the 200 cases 46 (23%) were instances of mongolism. The condition is tentatively attributed to a biochemical error in the mother, which becomes more manifest with increasing age and leads to faulty organogenesis in a predisposed foetus. Metabolic studies of mothers should be undertaken in this connexion.

Of the remaining 154 admissions in our series, 122 (79%) had gross physical signs.

Factors productive of mental deficiency are briefly considered in terms of their operation before conception, during pregnancy, and post-natally.

We are grateful to all our colleagues at the Fountain Hospital for help and advice. Dr. E. A. Brown had done some preliminary work on the data which we presented from our records during the period when he held the Isaac Ettinger Clinical Research Fellowship, which is now held by one of us (J. M. B.).

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LUNG CANCER AMONG WHITE SOUTH AFRICANS

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In 1947 I emigrated from Liverpool, where bronchial carcinoma was common, and settled in Port Elizabeth, in the Eastern Cape. South Africa has a white population of just over 3,000,000, and their average family income is over £1,400 a year. The white population receives a high level of medical attention from South Africa's 8,000 doctors. For many years there have been medical schools in Johannesburg, Capetown, and Pretoria, and there are specialist thoracic surgeons in all the main cities. In a busy consultant and hospital practice, however, I was surprised to find that I rarely saw a patient with bronchial carcinoma, though other forms of cancer appeared to be as common as in Britain. The low incidence of bronchial carcinoma apparent in Port Elizabeth was particularly surprising because cigarettes were cheap (3s. for 50 was an average price), and most men appeared to be heavy smokers. Indeed, statistics of cigarette consumption show that the white South African has been by far the heaviest cigarette smoker in the world for many years. In view of the reports from other countries (Doll and Hill, 1950, 1952, 1954, 1956; Hammond and Horn, 1954; Stocks and Campbell, 1955; Medical Research Council, 1957) suggesting that cigarette smoking and lung cancer were associated, I felt that the lung cancer mortality among South Africans was particularly worthy of closer investigation.

Lung Cancer Mortality in South Africa

The incidence of bronchial carcinoma in South Africa was not known exactly before this study, because the South African Bureau of Census grouped together deaths from cancer of the trachea, bronchus, and pleura under the World Health Organization Classification of Diseases code number 162 (before 1949 the code number was 109). I therefore decided to investigate death certificates that had been codified under these numbers. The Minister for the Interior and the Director of the Bureau of Census and Statistics and his staff gave me every assistance. All information on death certificates is filed on Hollerith cards and all cards of the relevant code