MICROCEPHALY

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SMALLNESS of the cranium is one of the commonest findings in severe mental defect. Ashby and Stuart (1933 and 1934) found a correlation between brain weight and mental age of +0·15, but they regarded this as part of the more general positive correlation of +0·24 which they observed between body weight and mental age. In discussing this subject elsewhere (Hilliard and Kirman, 1957), Crome and Kirman have taken a more definite stand on this matter in so far as idiocy and imbecility are concerned and regard reduced brain weight, which is so often associated with a small cranium, as one of the major factors in reduced intelligence. Crome (1957) found marked reduction in size to be the commonest abnormality in brains of low-grade defectives.

The purpose of this paper is to examine the incidence of microcephaly among low-grade mental defectives in general, and in certain syndromes in particular; to consider the nature of the syndrome and its aetiology; and to formulate some conclusions which may be of value to those who are asked for advice as to the possibility of further children being affected by this condition.

The material presented here is derived from patients in the Fountain Hospital Group which provides for some 800 patients, most of them children of idiot or imbecile level, admitted under the age of 5 years.

DEFINITION

The term "microcephaly" is used loosely and lacks precision. If the term is to be valuable for purposes of prognosis, investigation of aetiology, or for study of genetics, then it is essential to use measurements and to relate these to norms for age and sex. For our purpose we have considered all cases with a cranial circumference smaller than three standard deviations below the mean for the age and sex. This definition is similar to that proposed by Böök *et al.* (1953), though they do not take sex into account. These authors also suggested that no data were then available which would allow of the practical application of their definition. We have used as a basis for comparison the norms provided by Westropp and Barber (1956) which are set out in Table I. These norms relate to head circumference, which we have used as a critical measurement throughout. Adequate standardization for the age ranges above 7 years is more difficult, but the Vickers and Stuart (1943) figures go up to the age of 10 years, though they are somewhat less satisfactory in several respects for our purposes than the British data. We are aware that exception can be taken to the use of the head circumference for this purpose since it does not provide full information

TABLE I*

Head Circumference for Boys and Girls During the First Seven Years of Life

Age	Boys			Girls		
	Number	Mean (cm.)	S.D.	Number	Mean (cm.)	S.D.
1 month ..	295	37·3	±1·54	282	36·5	±1·41
3 months ..	229	40·7	±1·43	230	39·8	±1·39
6 months ..	275	43·6	±1·45	262	42·5	±1·42
9 months ..	247	45·7	±1·40	259	44·6	±1·41
1 year ..	289	46·8	±1·40	275	45·6	±1·22
1½ years ..	255	47·9	±1·40	255	47·0	±1·30
2 years ..	264	49·1	±1·47	260	48·0	±1·32
2½ years ..	219	49·8	±1·39	221	48·8	±1·35
3 years ..	216	50·4	±1·35	227	49·5	±1·35
3½ years ..	226	51·0	±1·40	222	50·1	±1·45
4 years ..	233	51·2	±1·41	229	50·7	±1·46
4½ years ..	220	51·6	±1·45	217	51·0	±1·48
5 years ..	224	51·8	±1·47	225	51·2	±1·50
7 years ..	187	52·7	±1·48	194	52·2	±1·37

* Reproduced from Westropp and Barber (1956).

about the cranial capacity. We considered, however, that this shortcoming would be minimized by the size of the clinical material available. Another argument in favour of the use of the head circumference is that fact that this measurement is now commonly recorded in children's departments of hospitals and clinics so that records are often available for children, dating back to early infancy. Comparable data can also often be obtained on deceased patients and on siblings and other relatives who are not available for measurement.

Böök and his colleagues propose, in their definition of microcephaly, to exclude cases due to premature synostosis of the cranium. Whilst our view is that this is an extremely rare cause of microcephaly, there is some difference of opinion on the subject and it would seem undesirable, in the present state of our knowledge, to make any such arbitrary distinction.

In dealing with microcephaly, we are not primarily concerned with small-headedness which forms a part of one of the clinical entities within the field of mental defect, such as mongolism or phenylketonuria, since we assumed that reduction of head size in these conditions is attributable to the same factors which cause other features of the disease, though those cases with small heads may be regarded as severe forms of the condition. None the less, we propose in this paper to give some consideration to small-headedness within specific syndromes, in order to obtain a broad view of the subject.

The limitations of the earlier criteria of microcephaly are obvious, in that little account was taken of age. Thus, Brushfield and Wyatt (1926) working at this Hospital, found that, of 1,185 children under the age of 8 years, 147 had a head circumference of less than 17½ inches. Reference to the Westropp and Barber norms shows, however, that the significance of such a measurement would vary greatly at different ages.

The question of the possible sub-division of microcephaly into various groups, including the problem of "true" microcephaly, will be reviewed later in this paper in the light of the evidence available from our data.

INCIDENCE OF MICROCEPHALY

Table II shows the incidence of microcephaly among 100 consecutive admissions to the Fountain Hospital. Most of these children are of idiot or

imbecile level, though an occasional admission proves to have a somewhat higher level of intelligence. Apart from cases of mongolism, no attempt has been made to distinguish different clinical varieties of microcephaly at this stage.

TABLE II

Incidence of Microcephaly in 100 Consecutive Admissions

No. of Patient	Sex	Age	Head Circumference on Admission	Average Head Circumference for Age and Sex	Average Head Circumference Less 3 S.D.	Indexed Diagnosis
			(cm.)	(cm.)	(cm.)	
1. ..	F	6 10/12	48·9	52·2	48·29	Cerebral palsy. Spastic diplegia.
2. ..	M	1 7/12	*42·5*	47·9	43·70	Phenylketonuria.
3 ..	F	3	50·1	49·5	45·45	Phenylketonuria.
4. ..	M	4 6/12	48·3	51·6	47·25	Premature.
5. ..	M	2 11/12	47·6	50·4	46·35	Premature.
6. ..	M	3 1/12	47·0	50·4	46·45	Phenylketonuria. Chorea. Cerebral palsy
7. ..	M	3 7/12	48·3	51·0	46·80	Phenylketonuria.
8. ..	M	2 1/12	*44·5*	49·1	44·69	Microcephaly. Cerebral palsy. Strabismus. Spastic diplegia. Skull, asymmetry of. Illegitimate.
9. ..	F	3 5/12	*45·7*	50·1	45·75	Phenylketonuria.
10. ..	M	1 5/12	46·4	47·9	43·70	Phenylketonuria.
11. ..	M	1	43·8	46·8	42·60	Phenylketonuria.
12. ..	M	3 5/12	48·3	51·0	46·80	Petit mal. ? Familial. Caesarean birth.
13. ..	M	1 3/12	43·2	46·8	42·60	Epilepsy. Spastic diplegia. Strabismus. Birth injury. Blind. Cerebral palsy. Skull, asymmetry of.
14. ..	M	2 3/12	45·7	49·1	44·69	—
15. ..	F	2 9/12	59·0	48·8	44·75	Hydrocephalus. Cerebral palsy. Nystagmus. Strabismus. Spastic diplegia.
16. ..	F	3 2/12	*40·6*	49·5	45·45	Microcephaly. Strabismus.
17. ..	M	3 4/12	*45·1*	51·0	46·80	Cerebral palsy. Epilepsy—petit mal. Breech. Birth injury.
18. ..	M	11/12	46·4	46·8	42·60	Dislocation of hip. Blind. Familial. Cerebral palsy. Epilepsy. Strabismus. Nystagmus.
19. ..	M	2 5/12	48·3	46·8	45·63	Blind. Toxaemia of pregnancy.
20. ..	F	3 6/12	49·5	50·1	45·75	Phenylketonuria.
21. ..	M	2 5/12	49·5	49·8	45·63	Mongolism. Icterus gravis neonatorum.
22. ..	M	2	*43·8*	49·1	44·69	Twin. Birth injury. Cerebral palsy. Spastic diplegia. Premature.
23. ..	F	6 6/12	48·9	52·2	48·29	Premature. Twin. Familial.
24. ..	F	6 6/12	48·9	52·2	48·29	?Gastro-enteritis, effects of. Premature Twin. Familial.
25. ..	F	3 7/12	47·6	50·1	45·75	Cerebral palsy. Chorea. Epilepsy—petit mal.
26. ..	M	3	50·8	50·4	46·35	Familial? Meningitis (meningococcal). Premature.
27. ..	M	1 4/12	47·0	47·9	43·70	—
28 ..	M	1 1/12	43·2	46·8	42·60	Icterus gravis neonatorum. Premature. Skull, asymmetry of.
29. ..	M	5 3/12	49·5	51·8	47·39	—
30. ..	M	6 7/12	55·2	52·7	48·26	?Birth injury. Cerebral palsy. Toxaemia o pregnancy. Ataxia. Cleft palate. Meningitis—tuberculous.
31. ..	M	5	48·9	51·8	47·39	Mongolism.
32. ..	M	4 1/12	*42·5*	51·2	46·97	Familial. Psychosis—maternal. Microcephaly. Cerebral palsy. Spastic diplegia.
33. ..	M	6 5/12	*47·0*	52·3	48·26	Strabismus. Epilepsy. Gastro-enteritis, effects of.
34. ..	M	3 11/12	48·9	51·2	46·97	Nystagmus. Strabismus.
35. ..	F	4 9/12	48·3	51·2	46·56	?Deaf. Premature. Athetosis. Cerebral palsy. Strabismus.
36. ..	F	5 8/12	50·8	51·7	46·70	—
37. ..	M	4 8/12	47·6	51·6	47·25	Strabismus. Mongolism.
38. ..	M	3 2/12	49·5	50·4	46·35	—
39. ..	F	4 7/12	*42·5*	51·2	46·56	?Lens opacities. ?Retrolental fibroplasia. Cerebral palsy. Hemiplegia, left. Strabismus, internal. Premature. Meningitis, influenzal.
40. ..	F	1 4/12	43·2	47·9	43·10	Mongolism.
41. ..	M	2 5/12	45·7	49·8	45·63	?Macular degeneration (exudate). Premature. Obscure retinopathy. Optic atrophy.
42. ..	M	3 5/12	47·1	51·0	46·80	Cerebral palsy. Hemiplegia, left. Epilepsy. Strabismus, external. Birth injury.
43. ..	M	6 5/12	48·3	52·3	48·26	Toxaemia of pregnancy. Familial.
44. ..	F	4 10/12	47·1	51·2	46·70	Epileptic. Cerebral palsy—atonic variety.
45. ..	M	2 4/12	48·3	49·8	45·63	Twin.
46 ..	F	1 7/12	53·3	47·0	43·10	Hydrocephalus.
47. ..	M	3 8/12	47·1	51·0	46·80	Mongolism.
48. ..	M	3 9/12	53·3	51·0	46·80	Epilepsy.
49. ..	F	9 7/12	50·8	52·2	48·29	Abortion—attempted. Psychotic features.
50. ..	F	3 8/12	48·3	50·1	45·75	Pregnancy—bleeding in. Cerebral palsy. Athetosis. Strabismus.

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TABLE II—(*continued*)

No. of Patient	Sex	Age	Head Circumference on Admission (cm.)	Average Head Circumference for Age and Sex (cm.)	Average Head Circumference Less 3 S.D. (cm.)	Indexed Diagnosis
51. ..	M	5 4/12	48·3	51·8	47·39	Mongolism.
52. ..	M	4 10/12	48·3	51·8	47·39	Illegitimate. Cataract. Galactosuria. Icterus gravis neonatorum. Skull, asymmetry of.
53. ..	F	2 10/12	45·7	49·5	45·45	Mongolism.
54. ..	M	2 9/12	*40·6*	50·4	45·63	Strabismus. Microcephaly. Cerebral palsy. Spastic diplegia. Epilepsy. Optic atrophy.
55. ..	F	3 4/12	*45·7*	51·0	45·75	Nystagmus. Strabismus. Cerebral palsy. Spastic diplegia.
56. ..	M	2 6/12	47·1	49·8	45·63	Mongolism. Strabismus. Nystagmus
57 ..	M	5 8/12	52·1	52·3	47·39	Epilepsy. Cerebral palsy. Deaf. Meningitis—tuberculous. Hemiplegia, right. Skull deformity. Optic atrophy.
58. ..	M	2 11/12	47·1	50·4	46·35	Mongolism.
59 ..	F	3	46·4	49·5	45·45	Icterus gravis neonatorum. Strabismus. Cerebral palsy. Spastic diplegia.
60. ..	F	3 10/12	48·3	50·7	46·32	Mongolism.
61. ..	F	2 3/12	45·7	49·1	44·04	Pregnancy—bleeding in. Premature. Strabismus.
62. ..	M	3 10/12	45·1	51·2	46·97	Mongolism.
63. ..	M	6 8/12	53·3	52·7	48·26	Familial. Epileptic.
64. ..	M	4 2/12	50·8	51·2	46·97	Mongolism.
65. ..	M	3 4/12	47·1	51·0	46·80	Toxaemia of pregnancy. Cerebral palsy. Spastic diplegia.
66. ..	M	10 5/12	50·8	52·7	48·26	Keratitis, interstitial. Corneal opacity.
67. ..	M	3 8/12	47·1	51·0	46·80	Mongolism.
68. ..	F	4 5/12	50·8	51·0	46·56	Deafness? Epileptic. ?Encephalitis.
69. ..	F	2 8/12	48·3	48·8	44·75	Cerebral palsy. Spastic diplegia. Meningitis—tuberculous. Strabismus.
70 ..	F	4	49·5	50·7	46·32	Caesarean section. Hemiplegia, left. Strabismus. Nystagmus
71. ..	M	2 10/12	*45·7*	50·4	46·35	Epilepsy. Skull, asymmetry of.
72. ..	M	2 10/12	48·3	50·4	46·35	?Deaf. Icterus neonatorum. Rhesus factor incompatibility.
73. ..	M	2 8/12	49·5	49·8	45·63	?Deaf.
74. ..	F	10 1/12	50·8	52·2	48·29	Ataxia. Cerebral palsy.
75. ..	F	5 3/12	48·3	51·2	46·70	Premature. Psychosis—maternal. Birth injury.
76. ..	F	5 6/12	*42·9*	51·7	46·70	Ataxia. Cataract Cerebral palsy. Strabismus. Microcephaly. Prematurity. Spina-bifida occulta.
77. ..	M	2 2/12	74·9	49·1	44·69	Hydrocephalus. Blind. Consanguinity.
78. ..	M	4 4/12	48·3	51·2	47·25	—
79. ..	F	5	*40·0*	51·2	46·70	Prematurity. Microcephaly. Strabismus. Irradiation, effects of.
80. ..	F	9	49·5	52·2	48·29	Mongolism.
81. ..	M	5	47·1	51·8	47·39	Mongolism. Strabismus.
82. ..	M	1 10/12	*43·8*	49·1	44·69	Ataxia. Strabismus. Epilepsy. Birth injury. Cerebral palsy.
83. ..	M	1 3/12	41·9	46·8	42·60	Mongolism.
84. ..	F	6 7/12	48·3	52·2	48·29	—
85. ..	M	1 7/12	64·8	47·9	43·70	Hydrocephalus. Spina bifida. Strabismus Cerebral palsy.
86. ..	M	2	45·1	49·1	44·69	Cerebral palsy. Athetosis. Epilepsy. Skull, asymmetry of.
87. ..	M	3 11/12	*46·4*	51·2	46·97	—
88. ..	F	5 4/12	50·1	51·8	46·70	Phenylketonuria. Familial. Spina bifida occulta. Toxaemia of pregnancy.
89. ..	F	3 10/12	*46·3*	50·7	46·32	Cleft palate.
90. ..	M	5	*44·5*	51·8	47·39	Familial. Icthyosis. Pyloric stenosis.
91. ..	M	2 10/12	47·6	50·4	46·35	Asphyxia neonatorum. Hypertelorism. Strabismus. external. Epilepsy.
92. ..	F	4 5/12	45·1	51·0	46·56	Mongolism. Cataract, bilateral.
93 ..	M	4 11/12	51·4	51·8	47·39	Epilepsy. Illegitimate. Familial. Psychotic features.
94. ..	F	3 1/12	*45·1*	49·5	45·45	Familial. Spina bifida occulta.
95. ..	M	2 2/12	50·2	49·1	44·69	Strabismus, Right ptosis. Epileptic.
96. ..	M	3 8/12	48·3	51·0	46·80	—
97. ..	M	4 3/12	*37·5*	51·2	46·97	Premature. Strabismus. Microcephaly. Microphthalmia. Spina bifida, occulta.
98. ..	F	4	48·9	50·7	46·32	Epileptic. Pinna, malformation of. Twin. Toxaemia of pregnancy.
99. ..	F	1 7/12	41·9	47·0	43·10	Mongolism.
100. ..	M	1 11/12	44·5	49·1	44·69	?Mongolism.

Microcephalic measurements are italicized in Column 4 (excluding those due to mongolism).

Twenty-six of the 100 patients had a head circumference which was more than three standard deviations below the mean. Of these, six were children with mongolism, leaving 20 who might be classed as microcephalic. This incidence is higher than that found by Brushfield and Wyatt, presumably because of the different criteria used. Microcephaly as defined for our purpose

is usually associated with imbecility or idiocy and only rarely with feeble-mindedness (this question is referred to subsequently). Since rather more than half of the patients in mental deficiency hospitals are classed as feebleminded (O'Connor and Tizard, 1956), it follows that the proportion of microcephaly in most mental deficiency hospitals should be of the order of 10 per cent. or somewhat less. The fact that microcephalics tend to die early would tend to reduce this estimate still further. Penrose's (1938) figure is 1·7 per cent. of cases of "the traditional type" of microcephaly in an institutional population, i.e. 22 out of 1,280 patients. He does not say, however, how many patients not of the traditional type had little heads.

In defining microcephaly in this connection, Penrose states that the head is significantly smaller than that of other patients of the same mental grade. It will be seen from Figure 1 that there is indeed a marked mean reduction of

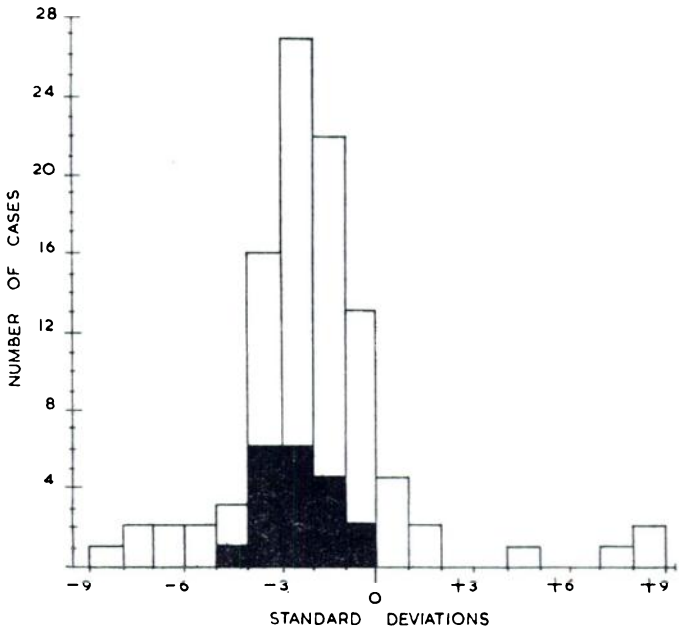

FIG. 1.—One hundred consecutive admissions to Fountain Hospital showing distribution of head circumference in relation to mean. Cases of mongolism are shown in black.

cranial circumference for the group of cases of severe mental defect as a whole: the mean of the group falling between 2 and 3 standard deviations below the mean of normal children. None the less, it is convenient to take for special consideration the group which falls below the limits we have specified, since reduction in head size is in them a leading feature of their abnormality.

It is probable that in this, say 20 per cent., of imbeciles and idiots with small heads, we are dealing with cases due to specific factors producing small-headedness, e.g. specific genetic factors or irradiation; we are also studying the action of certain factors which in milder form produce some interference with brain development and function, but which in exceptional instances produce microcephaly. Such factors are, for example, those producing occasional cases

with phenylketonuria or rubella embryopathy. A further example is provided by a recently admitted 14 month girl with sucrosuria and a head circumference of 15¾ inches (40 cm.).

Skull Circumference Post-mortem

Table III gives the skull measurements and brain weight of a series of 64 children under the age of 5 years and 3 months, dying at the Fountain Hospital.

Table III

Head Circumference, Cranial Index and Brain Weight in 64 Mental Defectives Examined Post-mortem

No. of Patient	Age at Death	Head Circumference: Actual (cm.)	Head Circumference: Mean Less 3 S.D. (cm.)	Cranial Index	Brain Weight (Gm.)	Notes
1	1 3/12	46·4	42·60	0·72	1,003	
2	1 2/12	*40*	41·94	0·91	730	Mongolism
3	1 3/12	44·5	43·70	0·94	970	Mongolism
4	9/12	42	41·50	0·92	810	Mongolism
5	10/12	44·5	40·37	0·86	780	
6	5/12	*38*	39·25	0·64	610	Acrocephaly
7	1 1/12	60	41·94	0·86	—	
8	1 7/12	44	43·10	0·66	705	
9	1 9/12	*40*	44·69	0·86	540	
10	1 4/12	*34*	43·10	0·82	220	
11	1 4/12	*40·5*	43·70	0·78	630	
12	11/12	43·5	42·60	0·80	725	
13	1 8/12	*41·5*	43·10	0·89	755	Mongolism
14	1 7/12	*42*	43·70	0·92	530	
15	1 9/12	*41·8*	43·70	0·89	760	Mongolism
16	1 6/12	61	43·70	0·94	?	
17	1 6/12	44	43·70	0·72	880	
18	1 7/12	*43*	43·10	0·91	820	Mongolism
19	2	*43·5*	44·69	0·79	810	
20	2 1/12	*43*	44·04	0·76	560	
21	1 11/12	*42·5*	44·69	0·88	765	
22	1 11/12	54·5	44·04	0·76	?	
23	2	*43·5*	44·69	0·77	430	
24	1 10/12	48	44·69	0·81	1,130	
25	2 3/12	46	45·63	0·88	1,125	
26	1 10/12	58	44·69	0·76	?	
27	2 3/12	44·5	44·04	0·73	795	
28	2	47	44·69	0·83	1,100	
29	2 1/12	*41·6*	44·69	0·85	660	
30	2 8/12	47	45·63	0·79	975	
31	2 4/12	*40*	45·63	0·75	490	
32	3 1/12	*44·5*	46·35	0·85	915	Mongolism
33	3 1/12	*43·5*	45·45	0·94	910	Mongolism
34	3 2/12	45·5	45·45	0·79	1,027	
35	2 11/12	*44·3*	46·35	0·85	890	Mongolism
36	3	45·5	45·45	0·94	860	
37	3	45·6	45·45	0·83	1,010	
38	2 11/12	*45*	46·35	0·82	1,005	Mongolism
39	3 2/12	47·1	45·45	—	1,015	
40	3 1/12	*43·7*	45·45	0·93	870	Mongolism
41	3 5/12	*42·6*	46·80	1·03	745	Mongolism

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TABLE III (*continued*)

No. of Patient	Age at Death	Head Circumference: Actual (cm.)	Head Circumference: Mean Less 3 S.D. (cm.)	Cranial Index	Brain Weight (Gm.)	Notes
42	3 7/12	47	46·80	0·82	1,075	
43	3 6/12	*39·5*	46·80	0·86	785	
44	3 9/12	47	46·97	0·72	1,340	
45	3 6/12	*42·5*	46·80	—	840	Mongolism
46	3 8/12	54	45·75	0·68	1,080	
47	3 10/12	*46*	46·97	0·85	895	
48	3 11/12	*46*	46·32	0·82	1,000	
49	4 2/12	54	46·97	0·80	1,665	
50	4	*45*	46·97	0·87	745	
51	4 2/12	*38·5*	46·97	0·85	515	
52	4	*44*	46·97	0·72	875	
53	3 10/12	*46*	46·97	1·21	1,020	Mongolism
54	4	51	46·97	—	1,295	
55	4 4/12	49·6	47·25	1·04	1,330	Mongolism
56	4 6/12	*44*	46·56	0·83	795	
57	4 6/12	51·5	47·25	0·69	1,440	
58	4 11/12	*42·3*	46·70	0·84	640	
59	5 3/12	48	46·70	0·86	1,060	
60	4 10/12	*42·5*	47·39	0·88	765	
61	4 10/12	*46·5*	46·70	0·97	960	Mongolism
62	4 11/12	*45*	46·70	1·02	1,345	Acrocephaly
63	5 1/12	48	47·39	0·79	1,100	
64	5 1/12	49·5	47·39	0·81	875	

All cases below this age, on whom an adequate post-mortem examination had been completed, were included. This number was derived from 91 consecutive deaths in this age group. In 12 cases, permission for post-mortem examination was refused; in 7, adequate particulars are not available; and in 8, the post-mortem was carried out by the coroner's pathologist and a detailed report was not furnished.

It was thought that the measurements obtained in this way might be slightly more reliable than those carried out in the course of the clinical examinations when the children are often restless and difficult to measure. It was considered, however, that the post-mortem sample would contain a high proportion of microcephalics, particularly those of severe degree and those complicated by cerebral palsy, since the expectation of life in these groups is poor.

In fact, 34, or just over half, of the children dying in this series of 64 had head circumferences which placed them in the microcephalic range. Thirteen of these 34 children were cases of mongolism, one of classical acrocephaly-syndactyly and one acrocephaly. If these are excluded, there remain 19 microcephalics, constituting 30 per cent. of the total, as opposed to 20 per cent. of the series of admissions. This strengthens the impression that mentally defective children with small heads are more liable to die early than those who have larger heads. This finding also applies to the cases of mongolism since, out of 16 children with this condition in the post-mortem group, 13 could be classed as microcephalic, a proportion of 81 per cent. compared with 33 per cent. of young children with mongolism at present in a ward in the hospital.

Since measurements of length and breadth of the skull were available in most of the post-mortem cases, it was thought that an examination of cranial index might be useful. Data on 19 cases of microcephaly and 30 other mental

defectives were compared. For this purpose also, the children with mongolism were excluded. It was found that the average cranial index for the microcephalic children at post-mortem was 0·83, whilst that for the non-microcephalic children was 0·76. It appears clear from these facts that, even if mongolism is excluded, there is no tendency for children with small heads to be relatively long headed. This is of interest in view of the general belief summarized by Penrose (1954) that there is "A class of cases clinically distinguished from the rest of defectives by the fact that the head is diminished greatly in the vertical measurement and in width, but is less abnormal in length . . . These cases with low cephalic index can be fairly well distinguished from the rest . . ." Penrose goes on to say that "The group of relatively long-headed microcephalics includes a type which is due to a single recessive gene and which has been termed 'true microcephaly'." There was insufficient material in the post-mortem cases to provide a significant comparison between a presumed genetic group and other cases of microcephaly. None of these patients was known to be the child of a consanguineous marriage, none was known to have mentally defective siblings and only 2 had other defectives in the family. The cranial indices of these two were 0·88 and 0·79.

The Nature of the Syndrome

Whilst a number of authorities are agreed on the existence of "true microcephaly", they are not unanimous in their definition of this concept. Penrose, in the passage already quoted, refers to "relatively normal musculature" and a "relatively normal chin". Tredgold (1952), together with a number of other authorities, describes the chin in this condition as "receding", whilst it is interesting to note that Sheldon (1955) chooses a photograph of a child with spastic diplegia to illustrate the condition. In this connection, it should be pointed out that there is a tendency to look upon congenital spastic diplegia as something of a genetic and clinical entity, usually with a normal sized head (Penrose, 1955 and Böök, 1953). Penrose, however, stresses the importance of phenocopies and considers that perhaps a quarter of cases of congenital spastic diplegia are due to recessive genes, whilst Böök admits that a "symptomatological clear-cut diagnosis cannot yet be secured", referring to the syndrome of oligophrenia and congenital spastic diplegia.

Much of the material which has formed the basis in the past of these clinical descriptions is highly selected and it is possible to obtain, as Brushfield and Wyatt (1926) did in studying "true microcephaly", a series of typical cases by the simple process of excluding all those which are atypical. These authors considered that only 70 of their 147 cases conformed to their criteria of "true microcephaly", i.e. 6 per cent. compared with 12 per cent. of all the children in the hospital with small heads. Incidentally, they include among their criteria occipital flattening, which suggests that they were not interested in dolicocephaly as a distinctive feature. Interestingly enough, they found five cases in which an additional sibling was affected but only chose to include two of these among their true microcephalics.

The material presented by Komai and his colleagues (1955) emphasizes the importance of selection in regard to the clinical description, since no less than 44·8 per cent. of their 143 cases were the children of first cousin marriages and the number of sibships involved was only 78. It would appear that their attention must have been directed primarily to the children of consanguineous marriages and to sibships containing more than one example of the condition,

though they do not state this. The incidence of consanguinity among the general population of Japan is assumed by these same authors to be 7 per cent. This would fit in with expectation if all their cases were genetically determined and if the genetically determined form had an incidence of 1/40,000 of the population, i.e. about the same as that of phenylketonuria.

Analysis of Case Material in the Fountain Hospital

In the course of the past 10 years, 118 cases in the Fountain Hospital have been indexed as microcephaly. This number does not include any examples of mongolism or of acrocephaly. For a number of reasons, a few cases fail to be classified in the index. The data on these 118 cases were all scrutinized on the basis of the head circumference at the time of admission, and those instances were excluded where information was lacking or where the circumference was less than three standard deviations below the norm for the age and sex. This left a total of 102 cases which could be studied. Some data on this group of cases are set out in Table IV. In this material there were two consanguineous unions, one of first cousins and one of brother and sister, resulting in affected

Table IV

One Hundred and Eighteen Cases Classed as Microcephaly Showing Incidence of Microcephaly and Mental Defect in Siblings and Near Relatives

Gross total		118
Confirmed by measurement		102
With parental consanguinity		2
With microcephalic siblings:		6
By measurement	4	
No measurement	2	
With deformed stillborn sibling		2
With non-microcephalic defective sibling		1
With other mentally defective relatives*:		9
Of which microcephalic	1	
Normal head size	4	
Hydrocephalic	1	
No measurement	3	

* 3 of these also had microcephalic siblings and are included above.

patients. In a further 9 cases, there were defective siblings. In 4 of these instances, the sibling was microcephalic on measurements. Of the remainder, one was a stillborn "deformed" twin. Another case was that of a stillborn sibling described as microcephalic. One was "microcephalic, dying 8 days after birth". One defective sibling was not microcephalic, though spastic and suffering from petit mal. The ninth case had a sibling who was hemiplegic at birth, with a small head. No skull measurements were obtained, but the brain weighed 210 g. as compared with the mean for the age of 382 g.

In 9 instances, there were other mental defectives known amongst close relatives. Three of these 9 were also included in the group with microcephalic siblings and one had a microcephalic cousin. In 4 cases, affected relatives were known to have normal-size heads. One defective relative was grossly hydrocephalic. In the remaining 3 cases, details of the head size of the relative are not available.

The Significance of the Cranial Index

Of the features mentioned by different authors as characteristic of "true" microcephaly, the only one which lends itself to objective measurement is that

of long-headedness. A comparison is summarized in Table V of the group of cases in which we thought a genetic factor might be implicated and another group in which there was no evidence of any such genetic factor.

TABLE V

Cranial Index in Microcephaly

	Number	Average C.I.
Group with:		
1. Parental consanguinity	5	·78
2. Microcephalic siblings	15	·80
3. Siblings M.D., not microcephalic	5	·78
4. Other relatives microcephalic	3	·80
5. Other relatives M.D., not microcephalic	11	·79
6. Probably environmental origin	6	·81
7. No defective relatives known	85	·81
(1 case included in both group 1 and 2)		
A. "Familial" cases, groups 1–5, N=39		·79
B. Environmental and unknown cases, groups 6–7, N=91		·81

	A	B
Average	·79	·81
Median	·79	·82
S.D.	·06	·11

There is no significance in the difference between the two means.

These two groups were made up by bringing together patients from four different sources; those already indexed as microcephalic and mentioned above, additional cases from the 100 admissions and from the post-mortem series, and finally from a special scrutiny of cases classified in our hospital index as "familial".

It will be seen from the details of the sub-groups given in Table V and Figure 2 that the average cranial indices lie very close to each other, suggesting

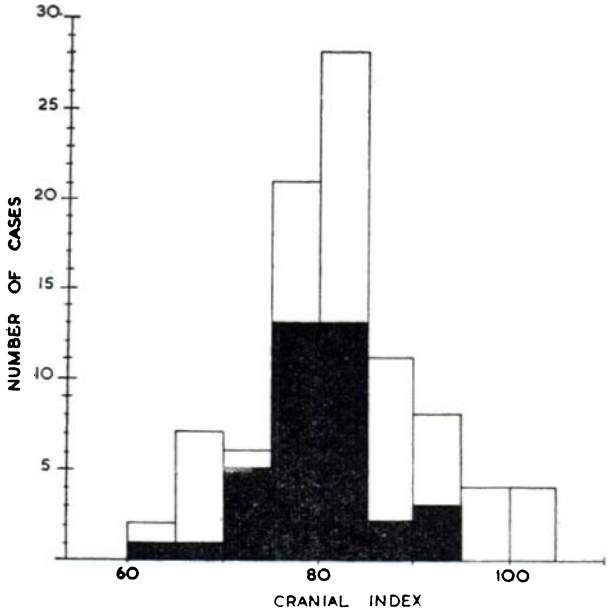

FIG. 2.—Cranial index in microcephaly. The figure for the familial cases (black) is superimposed on that for the remainder (white).

that this criterion has no value in distinguishing between genetically and environmentally determined cases of microcephaly. A comparison was also made between the same sub-groups in respect of head size; rather more "non-familial" patients have smaller heads. $\chi^2=4\cdot62$, significant at between the 2 and 5 per cent. level.

The Siblings of Microcephalic Patients

The status of the siblings of our patients is shown in Table VI. Since we wished to assess the risk of another sibling being affected, it was important to avoid choosing patients because they were known to have an affected sibling.

Table VI

Colchester Survey of 1,148 Mentally Defective Patients (Penrose, 1954)
Siblings of 114 Microcephalics

Total number of patients (from index, post-mortem and admission series)	114	
Total of siblings	166	
Half siblings	24	
Miscarriages	39	(+3 potential half siblings)
Mentally defective siblings	10	
Microcephalic siblings	7	(on measurement)
Probably microcephalic	2	
Not microcephalic	1	
Deformed stillborn (included under miscarriages)	2	
Percentage mentally defective of total	6·0	

Of 4,580 siblings:

Imbecile and idiot	164 or 3·6 per cent.
"Feebleminded" imbecile and idiot	431 or 9·4 per cent.

For this analysis therefore, the material was confined to the first three groups mentioned in the previous section, that is, the indexed cases, the post-mortem series, and the series of admissions. The cases indexed as familial were not drawn upon as such, being included only if they were contained in one of the other three groups.

Every effort was made to obtain information about all the siblings. Basically, details were obtained from three sources: the social worker's history taken during a visit to the home; a history supplied by the local authority; and a questionnaire completed by the parents. Supplementary letters were written for further information to hospitals where the patient had previously been treated; to the hospital, if any, where he was born; to the general practitioner in some cases. In the case of siblings who had died, hospital records often supplied valuable information. In some cases additional visits to the home were made, or the relatives attended, bringing siblings with them in case of doubt as to microcephaly or mental deficiency. Whenever there was a question of backwardness, efforts were made to obtain head measurements of the sibling concerned.

The 114 patients considered in this connection had 166 siblings, of whom 10, or 6 per cent., were mentally defective. Of these 10, one was not microcephalic on measurement, 7 were within the microcephalic range, and the remaining 2, though not measured, appeared obviously microcephalic to observers. In one of these cases the sibling died when 25 days old. No external measurements were obtained but the brain was recovered and weighed 210 g.

against a normal average of 358 g. for the age. The head was said to be abnormal in shape and the mother complained that the baby had a hemiplegia. When admitted to hospital she was hypotonic, unable to suck, and appeared to be unconscious. In the other case which was not measured, the sibling died at 8 days and was certified at death as a case of microcephaly, being described in the notes as of the "anencephalic" type, meaning presumably that the cranium was very small. Some details of the affected siblings are set out in Table VII.

TABLE VII

Ten Mentally Defective Siblings of Microcephalics

Case No.	Microcephalic	Spastic	Epilepsy	Head Circumference (S.D. below Mean for Sex and Age)
1	−	+	P	1·2
2	+	Death at 8 days certified as microcephaly		
3	+	−	−	4·3
4	+	Died at 25 days, hemiplegic, head and brain small		
5	+	−	−	3·9
6 (One Sibship)	+	+	−	6·6
7 (One Sibship)	+	+	−	5·3
8 (One Sibship)	+	+	+	3·3
9	+	−	−	5·9
10	+	+	+	3·5

P=petit mal.

The fact that 9 out of 10 of the mentally defective siblings were microcephalic, strongly suggests genetic factors with a specific mode of operation. In order to assess the significance of the findings, it is however desirable to know the incidence of mental defect among siblings of mental defectives in general. The figures given by Penrose (1954) show an incidence of 431 "defectives" among 4,580 siblings. The figures include the "feebleminded" and results more comparable to ours will be obtained by taking only the idiot and imbecile siblings, numbering 164, which gives a percentage of 3·6. A further difficulty in making such a comparison is that Penrose's Colchester survey of 1,148 patients includes a high proportion of feebleminded and dull or borderline cases. If only the 653 idiot and imbecile cases in the Colchester survey (1938) are taken into account, they had 2,429 siblings whose ability was assessed, and of these 109 were considered idiots or imbeciles, a proportion of 4·5 per cent. The chief reason why more siblings are recorded in the Colchester survey than in our cases is that most of the patients in that survey were adults, whereas most of ours are young children.

In order to afford a direct comparison between the siblings of our patients with microcephaly and the general run of patients in this hospital, we have carried out a survey of the 375 siblings of 200 consecutive admissions. The number of these known to be mentally defective is 12, or 3·2 per cent. Thus, although the incidence of affected siblings is higher in the microcephalic group (6·0 per cent.), it is by no means as high as would be expected (25 per cent.), if the view of Komai and his colleagues (1955) were accepted, that the great majority of microcephalic cases is "undoubtedly of genetic origin".

It may be argued that the evidence on this point is incomplete unless the miscarriages are taken into consideration. It is known that, in our series, 2 of the babies which miscarried were malformed. It is possible that more of the

39 miscarriages might have resulted in affected infants and that they in fact miscarried because of the abnormality. This seems unlikely, however, since the proportion of miscarriages in the present series at 12 per cent. is lower than the 20 per cent. of pregnancies which is accepted as usual (Brews, 1948).

Microcephaly and Birth Weight

The average birth weight for 123 microcephalic children was 6 pounds 3 ounces. The mean birth weight for normal children is in the region of 7 pounds 4 ounces. The incidence of premature birth (i.e. birth weight of less than 5½ pounds) was 38 (31 per cent.), while there were 12 (10 per cent.) children with a birth weight of less than 4 pounds. The incidence of prematurity in patients in the Fountain Hospital as a whole is 29 per cent. Thus microcephaly is significantly associated with a low birth weight, as is severe mental defect in general.

Our figures did not show any significant relationship between maternal age and prematurity; between maternal age and familial incidence; or between familial incidence and prematurity.

Associated Abnormalities

The clinical conditions associated with microcephaly are set out in Table VIII. A glance at these findings emphasizes the heterogeneity of the material and reinforces the impression that in microcephaly we are dealing with a symptom which is the end product of a variety of disease processes. A majority

Table VIII

Clinical Findings in 131 Cases of Microcephaly

	No. of Cases
C.N.S. findings:	
Cerebral palsy	86
Spastic diplegia	70
Hemiplegia	4
Ataxia	2
Athetosis	4
Atonia	3
Unclassified	3
Epilepsy	57
Deaf	2
Ophthalmic findings:	
Strabismus	47
Blindness	26
Optic atrophy	18
Nystagmus	16
Cataract	11
Retinal dystrophy	3
Microphthalmia	3
Retrolental fibroplasia	2
Corneal opacity	2
Macular coloboma	1
Aniridia	1
Psychotic features	2

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TABLE VIII—(*continued*)

	No. of Cases
Other findings:	
Spina bifida occulta	9
Plagiocephaly	8
Congenital abnormality of heart	4
Pyloric stenosis	3
Congenital dislocation of hip	3
Icthyosis	2
Deformity of palate	2
Umbilical hernia	2
Arachnodactyly	2
Hypospadias	1
Supernumerary nipple	1
Hypertelorism	1

of the cases were suffering from cerebral palsy and, of these, nearly all had spastic diplegia, though there were 4 clear-cut hemiplegias and a few instances of the rarer athetotic, ataxic and atonic forms. As mentioned below, rhesus incompatibility does not seem to produce microcephaly, so that the classical cases of athetosis due to that cause are not included in the present group, nor do our cases which we are now considering show that relatively good preservation of intelligence which characterizes athetosis due to blood group incompatibility. The next commonest complication after cerebral palsy was epilepsy, a symptom which correlates highly with spasticity. Most of the fits were major, but some minor attacks were recorded.

The somatic findings include some which may be purely coincidental, whilst others such as the heart anomalies are probably due to the same adverse factors which produced the microcephaly.

The high incidence of ophthalmic findings is very striking. Strabismus is very common in severe mental deficiency and is attributed to brain lesions. Blindness is most commonly due to optic atrophy and represents an extension of the cerebral abnormality into the retina or optic tract. The cataract may be regarded, like the congenital heart lesions, as separate evidence of somatic damage, whilst the retrolental fibroplasia may well be a secondary complication due to the low birth weight of the microcephalic group and consequential greater risk of exposure to high oxygen concentration. The possibility should, however, be borne in mind of this lesion being also due to the same cause as that which produced the encephalopathy (Williams, 1957; Crome, 1958).

MICROCEPHALY AND SPASTIC DIPLEGIA

It will be seen from Table VIII that some half of the cases of microcephaly in our series suffer from spastic diplegia. Table VII shows that at least 5 of 10 mentally defective siblings of microcephalics were also spastic, including one sibling who was not microcephalic. In Table IX an attempt is made to compare 19 microcephalics with their mentally defective siblings in respect of cerebral palsy. The 19 cases were obtained by adding some of the familial cases to those derived from other sources. The numbers are too small to permit of any definite conclusions, but there is an obvious tendency for the patients with cerebral palsy to have affected siblings with the same condition. In fact in this series the combination of microcephaly and cerebral palsy occurring twice in the sibship appears six times, whilst simple microcephaly, uncomplicated by palsy, is found twice in only one sibship. The table shows also that several permutations of the three features considered are possible, suggesting that, whereas a specific

TABLE IX

Microcephalic Patients and Their Mentally Defective Siblings with Reference to Cerebral Palsy

Case No.		Affected Siblings
1	+	ø
2	+	?
3	+	+
4	+	+
5	+	+++
6	+	+
7	+	?
8	+	?
9	+	o
10	+	+
11	+	+
12	+	ø
13	+	ø
14	o	ø[1]
15	o	o
16	o	ø
17	o	+[1]
18	o	ø
19	o	ø

+ =microcephaly and cerebral palsy.
o =microcephaly without cerebral palsy.
ø =mentally defective without microcephaly or cerebral palsy.
[1] = ½ sibling.

genetic factor may produce a regular pattern as in Case 10, in other cases the genetic factor may have a variable manifestation, producing a degree of microcephaly in one sibling and mental deficiency without microcephaly in another. It will be appreciated that, since an arbitrary standard of microcephaly has been set, the differences in actual head size between siblings differently classified in this respect may sometimes be minimal.

MICROCEPHALY RESULTING FROM NON-GENETIC CAUSES

Environmental Factors

It is generally agreed that some cases of microcephaly are due to external causes. Murphy (1929) has been instrumental in drawing public attention to the possibility of microcephaly due to therapeutic irradiation of the mother during pregnancy and it seems likely that sufficient care is now taken to ensure that such cases occur very infrequently. Goldstein and Wexler (1931) also refer to this cause of microcephaly. From the work of Plummer (1952), who found that 7 out of 11 children born to mothers who had been exposed to the effects of the atomic explosion at Hiroshima, were microcephalic, and Yamazaki *et al.* (1954), who found 4 out of 16 microcephalics among the Nagasaki children who had been similarly exposed *in utero*, it appears that microcephaly is the commonest abnormality in humans resulting from exposure to irradiation at an early stage of development. It is to be hoped that it will be possible to prevent the recurrence of such cases in future.

A Case of Irradiation Microcephaly

Although the occurrence of this form of microcephaly is well recognized, it may be useful to record an additional case which occurred within recent years. A woman of 41, who had been married for many years, had no children and had never been pregnant. She was fat and she complained of severe,

persistent backache. Ankylosing spondylitis was diagnosed, and, as other treatments proved ineffective, she was given X-ray therapy on two occasions; the first time the upper part of the lumbar spine was irradiated and, on the second occasion, treatment was applied directly to the pelvis. In view of the long period of infertility and the obesity, pregnancy was not suspected at the time of the treatment. However, the last menstrual period occurred one month after the first irradiation. Cessation of the periods was attributed by the patient to the effect of the treatment and she did not mention when she attended for the second treatment, presumably in the fourth month of her pregnancy, that the periods had not occurred as usual. The estimated effective dose to the foetus was 350–400 r. spread over 13 days. The baby weighed 2½ pounds at birth and was microcephalic. The head circumference was 38·7 cm. at 2 years, and 40·0 cm. at 5 years. She sat up at 19 months. At the age of six years she was an imbecile with a developmental quotient of about 20. She could run about, fed herself with bread and butter, and attended the occupation centre, but had no speech. She was small for her age and had marked internal squint. The length of the skull was 17·55 cm. and the breadth 14·55 cm., cranial index 0·78 cm. The forehead was sloping. No trace of the fontanelle could be felt, but radiologically the sutures were still clearly visible (Figs. 3 and 4). The appearance of the patient did not differ from that of others with no known aetiology or those which are described as microcephalia vera. As usual in cases of microcephaly (Spitzer and Quilliam, 1958), the facial skeleton was well formed and dentition normal, in contrast with such conditions as mongolism (Spitzer and Mann, 1950). There were well-developed frontal sinuses.

Other Environmental Causes

The role of other external factors in producing microcephaly is less well defined. Komai *et al.* (1955) take the view that the evidence for the production of microcephaly by non-genetic agents other than irradiation is not convincing.

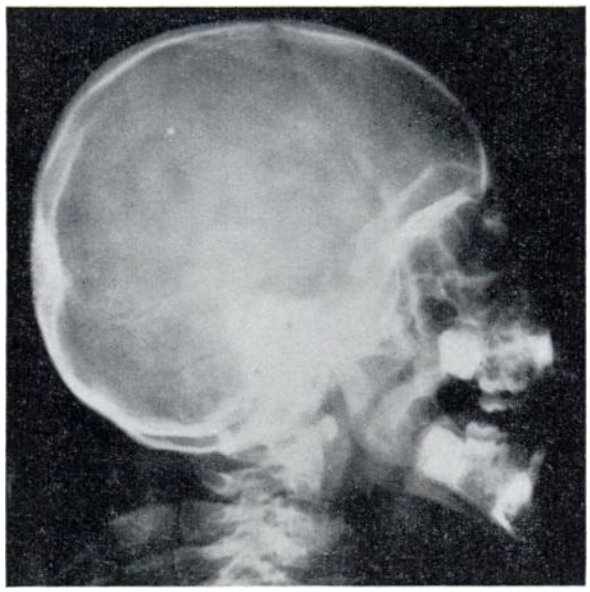

FIG. 3.—Irradiation microcephaly. Lateral view of skull at age of 6 years. Sutures still clearly visible.

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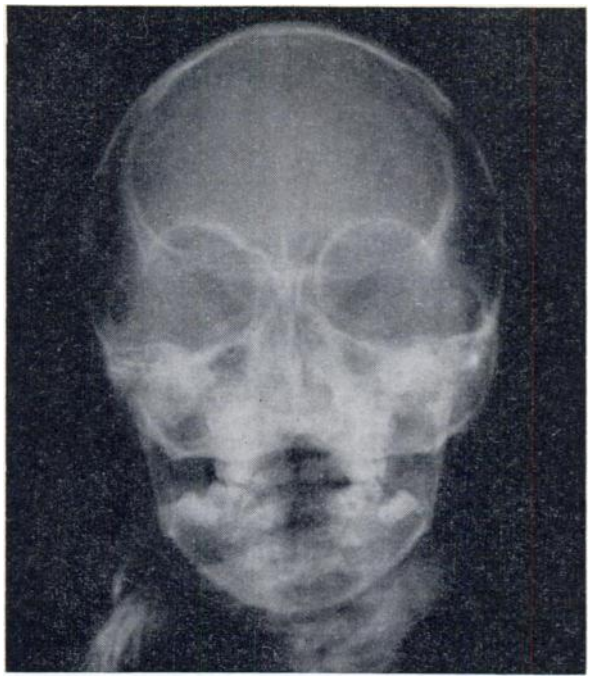

FIG. 4.—Irradiation microcephaly. Front view of skull.

Böök (1953) refers to asphyxia at birth, brain infection, encephalitis, maternal rubella and some other maternal infections as possible causes, but points out that the evidence for some of these is not very soundly based. In order to permit further conclusions to be drawn on this aspect of the matter, certain known causes of intra-uterine and neonatal pathology will now be reviewed in respect of head size.

Rubella

Among the case records of the Fountain Hospital, which provides for mentally defective children, there are 7 cases in which the defect was almost certainly due to maternal rubella, and a further three likely cases. Most of these were reported previously, Kirman (1955). Some data on these 10 cases are set out in Table X and Figure 5. It will be seen that, although the cranial circumference of these children is, on average, significantly less than the normal for

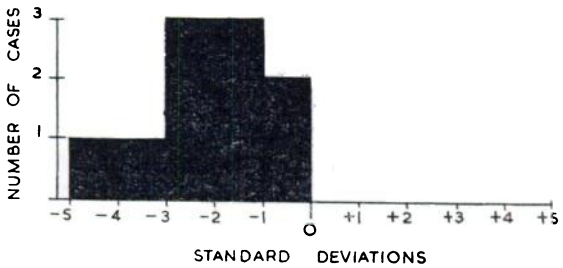

FIG. 5.—Ten cases of rubella embryopathy showing effect upon cranial circumference assessed in terms of standard deviations from the mean for age and sex.

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TABLE X

Ten Cases of Mental Defect with History of Maternal Rubella in Early Pregnancy

No.	Sex	Admission Age	Skull Circumference (cm.) Actual	Average for Age	Less 3 S.D.
1(?)	M	4 8/12	*47·0*	51·8	47·39
2 ..	M	5 11/12	48·1	52·3	47·45
3 ..	M	7 2/12	52·6	52·7	48·26
4(?)	M	9 6/12	50·0	52·7 (7 yrs+)	48·26 (7 yrs+)
5 ..	M	2 8/12	46·4	50·4	46·35
6 ..	M	6 10/12	*45·7*	52·7	48·26
7 ..	F	6 10/12	50·0	52·2	46·09
8(?)	M	4	48·3	51·2	46·97
9 ..	F	4 1/12	50·0	50·7	46·32
10 ..	F	3 5/12	47·0	49·5	45·45

Those marked (?) are in some doubt. Cases 1 and 6 lie within the microcephalic range.

the age and sex, in only two cases is the measurement more than three standard deviations less than the normal average. In other words, there were two cases of microcephaly among 10 mental defectives whose condition was probably due to rubella. Although this incidence is not high, it is important since it extends the concept of secondary microcephaly beyond the cases determined by radiation, which is all that some authorities are willing to allow. Both of the microcephalic patients had a complete rubella syndrome with bilateral cataract, deafness, congenital abnormality of the heart, and severe mental defect. In one case the mother was ill with a generalized red rash and headache during the first month of pregnancy. She did not see a doctor but a nurse told her that she had measles. In the other case it was, unfortunately, not possible to trace the mother directly, as she was in the Congo, but there was an indirect report from the local health authority which had dealt with the child in this country that the mother had had rubella during the pregnancy.

Of 52 cases of rubella embryopathy in New South Wales (Director-General, 1945), 44 showed a degree of "microcephaly" and 7 were greatly below average, but measurements are not given. Swan and his colleagues (1946) gave a series of head circumferences showing that 7 of 49 children suffering from rubella embryopathy were microcephalic as judged by the standards adopted in this paper.

Kernicterus

It seems clearly established that damage to the foetus in the early stages of pregnancy can cause microcephaly. The effect of brain lesions incurred at a later stage of development on skull growth is, however, much less certain. Since the diagnosis of birth injury is always a very difficult problem, it was thought that a series of cases of kernicterus might provide a good example of the effect of a clearly recognized brain lesion occurring in the immediate neonatal period. Twenty cases of icterus gravis neonatorum were found among the patients in a mental deficiency hospital and are set out in Table XI. The first 18 of these patients were thought to be suffering from the effects of blood group incompatibility. Most of them were reported previously by Crome *et al.* (1955). In all of these cases it seemed reasonable to suppose that the icterus neonatorum was the prime or sole cause of the mental defect. In the last two patients there

TABLE XI

The Skull Circumference in 20 Cases of Icterus Gravis Neonatorum

No.	Sex	Admission Age	Skull Circumference (cm.) Actual	Average for Age	Less 3 S.D.
1 ..	M	2 7/12	47·6	49·8	45·63
2 ..	F	1 7/12	43·2	47·0	43·10
3 ..	F	2 1/12	47·0	48·0	44·04
4 ..	M	1 2/12	48·3	46·8	42·60
5 ..	M	2 5/12	47·6	49·8	45·63
6 ..	M	2 11/12	49·5	50·4	46·35
7 ..	F	2 11/12	48·3	49·5	45·45
8 ..	M	5 3/12	49·5	51·8	47·39
9 ..	F	3 4/12	46·4	50·1	45·75
10 ..	F	2 3/12	45·1	48·8	44·75
11 ..	M	3 10/12	50·8	51·2	46·97
12 ..	M	2 2/12	48·3	49·1	44·69
13 ..	F	2 7/12	—	—	—
14 ..	M	5 3/12	50·8	51·8	47·39
15 ..	F	8 0	48·9	52·2	48·09
16 ..	M	5 3/12	52·1	51·8	47·39
17 ..	M	1 4/12	47·0	47·9	43·70
18 ..	M	2 10/12	48·9	50·4	46·35
19 ..	M	3 6/12	50·8	51·0	46·80
20 ..	F	4 0	46·4	50·7	46·32

was also icterus gravis and a strong possibility that the brain lesion was causally related to the jaundice, though blood group incompatibility was not demonstrated. The children in this group showed a great diversity of clinical signs, and it was difficult to distinguish between mental retardation secondary to athetosis, deafness or other physical handicaps, and that ascribable more directly to damage to higher cerebral centres. Crome's finding that lesions were by no means confined to the lower centres is relevant.

It will be seen from Figure 6 that these children as a group showed marked

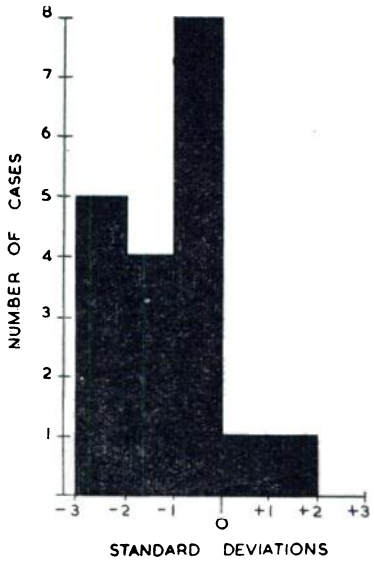

FIG. 6.—Nineteen cases of icterus gravis neonatorum showing effect upon cranial circumference assessed in terms of standard deviations from the mean for age and sex.

reduction in cranial circumference, though not to the extent of gross microcephaly. Thus, this form of neonatal brain lesion is capable of producing some retardation in cranial growth but is not commonly a cause of marked microcephaly.

Meningitis

Table XII and Figure 7 show the findings in regard to head circumference in 35 cases of mental defect ascribed to meningitis. The problem of head size

TABLE XII

Head Sizes in 35 Cases of Meningitis

No.	Sex	Infection	Age at Onset	Admission Age	Skull Circumference (cm.) Actual	Average for Age	Less 3 S.D.
1.	F	T	13/12	2 8/12	48·2	48·8	44·75
2.	F	M	12/12	4 8/12	55·5	51·0	46·56
3.	M	I	4/12	11 7/12	54·6	52·7	48·26 (7+)
4.	M	I	7/12	4 6/12	51·4	51·6	47·25
5.	F	U	8/52	3 4/12	52·0	50·1	45·75
6.	F	I	2/12	4 7/12	*42·5*	51·0	46·56
7.	F	M	5/12	5 11/12	54·6	51·7	47·35
8.	F	T	16/12	4 5/12	47·0	51·0	46·56
9.	F	P	15/12	4 10/12	48·9	51·2	46·70
10.	M	P	7/12	2 6/12	48·3	49·8	45·63
11.	F	U	5/12	7 10/12	52·7	52·2	48·29
12.	F	T	18/12	5 5/12	52·0	51·5	46·70
13.	M	M	7/12	2 9/12	51·4	50·4	46·35
14.	F	T	7/12	2 9/12	47·5	49·5	45·45
15.	F	U	4/12	2 11/12	50·8	49·5	45·45
16.	M	U	uncertain	8/12	43·2	45·7	41·50
17.	F	M	5/12	2 3/13	60·3	48·8	44·04
18.	M	T	18/12	2 6/12	49·5	49·8	45·63
19.	M	M	9/12	2 4/12	45·7	49·8	45·63
20.	M	T	4 6/12	5 3/12	49·5	51·8	47·39
21.	M	T	2 2/12	8 2/12	48·3	52·7	48·26
22.	M	T	10/12	4 8/12	54·6	51·6	47·25
23.	M	T	3 2/12	6 7/12	58·2	52·7	48·29
24.	M	P	6/52	2 6/12	45·7	49·8	44·75
25.	F	T	uncertain	4 10/12	57·1	51·2	46·70
26.	M	T	12/12	5 0	52·0	51·8	47·39
27.	F	T	12/12	4 5/12	53·3	51·0	46·56
28.	F	Py	1/52	4 0	52·0	50·7	46·32
29.	M	P	9/12	1 10/12	49·5	49·1	44·69
30.	F	T	8/12	2 1/12	45·7	48·0	44·04
31.	F	P	6/52	2 5/12	50·2	48·8	44·75
32.	M	M	2 0	3 2/12	50·2	50·4	46·35
33.	F	T	uncertain	9/12	45·7	44·6	40·37
34.	M	U	9 days	11/12	66·0	46·8	42·60
35.	F	T	2 11/12	3 7/12	50·2	50·1	46·80

T = tuberculous
M = meningococcal
I = influenzal
P = pneumococcal
Py = pyocyaneus
U = unknown

after meningitis is complicated by hydrocephalus, and amongst these cases it will be seen that there are two children with an extreme degree of this condition, having a head circumference respectively 11 and 13 standard deviations greater than the average. Two other cases exceeded the average by more than three standard deviations. At the other extreme was one case within the microcephalic range with a head 5·7 standard deviations less than the average. This one case of microcephaly might have been attributed to the severe attack of influenzal meningitis which she had at the age of 2 months. Account must be taken, however, of the fact that she was premature, weighing only 4½ pounds at

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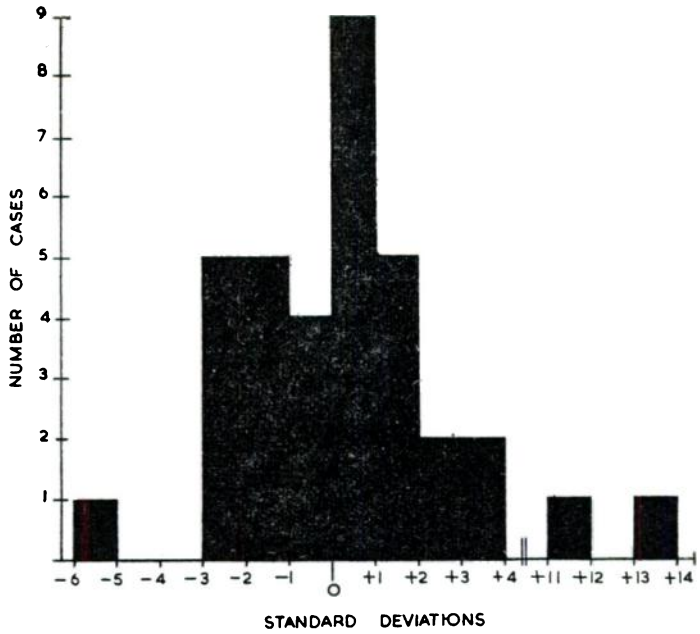

FIG. 7.—Thirty-five cases of infantile meningitis and mental defect showing cranial circumference assessed in terms of standard deviations from the mean for age and sex.

birth, with a head circumference of 12½ inches (31·8 cm.), which places her 2·9 standard deviations below the Vickers and Stuart mean before her illness. She also appeared to have a minor degree of retrolental fibroplasia. At 6 years she was a helpless, hemiplegic idiot, head circumference 43·2 cm. (17 inches), breadth 12·1 cm. (4¾ inches) and length 15·2 cm. (6 inches). She was very ill during the meningitis, collapse occurred at one stage and the cerebro-spinal fluid remained grossly abnormal for a month. In view of the early history, it cannot be stated with certainty that the small head is due to the meningitis, and it is quite possible in this, as in some other of our cases, that more than one factor is involved.

There is therefore no clear evidence in our data to incriminate meningitis as a cause of microcephaly, though its occasional operation, and likewise that of other severe illnesses soon after birth, to produce reduced head size, cannot be excluded.

Evidence from Twins

Brandon *et al.* (1959) give an account of two pairs of twins, one of each pair being microcephalic, the other quite normal in intelligence and head size. In both cases the twins were identical. It was thought that environmental factors operating during pregnancy were responsible for the microcephaly, though birth trauma could not be entirely excluded as a factor. This is a further piece of evidence in favour of the occurrence of "acquired" microcephaly. Hinden (1956) recorded a similar case.

Mongolism

The unknown factors responsible for this syndrome are a common cause of smallheadedness. As shown in Table XIII, children with mongolism tend to have small heads for their age. Of the 30 cases which figure in this table, 10

TABLE XIII

Head Sizes in 30 Cases of Mongolism

No.	Sex	Admission Age	Skull Circumference (cm.) Actual	Average for Age	Less 3 S.D.
1 ..	F	1 3/12	45·7	45·6	41·94
2 ..	F	8/12	41·9	44·6	40·37
3 ..	F	3 10/12	*45·7*	50·7	46·32
4 ..	F	3 10/12	48·3	50·7	46·32
5 ..	F	3	*43·8*	49·5	45·45
6 ..	M	1 6/12	43·8	47·9	43·70
7 ..	M	11/12	43·2	46·8	42·60
8 ..	M	6 3/12	46·4	52·3	48·26
9 ..	M	1 1/12	44·5	46·8	42·60
10 ..	M	1 11/12	45·7	49·1	44·69
11 ..	M	4 6/12	*45·1*	51·6	47·25
12 ..	M	3 1/12	47·0	50·4	46·35
13 ..	M	1 8/12	47·0	47·9	43·70
14 ..	M	2 9/12	50·2	50·4	45·63
15 ..	M	3 6/12	47·0	51·0	46·80
16 ..	M	3 8/12	*46·4*	51·0	46·80
17 ..	M	1 11/12	*43·2*	49·1	44·69
18 ..	M	1 9/12	45·7	49·1	43·70
19 ..	M	3 11/12	48·9	51·2	46·97
20 ..	M	3 7/12	*44·5*	51·0	46·80
21 ..	M	1 8/12	*41·9*	47·9	43·70
22 ..	M	3 10/12	50·8	51·2	46·97
23 ..	M	3 10/12	45·1	51·2	46·97
24 ..	M	4 11/12	49·5	51·8	47·39
25 ..	M	11/12	45·7	46·8	42·60
26 ..	M	5 5/12	50·2	51·8	47·39
27 ..	M	3 8/12	47·0	51·0	46·80
28 ..	M	4 1/12	*45·7*	51·2	46·97
29 ..	M	2 8/12	50·8	49·8	45·63
30 ..	M	3 11/12	48·9	51·2	46·97

could be classed as microcephalic using the criteria outlined above. They are distinguished from ordinary cases of microcephaly by the fact that there is a very general dystrophy affecting almost all the organs, whilst in microcephaly there is a tendency for the abnormality to be localized in a very striking manner to the cranium and its contents (see Figs. 3 and 4). Another distinguishing feature is the relative brachycephaly of the children with mongolism. It is known that the factors which produce mongolism are active in the early part of pregnancy and probably exert their main effect about the sixth week. In this respect, i.e. in the time relationship, they may be similar to the factors producing ordinary cases of microcephaly; on the other hand, so far as the retardation of head growth is concerned, the factors producing mongolism are less potent since it is rare to find cases of severe microcephaly in mongolism. It will be seen from Figure 8 that all the cases shown as microcephalic in the table can be classed as examples of a medium degree of severity. In view of the fact that low birth weight is noted very commonly among children with mongolism—29 per cent. were classed as premature in our series at the Fountain Hospital, that is to say, they had a birth weight of less than 5½ pounds—it was thought possible that those children who fell into the microcephalic range for skull circumference would also be those who had small birth weights. However, no clear relationship between these two measurements emerges. Out of 8 of the microcephalic mongolian children whose birth weight was recorded, only two were

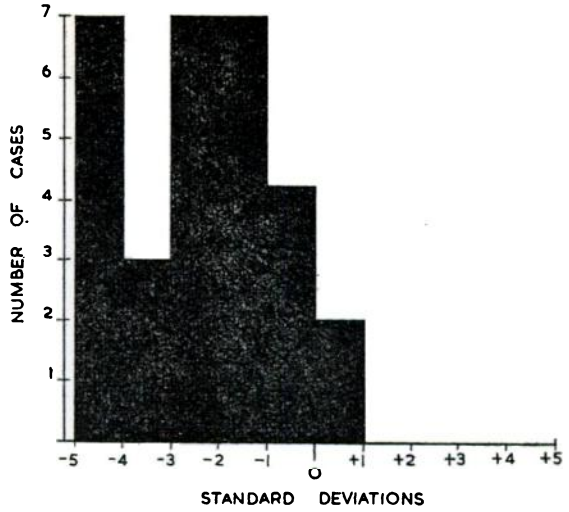

FIG. 8.—Thirty cases of mongolism showing cranial circumference assessed in terms of standard deviations from the mean for age and sex.

premature (as defined), which is the expected number if there were no relationship.

MATERNAL AGE

It was found that the average age of 133 mothers at the birth of their microcephalic child was 26·8 years. This was two years younger than the mothers of 100 consecutive mental defectives who were not microcephalic or mongols. This difference is significant at below the 1 per cent. level. For comparison the national average is 27·8 (based on Registrar-General, 1953).

INTELLIGENCE IN MICROCEPHALY

The following notes briefly summarize the findings in regard to mental capacity:

Intelligence test results were available on 108 microcephalic patients, and, although testing is difficult when dealing with children as backward as this, and many have developmental quotients rather than intelligence quotients, they are a guide to the abilities of these children. They have an average I.Q. of 11, with an S.D. of 12. The highest I.Q. found was 59, which was obtained by an adult. A large number of children had an I.Q. below 1. The distribution of intelligence is shown in Table XIV. Where more than one assessment has been made, there seems to have been a drop in I.Q. over the years. This may be

TABLE XIV

Distribution of intelligence in microcephaly

0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	Total
44	18	19	7	7	3	4	2	0	1	1	2	=108

due to the fact that these children develop relatively better physically than mentally and that the developmental type of test used when they are young gives higher scores than a test demanding intellectual ability. On the other hand, it may reflect a real tendency towards deterioration. Head size tended to fall off with intelligence. $\chi^2=7\cdot75$. This is significant at the 1 per cent. level.

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The average I.Q. of the "familial" group is 12·3 and for the "non-familial" is 10·4. These are not significantly different. The average I.Q. of the 32 children who died was 5·4.

Since these patients were all selected as mental defectives, they may not fully represent the intelligence of people with small heads. It may be that there are some persons within the microcephalic range who would achieve rather better scores than those shown. A closer relationship between intelligence and head size might be expected, until account is taken of the diversity of brain pathology in these cases and the fact that there is often a gross defect in quality as well as quantity of brain substance.

There is no real evidence to support the view often put forward that microcephalics have some sort of special temperament or that they are especially active, show "quick, furtive movements" or are friendly and fond of music. It is well nigh impossible to support similar claims with objective evidence even in the case of such a clear-cut entity as mongolism (Marrs, 1955).

Anatomical Findings

It is not proposed here to give a detailed account of the neuropathology of microcephaly. Crome (Hilliard and Kirman, 1957) has discussed the matter in general and in relation to the related abnormalities of microgyria (1952) and pachygyria (1956). A more recent study by the same author in preparation showed that of 176 otherwise unclassified mental defectives, 106 had brains which weighed less than 80 per cent. of the mean for the age. Most of these brains showed a variety of structural abnormalities apart from the smallness.

Among those patients in our series who had microcephalic relatives, the brains were available for study post-mortem in 6 cases. There was a further case where the parents were first cousins. As shown in Table 15, the findings

Table XV

Brain in Familial Microcephaly

Case No.	Family Data	Weight*	State of Brain
1.	Stillborn microcephalic sibling	110 (1,351)	Shallow sulci, with surface mantle and ectopic grey matter within.
2.	Microcephalic sibling	740 (1,275)	Microgyria.
3.	Microcephalic sibling	210 (358)	Massive destruction of white and grey matter, resembles leucodystrophy.
4.	Microcephalic cousin	834 (1,237)	Shrunken with gliosis.
5.	Microcephalic cousin	912 (1,237)	Both brains shrunken with gliosis especially occipitally.
6.	Microcephalic cousin	826 (1,253)	
7.	Parents first cousins	282 (950)	Shrunken with gliosis.

* Figures in parenthesis are mean brain weights for age.

were very diverse and support the view that, even in the genetically determined cases of microcephaly, the material is not homogeneous and that we are dealing with more than one factor and pathological process.

Cases 1 and 2 show an error which must have been determined very early in development, whilst in Cases 4–7 the early stages probably proceeded fairly normally, arrest occurring later in pregnancy. Case 3 showed a remarkable

picture of a highly destructive process with some resemblance to leucodystrophy, though this group of conditions is not usually associated with microcephaly. Cases 5 and 6 were maternal cousins and showed what appeared to be a specific type of lesion.

Penrose (1954) states that "The brain in true microcephaly is extremely small and may weigh less than 1,000 g. but it need not show pathological lesions. The cortical convolution pattern is much simplified." Wallin (1956) makes a similar statement. None of our familial cases conform to this description. It may be argued that this is because none of them are cases of "true" microcephaly. We prefer to advocate the abandonment of the use of this term in favour of an attempt to subdivide microcephaly in terms of aetiological factors, environmental or genetic, clinical features, e.g. presence or absence of palsy, and nature of brain lesion.

Conclusion

Microcephaly is a purely descriptive term and includes conditions with varying aetiology and pathology. If the phenomenon of microcephaly is to be investigated objectively, it is desirable that it should be defined in some manner such as that suggested, i.e. three standard deviations below the mean of head circumference for the age and sex.

It is not possible within the category of microcephaly as defined above to separate off a group of cases with "true microcephaly", since the criteria used to make this differentiation do not correspond to any real difference between the possibly "genetic" group of cases and the others.

Microcephaly can be determined by environmental factors and has been recorded in one of uniovular twins. Such factors include ionizing radiation; infection during pregnancy, notably rubella; probably a variety of other adverse factors in the intra-uterine environment; possibly also severe brain damage during or soon after birth. Such a severe illness as kernicterus does not, however, seem commonly to produce microcephaly, perhaps because of the selective nature of the brain lesions. Patients suffering from certain classified syndromes may also fall within the microcephalic range, e.g. in mongolism, acrocephaly, phenylketonuria and sucrosuria.

The evidence suggests that there may be more than one genetically determined form of the condition produced by different genetic factors.

Twenty per cent. of mentally defective children in our series, mongolism excluded, are microcephalic, as defined above. The death rate among the microcephalics is higher than among other mental defectives.

The high familial incidence in published material on microcephaly may be partially explained by selection of cases in favour of those with a familial incidence. The evidence from our data suggests that only a minority of cases are genetically determined.

The risk of another mentally defective child being born to a mother who has already had one microcephalic offspring is of the order of 6 per cent., as compared with a corresponding figure of 3·2 per cent. for other defectives in our hospital; the odds are heavily in favour of such a child being also microcephalic.

More than half the cases of microcephaly suffer from cerebral palsy, which usually takes the form of spastic diplegia. Epilepsy is common and there are often multiple lesions including eye abnormalities. Our material shows more evidence of the familial incidence of the form of microcephaly with spastic

diplegia than of the uncomplicated form. In a number of cases a mentally defective sibling was not microcephalic. This suggests the possibility that similar pathogenic factors may produce varying manifestations and that consequent reduction in head size may not always reach the microcephalic level.

Summary

The concept of microcephaly and of "true" microcephaly is critically reviewed. Cases with a head circumference more than 3 standard deviations below the mean for age and sex are accepted as microcephaly. One case presumed due to irradiation of the mother during pregnancy, 2 thought due to maternal rubella are described. One of each of two pairs of uniovular twins were also found to have microcephaly. No instances were recorded among 20 cases of icterus gravis neonatorum. One-third of children with mongolism fall into the microcephalic range. Of 100 admissions to the Fountain Hospital, mainly idiots and imbeciles, 26 were in the microcephalic range, of which 6 had mongolism. In 64 deaths at the hospital, 34 were of microcephalic size, including 13 with mongolism. In a series of 102 clinical cases, there were two sets of consanguineous parents, 9 instances of mentally defective siblings, and 9 instances of mental defect among other close relatives. There was no significant difference between the cranial index of the "familial" group and the others. A series of 114 unselected cases of microcephaly had 166 siblings, of whom 10 were mentally defective; of these, 9 were microcephalic. In 131 cases examined clinically, 86 had cerebral palsy, of which 70 had spastic diplegia. Fifty-seven had epilepsy.

Nineteen cases of microcephaly were compared with their mentally defective siblings in respect of cerebral palsy. Thirteen of the 19 had cerebral palsy and their sibling was similarly affected in 6 cases. Among the defective siblings of the 6 microcephalics without cerebral palsy, there was one with this condition. In 7 cases, the mentally defective sibling was not microcephalic, in 9 cases it was.

Maternal age was significantly lower than in the case of other defectives, mongols excluded.

One hundred and eight cases of microcephaly had an average intelligence quotient of 11, with a standard deviation of 12, range 0–59. A relationship was found between head size and intelligence, significant at the 1 per cent. level.

The morbid anatomy was very varied, 7 of the brains from "familial" cases were examined, 2 showed lesions dating from early, and 4 from late, pregnancy, whilst one had an atypical leucodystrophy.

It was concluded that only a minority of our cases were primarily due to specific genetic factors, the nature of the environmental factors involved being usually unknown. There are probably at least two specific genetic factors causing microcephaly. The risk of another child being affected is 6 per cent. in our series. There is as yet no clinical basis for distinction between genetic and non-genetic cases apart from family history.

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