pedantic names of older or newer coinage. We have got beyond the old classifications, and we are ceasing to be merely empirical therapeutists. We claim for dermatology a foremost place as a branch of scientific medicine, and without hesitation I assert of it that beyond all others it offers attractions to the student of the laws of disease in general, and to the seeker after the causes which disturb health and local nutrition."

That was true 70 years ago and it is true to-day. I feel that the reason why the ideas of the rightful place of dermatology expressed then so forcibly were not fulfilled was entirely a question of economics. In order to make a living in the days preceding the National Health Service the dermatologist had to see an enormous number of hospital patients in addition to those who provided his bread-and-butter. Before the appointed day there were, with very few exceptions, no full-time consultant dermatologists within 100 miles of London, the private patient living in this area preferring to be seen in "Harley Street." The dermatologists of that time were bogged down by the mass of patients, and I am always amazed that so much was accomplished under those circumstances.

We must make sure that this mistake is not repeated in the National Health Service and that an adequate number of consultant posts are created.

The magnificent conference held in Cambridge on the progress of the basic sciences in relation to dermatology was a striking demonstration of the virgin field waiting to be cultivated. We have the men to do it; we must ensure that their zeal is not stifled by financial stringency.

Dermatology will take its rightful place in medicine only if we, as dermatologists, give practical proof of the value of looking at the skin. I have tried to show how this is working in one general hospital. I know that this is being done in many hospitals in the country, and it must be done in all.

By retaining our training in general medicine and by having time to think, we can fulfil the hopes voiced by Dr. Ingram in his presidential address to the Dermatological Section of the Royal Society of Medicine: "Do not let us resist progress; let us embrace and foster research in all directions, but in these days of increasing specialization which tends to forget the patient and does not always regard medicine as a whole, we must be careful to preserve our heritage and graft progress on to that background."

The general physician with an interest in dermatology who founded this lecture would, I am sure, be pleased by the present trend of dermatology in this country, and so, I know, would the man who taught skin diseases to us both—Rupert Hallam.

In conclusion I would like to quote a recently qualified intelligent student who came to me for advice for becoming a dermatologist. In reply to my question of why he was particularly interested in this branch, he said that dermatology is now the least specialized of all branches of medicine.

The Cinderella child is now claiming the glass slipper, perhaps with the National Health Service as fairy godmother.

I thank all my colleagues on the staff of the United Oxford Hospitals who have been so kind to me since I joined them and who have asked me to see and allowed me to quote their cases; and the administrators of the teaching hospitals who answered my queries so promptly.

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THE BRAIN AND MENTAL RETARDATION*

BY

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Interest in the neural abnormalities associated with and often responsible for mental retardation is gradually increasing, and recent years have also seen a welcome convergence upon this subject by workers in widely separated fields.

The more common encephalopathies of mental retardation have been described from time to time—for example, Crome (1957) and Norman (1958)—while very detailed reviews of the subject by German authors are being published in the still incomplete compendium edited by Scholz (1956). Since neural malformations comprise the bulk of these encephalopathies, the full survey of this particular problem by Ostertag (1956), a contributor to the above compendium, is especially noteworthy, though many of the conditions considered by him are too severe for prolonged or, indeed, any post-natal survival. An outcome of the anatomical studies so far has been a descriptive classification of the anomalies. This is based on normal embryogenesis, many aberrations of development being "timed" in relation to certain stages of brain growth and differentiation.

In regard to aetiology, attention has long been centred on "endogenous" or genetic factors. In animals, such as mice or guinea-pigs, it is possible to produce neural (and somatic) malformations by selective breeding, and some of these—for example, hydrocephalus in mice—may be compared with certain forms of the human disease (Grüneberg, 1947). The resemblance is, however, remote, and at best only suggestive. More direct study of the causes of mental retardation and neural malformations in man reveals the great complexity of the genetic and environmental factors involved (Penrose, 1954).

Realization that maternal rubella and irradiation can act as teratogenic agents has stimulated search for further environmental causes. Experimental work has been fruitful. It is now established that many foetal anomalies may be produced at random or by design when pregnant animals are exposed to different drugs—especially the "antimetabolites"—for example, aminopterin, galactoflavin, acetylpyridine, methylfolic acid—as well as oxygen deprivation, irradiation, and deficiency or excess of certain vitamins in the diet. The literature on this subject is already voluminous and has not yet been comprehensively reviewed, but it may be useful

*Based on a paper read at a Fountain Hospital Evening Meeting on March 20, 1958.

to refer to the following sources: Hicks (1955), Giroud and Lefèbvres (1957), and Millen and Woollam (1957). This work is beginning to stimulate epidemiological investigation into human congenital disease (McDonald, 1958; Record, 1958).

At the same time, and independently, recognition of the social and medical importance of mental retardation has also been growing. Since this is still unmatched by adequate pathological knowledge, it seems useful to present some of the known facts and to restate outstanding problems on the basis of new material.

The Investigation

The material examined comprised 282 brains (mostly with spinal cords) obtained at necropsy on patients at the Fountain Hospital (240 cases), and other hospitals (42 cases). All patients dealt with under the Mental Deficiency Act were included in this series irrespective of their mental level. Only eight of the children not coming under the Act showed marked and lasting mental deterioration or retardation.

The ages of the patients are given in Table I. The mental level was as follows: idiots 146; imbeciles 93; feebleminded, educationally subnormal or normal 9; not assessed 34. The material is thus heavily biased in favour of the younger and more severely handicapped patients.

TABLE I.—*Ages of the* 282 *Patients*

< 1 year	14	3–4 years	34	11–20 years	41
1– years	47	4– ,,	29	Over 20 ,,	19
2– ,,	33	5–10 ,,	60	Not stated	5

Examination was by usual pathological and neurohistological methods. Some of the brains were studied in considerable detail, others only partially. Nevertheless, the examination is regarded as adequate in all cases for purposes of classification in this report. It is continuing, and further study might necessitate minor revision of some of the entries and tabulated results. This possibility was kept in mind in formulating conclusions. Some of the cases have been presented in other communications, and an earlier review of part of the material has also been published (Crome, 1954a).

All cases examined fell into two broad groups. The first (Table II) included instances of clearly defined diseases or syndromes, and each case was entered only once under the appropriate heading. The second group (Table III) included all the brains showing diverse structural abnormalities or none, obtained from patients of no distinct clinical pattern. Most of these brains presented multiple lesions, making it often impossible to classify the specimens under one heading only. The main changes were therefore entered, if necessary, under several appropriate headings. For example, a case showing reduction in weight, gliosis, and cavitation of the brain provided three separate entries.

TABLE II.—*Classified Syndromes.* 91 *Cases* (32.3% *of Total*)

Mongolism	36	Post-encephalitic encephalopathy	3
Hypertensive hydrocephalus	21	Cretinism	2
Tuberous sclerosis	7	Phenylketonuria	1
Gargoylism	4	Laurence–Moon–Biedl syndrome	1
Leucodystrophy	4	Hallervorden–Spatz disease	1
Cerebral lipidosis	3	Hydranencephaly	1
Residual kernicterus due to Rh incompatibility	3	Dermatomyositis	1
Residual kernicterus (not Rh)	1	Acrocephaly-syndactyly	1
		Central neurofibromatosis	1

TABLE III.—*Incidence of Main Abnormalities in* 191 *Unclassified Cases* (67.7% *of Total*)

Micrencephaly (176 brains weighed):		Calcification	15
Under 90% of average	142	Meningeal fibrosis	14
,, 80% ,, ,,	106	Marbling	14
Compensatory hydrocephalus	103	Incomplete cyclopia	6
Gliotic encephalopathy	63	Pachygyria	2
Marked smallness of corpus callosum	42	Ectopic nodules of grey matter	2
Optic abnormality	40	Porencephaly	2
Sundry abnormalities of form	33	Absence of corpus callosum without cyclopia	2
Cerebellar agenesis or atrophy	21	Arhinencephaly without cyclopia	2
No abnormality other than smallness	16	Megalencephaly (over 130% of average)	2
Microgyria	15	Gliosis with giant nerve cells	2
Gross cavitation of brain	15	No abnormality at all	8

The obvious limitation of the series is its smallness in relation to the large number of mentally retarded individuals in the community or special hospitals. It does not include, for example, a single certain instance of rubellar embryopathy, though there were 11 such cases at one time or another in this hospital. (Subclinical infection of the mother cannot, of course, be excluded as a cause of some of the encephalopathies in the series.) It includes only one case of phenylketonuria, though this is, with the exception of mongolism, the largest single clinical group at this hospital. The material lacks also examples of irradiation embryopathy, Sturge–Weber disease, and some other rarer syndromes. However, examination of brains is of necessity slow, and, small as it is, the series is among the largest studied in relation to mental deficiency.

Another limitation is that the study is concerned with the frail and young minority rather that the more robust and able majority of mentally handicapped individuals. For this very reason, however, it is full of pathological interest and lends itself most profitably to morphological study.

Classified Syndromes

Cases in this series were grouped in appropriate syndromes when they appeared to share significantly certain clinical, morphological, and, possibly, aetiological characteristics. What constitutes a syndrome is sometimes obvious but occasionally uncertain and debatable. Mongolism and gargoylism, for example, are clearly distinct entities, while, on the other hand, some morphological changes, such as microcephaly, seem to be merely common signs shared by patients with very varied conditions.

Hydrocephalus

The position of other conditions, such as hydrocephalus, is uncertain. The aetiology of hydrocephalus is manifold, but it is convenient from the viewpoint of clinical management to treat the "hypertensive" type as one group. Such cases (Table IV) present at one time or another signs of raised intracranial pressure, usually with enlargement of the head and evidence of obstruction somewhere in the pathway of the C.S.F.

TABLE IV.—*Hypertensive Hydrocephalus* (21 *Cases*)

With spina bifida cystica and Arnold-Chiari malformation (1 with retrolental fibroplasia)	8
Post-meningitic (3 after tuberculous meningitis)	7
After haemorrhage	2
With cerebellar agenesis and malformation of toes	1
With occipital meningocele	1
With cerebellar aplasia and spina bifida cystica but no Arnold-Chiari malformation	1
With no significant history and no demonstrable obstruction	1

or, more rarely, its over-secretion or under-absorption. In this they differ from the more common "compensatory hydrocephalus," which is considered with the unclassified cases in the next section. It is thought that the head of an infant with ununited sutures may enlarge to some extent and, for a time, without permanent damage to the brain. The cases of hydrocephalus in

this series, and probably most of the others with mental retardation, show, however, real secondary cerebral atrophy and other neural damage. This may be extreme, as in hydranencephaly, in which most of the cortex is the thickness of tissue-paper. Whether hydranencephaly is merely an extreme variant of hypertensive hydrocephalus or a separate disease is, however, still uncertain (Crome and Sylvester, 1958).

Hydrocephalus has often been produced in animals experimentally: by selective breeding (Grüneberg, 1947) and by excess or deficiency of vitamin A and B (Millen and Woollam, 1957; Giroud and Lefèbvres, 1957). It is difficult to compare with each other the types of hydrocephalus so produced, since anatomical details are usually omitted in the reports. Many seem to have been of the hypertensive variety, though obstruction in the C.S.F. pathway was not usually demonstrated. It is, of course, still more difficult to relate the experimental results to human conditions, and this problem is referred to again below.

Mongolism

Mongolism, the commonest single disease in low-grade mental deficiency, is still the enigma that it was, in spite of closer study. Its neural morphological changes are characterized by slight reduction in the weight of the brain and smallness of the frontal lobes and cerebellum: the ontogenetically and phylogenetically newer parts of the encephalon. The frequency of associated congenital heart defects—16 out of 36 cases in this series—suggests that the initial causative disturbance operates already at a very early stage of intrauterine life. Both hereditary and environmental factors are probably involved in its causation, as evidenced by the study of mongolism in twins and sibships, and its greater frequency among the children of older mothers.

Tuberous Sclerosis

The clinical and morphological features of tuberous sclerosis are too well known to call for much comment here. The chief neural change consists in the presence of hard glial nodules in many parts of the brain, and the condition is often associated with facial "adenoma sebaceum" and diverse malformations in other organs. A full review of this disease is available in German (Hallervorden and Krücke, 1956). Since the changes in the brain and other organs are so striking, it is perhaps surprising that no analogous condition has yet been reported in animals.

Residual Kernicterus

The most conspicuous lesions—loss of neural parenchyma with glial replacement—in residual kernicterus are found in the globus pallidus and corpus luysii, but the cerebral cortex, particularly the hippocampus, may also be involved. The frequent deafness is possibly caused by lesions in the cochlear nuclei, but this requires confirmation. In this series three cases were due to rhesus-factor incompatibility and one was of unknown origin. It is now generally recognized that while most of these cases of kernicterus are accounted for by blood-group incompatibility and prematurity, some are due to rarer causes—for example, hereditary spherocytosis, inclusion disease of infants, hepatitis, and other infection. The aetiology may also remain undetermined (Boon, 1957). Considerable advance has been made in the understanding of the pathogenesis of the condition (Billing, Cole, and Lathe, 1957). It was established that neural damage occurs when the excessive bile pigment produced by haemolysis (fat-soluble, indirect bilirubin) fails to be conjugated with glucuronic acid in the liver to form glucuronide (non-fat-soluble, directly reacting bilirubin). Hence it is hepatic inadequacy which is decisive in the inadequate disposal of the excessive fat-soluble and, presumably, neurotoxic pigment.

Leucodystrophy

The main change in the leucodystrophies is progressive diffuse degeneration of the white matter in the cerebral hemispheres. The grey matter is also often involved, but to a much smaller extent. Formerly all these cases were grouped together as "Schilder's disease," but it is now believed by some workers (Poser and Bogaert, 1956) that this group contains three separate diseases: early forms of disseminated sclerosis, leucodystrophy proper, and sclerosing leuco-encephalitis (van Bogaert's and Dawson's type of leuco-encephalitis with inclusion bodies). The leucodystrophies are often familial, and were so in two of the four cases in this series.

Cerebral Lipidoses

The specific lesion of the cerebral lipidoses is widespread distension of neurons by adventitious sudanophilic substances. The nerve cells gradually perish, and this is accompanied by marked glial proliferation and, eventually, dense scarring and contraction leading to considerable micrencephaly and ulegyria. Some brains in the recorded instances of neuronal lipidosis were, contrariwise, large, and a number of these showed spongy degeneration of the tissue. This group of diseases includes the variants of amaurotic family idiocy (Tay–Sachs disease) with retinal involvement and often a characteristic cherry-red spot at the macula; Niemann–Pick disease, with notable enlargement of the spleen and lymph nodes; and Gaucher's disease, in which neural change is inconstant. Variants of cerebral lipidosis in older individuals have also been described. The chemical composition of the adventitious intracellular substance is believed to be different in these diseases.

None of the three cases in this series could be classified with precision. One, following rhesus factor incompatibility and neonatal jaundice, showed the typical neuronal change, diffuse retinal atrophy without any macular lesion, and the presence of some adventitious cells in the spleen and lymph nodes without significant macroscopic enlargement of these organs. The second case showed typical neuronal change without involvement of the reticulo-endothelial system or retina. The third was clinically a case of Tay–Sachs disease with progressive mental deterioration and macular lesion; histologically, neuronal distension was absent, nerve cells showing merely a moderate excess of lipochrome pigment. This limited experience suggests that the morphologcial distinction between the different cerebral lipidoses may not always be as clear-cut as is often believed.

Gargoylism

Neuronal lipidosis, very similar to Tay–Sachs disease, has been observed in two unrelated dogs (Hagen, 1953), but it is not known if other members of the litters were affected and, if so, whether recessive inheritance was as aetiologically important as it is in the human condition. Neuronal lipidosis is often but perhaps not invariably present in gargoylism. When this is so,

affected nerve cells cannot be distinguished histologically from those in the other lipidoses. All the four cases in this series showed this change, but one of these was " incomplete," lacking the usual corneal and skeletal involvement of gargoylism.

Unlike the other lipidoses, neuronal changes in gargoylism are often not as widespread, and the brain is not appreciably reduced in weight. A characteristic feature of the brain in gargoylism is perivascular " lacunation," or formation of reticulated cavities around blood-vessels in the white matter. This change is, however, unspecific, occurring also in other conditions.

Other Abnormalities

Of the remaining cases the three with post-encephalitic encephalopathy followed respectively measles, whooping-cough, and, presumably, von Economo's encephalitis. Chronic inflammatory changes were present in all these cases. The case of dermatomyositis presented widespread large areas of focal necrosis in the brain, brain-stem, and cerebellum in varying stages of organization. The case of central neurofibromatosis showed several associated neural changes and was reported fully elsewhere (Crome, 1954b), while the examination of the case of Hallervorden–Spatz disease is not yet complete.

Thus all the cases discussed so far in this section showed definite and, usually, marked neural involvement. The series included, however, also a few instances of syndromes in which such changes are known to be less constant—namely, cretinism, phenylketonuria, Laurence–Moon–Biedl syndrome, and acrocephaly-syndactyly.

No specific or characteristic change has been so far described in the brains of cretins. These are often entirely normal, showing only slight or uncertain " degeneration " of nerve cells. One of the two cases in this series was that of a woman aged 53, whose brain showed bilateral massive calcification of the cerebellar white matter. In the second case the brain showed, pending fuller examination, only uncertain increase in the lipochrome content of nerve cells.

The position in regard to phenylketonuria is somewhat similar. The one case included here showed no certain change after a searching examination. (Three further cases have come to necropsy after the conclusion of the series. All showed some smallness of the brain—71%, 89%, and 90% of the average weight for age—the first was regarded clinically as microcephalic. Only one of these brains has so far been examined histologically, showing no detectable change.) Some of the previous reports on phenylketonuria also mentioned reduction in brain weight as well as pallor or myelin-staining, and, more recently, lack of pigmentation of the substantia nigra and locus caeruleus. Some of these changes have not yet been confirmed in adequately controlled series.

The shape of the brain in acrocephaly-syndactyly is greatly altered, in conformity with the outlines of the " tower "-shaped skull, but no certain histological abnormality of neural tissue has been recorded. The weight of the brain in the present case was within normal limits, and on dissection it presented no abnormality other than the already mentioned peculiarity of shape.

Comment on the Classified Syndromes

It may thus be concluded that the brain is structurally abnormal in most of the classified syndromes. In a few, however, changes are more uncertain, and it is noteworthy that some of these syndromes are characterized by biochemical or endocrine aberration—namely, cretinism, phenylketonuria. It seems reasonable to infer that the mental deficit in such cases may result from a biochemically imperfect functioning of a structurally normal or, at any rate, not strikingly abnormal brain. The reason that the brain is relatively normal may lie in some cases in the ability of the mother's liver to prevent the accumulation of toxic metabolites and thus to prevent the foetus from the consequences of his own metabolic errors. Biochemical disorder also plays a part in certain of the other syndromes accompanied by definite and marked structural change—for example, the lipidoses—and may be suspected to do so in others, like mongolism. In such conditions mental retardation is possibly the result of both sets of factors, structural and chemical. Often, however, and particularly among the unclassified cases to be considered next, structural abnormality is so gross as to obviate the need for any further hypothetical factors in explaining the mental deficit.

Unclassified Cases

Abnormalities in the brains of low-grade patients are, as already mentioned, usually multiple. They often vary from area to area, and, since it is almost impossible to examine the entire central nervous system fully, only the most conspicuous changes could be listed in Table III. In particular, no special study was made of lesions in the brain-stem and spinal cord, and these are not therefore listed separately.

The commonest single abnormality in this large group of cases was reduction in the weight of the brain compared with the average normal weights for the age as quoted by Coppoletta and Wolbach (1933). A breakdown of the weights is given in Table V.

TABLE V.—*Weights of* 176 *Brains, Expressed as Percentage of Average*

%	<40	40–	50–	60–	70–	80–	90–	100–	110–	120–	130+
No.	7	11	18	21	49	36	17	12	2	1	2

Microencephaly and Compensatory Hydrocephalus

Below a certain arbitrarily chosen level the brains may be regarded as micrencephalic. Thus, 106 of the 176 brains weighed less than 80% of the average normal, but allowance must be made for the still uncertain overlap between " normality " and " micrencephaly ": hence not every brain weighing less than, say, 80% of the average is necessarily abnormal, and not every brain weighing more than that is normal. However, the weights, as recorded here, mostly underexpress the degree of smallness, since this was usually accompanied by compensatory hydrocephalus, and the remaining fluid in the dilated ventricles was weighed with the brains. In this series all the brains were radiographed after removal and the photographs so obtained provided ready means of assessing the degree of ventricular dilatation, present in 103 cases. This was classified as follows: slight (ventricles dilated but do not exceed a quarter of the total brain area in the skiagram), 33 cases; moderate (not exceeding half of the total brain area), 33 cases; and marked (over half of total brain area), 37 cases. Cases of compensatory hydrocephalus are distinguished from the hypertensive variety, already considered, by absence of head enlargement or other

evidence of past or present rise in intracranial pressure and of anatomical obstruction. They are invariably associated, and commensurate with, agenesis or atrophy of the contiguous solid parts.

Though weights of foetal brains are not usually reported in publications dealing with the experimental production of neural malformations, illustrations and the recorded weights of whole animals leave little doubt about the smallness of the brain in most cases. "Microcephaly" is, indeed, mentioned by name as one of the commonest experimentally produced anomalies, having been observed at one time or another after almost any of the numerous agents employed.

Smallness of the brain in the present series was usually accompanied by some of the other lesions enumerated below. Of these, general or partial reduction in the size of the corpus callosum was particularly constant. Sixteen brains however, showed, no apparent abnormality other than smallness (Table VI). It is

TABLE VI.—*Sixteen Cases With No Structural Abnormality Other than Smallness (Below 90% of Average Brain Weight)*

Imbecile epileptic	83%	Epileptic idiot	86%
Idiot	80%	Feebleminded	85%
,,	73%	Epileptic imbecile	84%
,,	70%	Feebleminded with familial epilepsy	88%
Imbecile	88%	Plagiocephalic imbecile	83%
Feebleminded epileptic	76%	Feebleminded	74%
Feebleminded	77%	,,	76%
Imbecile	81%		
Epileptic idiot	70%		

noteworthy that the smallness was only moderate in this group of cases, the weights ranging between 70 and 80% of the average normal. They did not appear to constitute a special clinical group, presenting varied clinical features and levels of mental disability.

Gliotic Encephalopathy

One of the other frequent findings in micrencephaly, occurring however, also in relatively heavy brains, is gliotic encephalopathy—namely, loss of neural parenchyma and its replacement by glial tissue. Any part of the central nervous system may be so affected, and the stage reached by this process at death varies widely. Usually, in this series, the lesions were "burned out," presenting macroscopic induration with shrinking and discoloration of the affected area, and, microscopically, paucity of nerve cells and their processes with replacement by astrocytes and glial fibres. In the earlier stages there is active breakdown of myelin to neutral fat and phagocytic activity by microglial cells, often accompanied by formation of cavities. The entire brain or any part of it may be affected by gliotic encephalopathy and, accordingly, the condition is referred to as hemiatrophy, lobar sclerosis, ulegyria, or granular atrophy. The basal ganglia, the brain-stem, and the cerebellum may also be involved, and such changes in the last-named account for most of the cases of cerebellar atrophy listed separately in this series. A special variant of gliotic encephalopathy presents with abnormally orientated giant nerve cells (two cases in this series).

Such abnormal cells are also present in tuberous sclerosis and sometimes in pachygyria. Like micrencephaly, gliotic encephalopathy may be the result of many disease processes. It is often said that the human brain does not begin to react to disease or injury in this way until the seventh month of gestation; the earlier reaction being by mere arrest of growth with either subsequent full recovery or far-reaching alteration in the shape of the organ with perhaps local liquefaction and cavity formation. A brain with a malformation acquired in early intrauterine life may, however, sustain further damage later on, and is possibly particularly vulnerable to it. This may explain the not infrequent association of gross "early" malformation with gliotic changes.

Cavitation.—As mentioned already, small cavities are frequent in association with gliosis, and these may contain large numbers of fat-laden phagocytic cells. Cavities may be also present in many other conditions—for example, encephalitis, ischaemic softening, abscesses, leucodystrophy—or in the form of spongy degeneration—"status spongiosus"—attributed by some workers to chronic oedema of the brain. A special form of cavitation—perivascular lacunation—has been mentioned in connexion with gargoylism. While many such forms of cavitation were seen on histological examination in this series, all the 15 cases listed in Table III were of a grosser kind, showing numerous large, often trabeculated, cavities occupying large areas of the brain—"multilocular cystencephaly." Six of these cases had a history of difficult delivery followed by neonatal distress, and the condition may have been due to birth injury. Two of the other cases were probably infective in origin, and the aetiology of the rest was even more obscure.

Calcification.—This is another change associated with destructive lesions and gliosis. It may be apparent, on naked-eye or *x*-ray examination, in such conditions as tuberous sclerosis, Sturge–Weber disease, toxoplasmosis, or inclusion disease of infants. In the unclassified cases under discussion now, four instances of calcification were obvious to the naked eye, the remaining 11 cases coming to light histologically. In these cases calcification was often present in the vicinity of cavities, affecting individual nerve cells, their processes or capillaries. The larger foci of calcified granules were usually situated around the lateral ventricles.

Marbling.—An interesting but not fully understood lesion, sometimes associated with gliotic change and apparently never present without it, is "marbling," also referred to as "état marbré," status marmoratus, or the presence of "plaques fibromyéliniques." This occurs in the cerebral cortex and/or basal ganglia. It presents macroscopically as barely visible whitish streaks perpendicular to the surface of the usually ulegyric cortex, while in the basal ganglia the appearance is of irregularly arranged stouter white bundles, "veins of marble" ramifying upon the background of the gliotic and frequently distorted formation. Microscopically, there is invariable fibrous gliosis and, often, an impression of hypermyelination. Whether there is real excess of myelinated nerve fibres is, however, still questionable. The appearance of hypermyelination may, perhaps, be explained by displacement with condensation of pre-existent myelinated fibres and, at times, the vagaries of myelin staining (Belloni, 1952). Study of our material did not enable us to resolve this question. Whatever the nature of the lesion, it is widely held that the condition is often due to birth injury, and the history of some of the cases in this series is consistent with this view. Nevertheless, birth injury is probably not the only cause of marbling, a recent communication suggesting, for example, that this lesion may originate before birth (Scharenberg, 1957).

It should also be mentioned that slight inflammatory change—namely, leucocytic infiltration, perivascular

cuffing, and the presence of focal aggregations of microglial cells—was not uncommon in this series in circumstances excluding infection as a primary cause of the encephalopathy. In some cases such changes were terminal and in others possibly a reaction to non-septic destructive processes.

While all the changes mentioned so far in this section may be regarded as "reactive" and not different in kind from similar processes originating post-natally, those considered next are clearly of earlier intrauterine onset.

Sundry Abnormalities of Form

Cases grouped under this heading presented one or more of the following changes. (1) Relative smallness of a part of the brain without accompanying gliotic encephalopathy (excluding, however, cerebellar agenesis listed separately). (2) Exaggeration of the downward projection of the medial aspects of the frontal lobes, lending the brain a somewhat simian configuration. (3) Exposure of one or both of the insulae owing to underdevelopment of its operculi. (4) Simplification of the gyral pattern; in particular, underdevelopment of tertiary convolutions. (5) An atypical pattern of gyri—for example, absence or abnormal position of some of the gyri, irregularity in width (poikilogyria), or an excessive number of gyri (polygyria). The last-named is not to be confused with microgyria, which is considered below. (6) An increased ratio of grey to white matter in cross-section of the cerebral hemispheres. (7) Paucity of nerve cells, abnormal cortical lamination, and the presence of abnormally shaped nerve cells.

It was appreciated that some of the above changes, particularly if slight, may also occur as variations of normal brain form and structure. Since it was impossible to control this factor adequately, only the grosser instances were included in the total of 33, which is thus likely to be an underestimate.

Ectopic Nodules, Microgyria, Pachygyria

Ectopic nodules of grey matter, microgyria, and pachygyria may be taken together, since their pathogenesis is probably similar (Crome, 1956). Nerve cells in the embryo proliferate first near the ventricles and then migrate to the periphery, in the cerebrum, to the site of the definitive cortex. Interference with this migration results in failure of the cells to reach their destination and their later development in an abnormal situation. Such abnormal development may lead to the formation of large ectopic nodules near the ventricles, or diffuse neuronal layers within the white matter in cases of microgyria and pachygyria. In both these conditions the ectopic grey matter is separated from the more superficial portion of the cortex by a narrow zone of myelinated nerve fibres. (In addition to these well-defined conditions, it is also common to see fewer nerve cells scattered diffusely and sparsely in the white matter between the ventricles and the cerebral cortex. Some of this is, however, normal in young children and has not been listed as a distinct pathological change in this series.) Recent observations have increased our knowledge of these conditions.

A recurrent association between microgyria and inclusion disease of infants has been reported by Diezel (1954) and confirmed in an unpublished observation by Sabina Strich in this country. Inclusion disease of infants is widely held to be viral in origin. When this is proved, the association will constitute another definite example of viral embryopathy. No case of inclusion disease was found in the present series, but there is nothing to suggest that any malformation is always due to the same cause. Thus, Riggs, McGrath, and Schwarz (1956) were able to produce a condition in rats' embryos very similar to human microgyria and pachygyria by irradiating the pregnant animals five to nine days before birth, and a human case of pachygyria in an infant irradiated during gestation had been previously reported by Uiberrak (1942).

Incomplete Cyclopia Cavitation

Incomplete cyclopia is a convenient but perhaps not scientifically accurate description of the failure of the anterior portions of the two hemispheres to separate normally. (Cases of fuller cyclopia with a single eye and more complete fusion of the hemispheres are known to occur, but no not survive.) The condition was associated in four of the six cases in this series with absence of the olfactory nerves, and in all cases there was partial or complete absence of the corpus callosum, the lateral and third ventricles being represented by a single space. Absence of the corpus callosum (two cases) and absence of the olfactory nerves (two cases) may, however, occur in brains showing full separation of the hemispheres. Malformations somewhat analogous to human incomplete cyclopia have been reported in the offspring of rats kept on a diet deficient in pantothenic acid by Giroud, Delmas, Prost, and Lefèbvres (1957). Several types of absence of the corpus callosum have been described as a spontaneously occurring mutation in mice (King, 1936).

Cavitation of the brain, also referred to as "multilocular cystencephaly," "encephalomalacia," and "encephaloclastic porencephaly," must be differentiated from the rarer instances of porencephaly (two cases in this series) in which unilateral or bilateral funnel-shaped or slit-like clefts traverse much of the cerebral tissue, extending from the meninges up to or into the ventricular cavity. Unlike the "reactive" cavitation, this is a malformation of earlier gestation and is often associated with other gross errors of organ formation, such as microgyria.

One of the two examples listed as "megalencephaly" (brain weight was 130% of average) was associated with dystrophic changes in the white matter (Crome, 1953) and the other (unpublished) with microgyria and glioblastomatosis.

Abnormalities of the Optic System

Finally, it is necessary to mention the frequent association between the encephalopathies discussed above with abnormalities of the optic system. These included cataract (16 cases), retrolental fibroplasia (2 cases), marked microphthalmia (2 cases), coloboma (2 cases), choroidoretinitis (2 cases), and agenesis or atrophy of the more central parts of the optic pathway (40 cases). These figures certainly underexpress the incidence of such lesions, since not all eyes were examined and it is almost impossible to investigate the entire optic pathway fully. Unfortunately little is known of similar auditory abnormalities, since this system is much more difficult to examine anatomically, and no such study was attempted in this series. Deafness is, however, a frequent clinical symptom in mental deficiency, and it is very likely that the auditory system would, when examined, show corresponding changes.

Thus, with the exception of the eight cases showing no structural change whatever, referred to below, and some of the cases listed in Table VI, all the brains of unclassified patients showed obvious and usually gross abnormality, probably sufficient to explain the mental deficit. This is not to say that operation of still unknown biochemical errors can be ruled out in some of the unclassified cases. It is, indeed, safe to predict that new syndromes will in time be recognized among them, and this recognition might well be made by detection of such metabolic errors.

The Brain and Mental Retardation

Possibly the most obvious outcome of this study is the demonstration of the frequency of structural abnormality in the brains of patients with severe mental retardation, and this is in accord with previous experience. Moreover, the changes were usually easily demonstrable by ordinary pathological methods, and it seems likely that future refinements in technique will raise to the surface other, still submerged, anomalies. It is reasonable to infer that the mental deficit in most of these cases is a simple expression of cerebral inadequacy, but other factors, biochemical, metabolic, or endocrine, may well be responsible for both the structural and the functional changes. This is true, for example, of the lipidoses, metabolic disorders leading to progressive mental and morphological changes.

Nevertheless, 8 of the 191 unclassified cases presented no structural change (Table VII), while some of those listed in Table VI showed only slight and possibly

TABLE VII.—*Clinical Features and Percentage of Average Brain Weight in 8 Cases with no Structural Abnormality*

1. Low-grade imbecile, possibly psychotic	104%
2. Unclassified idiot	107%
3. Epileptic ,,	101%
4. Spastic and epileptic idiot	90%
5. Epileptic idiot	92%
6. Educationally subnormal epileptic with cerebral palsy	112%
7. Epileptic feebleminded	102%
8. Imbecile	90%

TABLE VIII.—*Cases Above Imbecile Level*

	Age	Clinical Features	Brain Weight	Pathological Findings
1	5	Epilepsy. Borderline E.S.N. level. Binet I.Q. 54	76% of av. normal	Slight micrencephaly
2	20	Laurence–Moon–Biedl syndrome	79% ,,	Laurence–Moon–Biedl syndrome
3	35	Dull normal to low average. Wechsler I.Q. 79. Matrices 83. Educational deprivation	80% ,,	Slight micrencephaly. Moderate ventricular dilatation
4	53	Feebleminded	82% ,,	Marked ventricular dilatation. Gliotic encephalopathy
5	20	,, epileptic	102% ,,	No structural abnormality
6	3	Educationally subnormal, possibly due to social causes	85% ,,	Slight micrencephaly
7	9	Epileptic, at least E.S.N. level, probably in the dull range	88% ,,	,, ,,
8	4	Epilepsy. Cerebral palsy. Familial. E.S.N. level	112% ,,	No abnormality
9	64	Average intelligence. Wechsler I.Q. 90%. Matrices 105	74% ,,	Slight microcephaly

insignificant reduction in brain weight. Most of these were, rather surprisingly, of low-grade mentality. Since constant structural change has not yet been demonstrated in some of the metabolic disorders associated with mental defect—namely, phenylketonuria, cretinism, galactosaemia, and Laurence–Moon–Biedl syndrome—it is possible that some of the present cases were likewise victims of hitherto unidentified biochemical abnormalities. However, one (Case 1) has been regarded as psychosis due to faulty rearing (Bourne, 1955). This factor may be of major importance in a few other cases of severe mental defect, while it must always be considered in less severely retarded individuals.

It is unfortunate that neither this nor any of the previously published work illumines the numerically major problem of mental retardation: the feebleminded and the educationally subnormal. Only nine such cases could be studied in the present series (Table VIII), and it is impossible, of course, to generalize on this basis. It seems plausible, however, to assume, pending confirmation, that some of the higher-grade mentally retarded individuals would show similar but milder neural changes to the low-grade cases, and that in others they would be entirely undetectable by present methods. The retardation in the latter may then be explained by the cumulative effect of adverse but not individually decisive pathogenetic factors, such as indifferent hereditary endowment, educational deprivation, domestic difficulty, minor disease, and so on. Future work will no doubt clarify this issue.

Aetiology

Scrutiny of the case records in this series revealed many possibly aetiologically significant entries, such as maternal illness before or during pregnancy, antepartem haemorrhage, trauma to mother or child, occasional family history of similar disease, blood-group incompatibility, and so on. The presumed cause could seldom be confirmed by the pathological findings, and it is still impossible to express numerically the relative or absolute incidence of the known causes of mental defect. A valid assessment of the data would require a special study with appropriate controls: this has not been done. The present views on the aetiology of mental defect have been considered by us (Crome and Kirman, 1957).

One of the tasks is to apply the results of the experimental studies and knowledge of the few known causes of congenital neural disease in man to the still unsolved problem of the majority of cases of mental retardation. In some instances the cause may be identical in both experimental and human conditions. We know, for example, of irradiation microcephaly in Japan after the atomic bombardments, and in other countries after the therapeutic application of *x* rays during pregnancy. It seems unlikely, however, that such large doses of irradiation are received with any frequency and could thus account for many cases of mental retardation. But it is possible that in certain circumstances some human embryos are vulnerable to smaller amounts of irradiation. Similarly, though many forms of neural malformation analogous with those occurring in man have been produced experimentally, it does not follow that the same causes—that is, gross vitamin excess or deficiency, anoxia, drugs, selective breeding—operate frequently in an identical manner in man.

Gross dietary vitamin deficiency is probably rare in the more highly developed countries, but conditioned vitamin deficiency is possible in such states as hyperemesis gravidarum, toxaemia, and infection. Vitamins may not be properly utilized or converted into active forms. Hoët (1956, quoted by Giroud and Lefèbvres, 1957) found, for example, carotenaemia in diabetic and pre-diabetic pregnant women and suggested that this is due to failure of full conversion to vitamin A resulting in conditioned vitamin deficiency. Endocrine factors are also known to play a part. Thus Millen and

Woollam (1957) were able to enhance the teratogenic effect of excess of vitamin A by the administration of cortisone and to diminish it by giving insulin. The supply of oxygen and nutrients to the foetus may be impeded or arrested by ante-partum haemorrhage.

Whatever the cause, it need not necessarily produce clinical signs in the mother. It is known, for instance, that the incidence of stillbirths and of congenital abnormality may be raised in an epidemic of German measles in the children of mothers who themselves remain free from overt disease (Lundström, 1952). Again, as in the case of irradiation, some embryos may be rendered vulnerable to a relatively slight deficiency of food or vitamin or oxygen lack through restriction of their adaptive capacity by an unfavourable combination of hereditary and other environmental factors. All these possibilities will no doubt be tested by future work, and steps in this direction are already being taken.

The results of a prospective study by McDonald (1958) and by Record (1958) presented at a discussion at the Royal Society of Medicine suggested, for example, that there may be a significant correlation between maternal tuberculosis and maternal anaemia, and the incidence of stillbirths and major congenital defects. These valuable studies are fraught, however, with many special difficulties and cannot replace the time-honoured careful clinical and pathological case studies. Moreover, it is clear from reported experimental work that genetic factors are by no means unimportant. Different strains of animals often react differently to the same teratogenic agent. It was shown, for example, by Andersen (1949) that the incidence of diaphragmatic hernia produced in the foetus by deficiency of vitamin A in the maternal diet varied from 0.9 to 18.9% in two different strains of rats. The shift in emphasis towards environmental factors in the causation of congenital disease does not obviate the need for further genetic studies, though these will have to be conducted with less exclusiveness than formerly. Clinical experience also suggests that inheritance is decisive in such syndromes as the lipidoses, gargoylism, phenylketonuria, and tuberous sclerosis, and that it may contribute significantly to the causation of many other conditions, including mongolism.

Summary

The morphological findings in 282 brains obtained at necropsy from mental defectives and other mentally retarded individuals, mostly of low grade, fell into two groups: 91 (32.3%) were classified as recognized syndromes with characteristic clinical and pathological disease patterns; and 191 (67.7%) could not be so classified. The neuromorphological features of both groups are briefly described. Most cases showed gross and obvious neural abnormalities, but there were certain noteworthy exceptions. In the group of the classified syndromes a few, such as phenylketonuria and cretinism, are known to be associated with only inconstant and doubtful neural lesions, even though many of the phenylketonuric brains are small. Of the 191 unclassified cases only 8 showed no morphological change, while 16 others presented only some micrencephaly, the weights of the brains ranging from 70 to 88% of the average normal for age. The study thus confirms the widely held view that severe mental retardation is usually associated with encephalopathy. However, in a minority of cases biochemical metabolic errors appear to play a major part, impairing, sometimes severely, the work of structurally not very abnormal brains.

The anatomical basis of the milder grades of mental retardation remains largely unknown.

Advances have been made in the aetiology and pathogenesis of certain conditions associated with mental retardation, particularly by experimental teratologists employing such methods as irradiation, drugs, and excess or restriction of vitamins in the diet of pregnant animals. This knowledge is yet to be extended to human conditions.

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"Pasteur's remark that 'in the field of observation, chance favours only the prepared mind' is so well known that it is almost a scientific cliché. . . . The preparation of a mind is worth some consideration particularly since this topic is frequently neglected in favour of the more striking (if inexplicable) whims of chance. . . . How, then, does one achieve the prepared mind? The more one observes the results of the varied educational experiments that form each department's courses, and the more one studies the lives and achievements of great biologists, the more two features become clear. So far as training is concerned, the essential feature is enthusiasm, whatever the stimulus, and its canalization into some form of biological activity. The second feature is the cultivation of diversity; diversity of reading, of observation, of experiment, of intellectual experience." ("Becoming a Biologist": Professor J. H. Burnett, *The Biological Journal*, Spring, 1960.)