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Toxoplasma skin- and dye-test surveys of severely subnormal patients in Lincolnshire*

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Cerebral damage is one of the four cardinal features of the classical syndrome of congenital toxoplasmosis described by Sabin (1942). Feldman (1958) tabulated the frequency with which the various manifestations were found by Eichenwald in 180 proven cases and showed that psychomotor retardation was present in 45%. Thalhammer (1962) showed that, in addition to these recognizable cases, there was serological evidence that many patients, lacking other features of toxoplasmosis and with otherwise unexplained brain damage, might, in fact, be cases of this disease. He found a 20% excess of positive dye tests in severely subnormal children attending his paediatric clinic in Vienna, as compared with normal controls, and suggested that congenital toxoplasmosis might have caused this proportion of cases. Butler (1959) indicated the need to ascertain serologically the proportion of known defectives whose condition is attributable to toxoplasmosis.

Dye-test surveys of subnormals have been undertaken by Cook & Derrick (1961) in Australia, and by Fleck (1963) in Swansea. These did not suggest that toxoplasmosis was a significant cause of mental deficiency in the populations they studied. Fair (1959), using the skin test in a large series in America, reached the same conclusion. In view of evidence of the prevalence of toxoplasmosis in Lincolnshire (Beattie, 1957; Robertson, 1960, 1962), it was decided to examine all subnormals in hospitals in the county.

METHOD AND MATERIALS

There are four hospitals for the mentally subnormal in Lincolnshire and these were visited in turn. Of 918 patients 917 were subjected to the skin test. At one hospital only those patients who were under the age of 11, or who were positive to the skin test or had epilepsy or eye disease were examined seriologically. At the remaining hospitals the serological testing was extended to include all adult patients in order to establish the comparability of skin and dye tests.

Skin-test antigen was made by Eli Lilly and Co. (U.S.A.) and supplied through their English subsidiary free of charge. The antigen was given by intradermal injection of 0·1 ml. into the left forearm and, initially, mouse spleen control antigen was given in the right forearm. Subsequently, the use of control material was discontinued, as only one patient had shown any reaction to it.

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The tests were read on the third day, the diameter of any area of induration being measured. (Induration exceeding 7 mm. in diameter was taken to indicate a positive result.)

RESULTS

Dye-test results

Of the 717 sera taken from subnormal patients in the four hospitals, thirteen leaked in transit and, of the remainder, forty-nine were from cases selected on account of special clinical features or positive skin test. Table 1 shows the incidence of dye-test positivity in the remaining 655 cases.

In order to assess the significance of these figures it is necessary to compare them with figures for the general population.

Table 1. *Dye-test results in wards where all were tested*

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128 −1/256	+1/256 −1/512	+1/512 −1/1024	+1/1024 −1/2048	+1/2048 −1/4096	+1/4096 and over	Total	Total +ve	% +ve 1/8
1–9	36	3	1	2	2	2	—	—	1	47	11	23·4
10–19	93	10	12	6	—	1	—	1	—	123	30	24·4
20–29	74	16	24	2	—	—	—	—	—	116	42	36·2
30–39	60	13	17	1	—	—	—	—	—	91	31	34·1
40–49	67	26	21	1	—	—	1	—	—	116	49	42·2
50–59	35	32	31	2	—	—	—	—	—	100	65	65
60+	26	21	12	2	1	—	—	—	—	62	36	58
Total	391	121	118	16	3	3	1	1	1	655	264	40·3

In this and other tables, +1/8, −1/32 signifies positive at 1/8 and negative at 1/32.

Table 2. *Dye-test titres of* 220 *normal children in Lincolnshire*

(Sera tested at Leeds in 1962–63.)

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128 −1/256	+1/256 −1/1024	+1/1024 −1/2048	+1/2048	Total	Total +ve	% +ve
1–4	171	—	—	1	1	1	1	175	4	2·3
5–9	44	—	—	—	1	—	—	45	1	2·2
Total	215	—	—	1	2	1	1	220	5	2·3

Children

The best estimate available of the incidence in children in the area comes from tests undertaken in the same year on sera I took from children in the north of the county in connexion with another investigation. These sera were tested at the same laboratory, and the incidence of dye-test positivity is shown in Table 2. Only 2·3% of normal children below the age of 10 have positive dye tests, whereas 23·4% of subnormals of the age are positive at a titre of 1/8.

The difference between the percentages positive is 21·1. As the standard error is 3·83, the difference in proportions is $5\frac{1}{2}$ times the standard error and the difference is significant.

Adolescent

Unfortunately, few sera from adolescents in the general population have been tested and no comparison between subnormals aged 10–19 and normals is possible.

Young adults

As can be seen from Table 1, the percentage of positives did not differ appreciably between defectives in their third and fourth decades of life. They are therefore considered together. As a standard of comparison the best figure available for the general population of these ages is a group of sera from expectant mothers, sera from mothers of stillborn, premature or control normal babies, or cord blood from their babies, and a few sera from other women and some men between 20 and 40 years of age. These sera were tested at the same time as those of the subnormals and at the same laboratory.

Table 3 compares the incidence of positive dye tests of subnormals of this age with that found in these controls. The high proportion of females in the control group is acceptable because as Table 6 shows, at this age there is no significant difference in incidence between the sexes.

The slight excess of positives in the subnormals is not statistically significant. (Difference/standard error = 1·02.)

Table 3. *Dye-test titres of young adults*

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128	Total	Total +ve	% +ve 1/8
Subnormals aged 20–40	134	29	41	3	207	73	35·2
Controls aged 20–40	76	13	17	2	108	32	29·5

Table 4. *Percentages of subnormals aged* 40–59 *with positive dye test compared with those reported by Beattie in blood donors in rural districts in Lincolnshire*

	1/8 or over	1/32 or over	1/128 or over	1/256 or over	No. tested
Subnormals aged 40–59	52·8	25·9	1·9	0·5	216
Blood donors from rural areas (Beattie, 1958)	49	24	3·6	0·2	505

Older adults

The best standard for comparison available for the older adults is the data published by Beattie (1958) on blood donors in urban and rural areas in Lincolnshire. These sera were taken some years earlier and were tested at a different laboratory. As most blood donors are aged between 40 and 59 years, it is reasonable to compare them with subnormals of this age range, but allowance must be made for differences between laboratories and in time.

Table 4 compares the subnormals in the age range 40–59 years with the figures published by Beattie and shows clearly that, by this age, the incidence in adult defectives approximates to that found in normal rural populations.

Clinical groups

Table 5 compares the incidence of positive dye tests in mongols and epileptics with that in the remaining subnormals.

It is interesting that the incidence of antibodies is as low in the epileptics as in

the mongols since epilepsy is one of the classical signs of congenital toxoplasmosis whereas mongolism, being due to a chromosome anomaly, appears on rational grounds unlikely to be caused by toxoplasma infection. The higher incidence of antibodies in the miscellaneous group than among mongols and epileptics is found in adults, but not in children. This suggests that the excess of dye-test positives in the miscellaneous group may be due to acquired rather than congenital infection.

On comparing the age and sex specific positivity rates (Table 6) it was noted that there was a higher incidence of antibodies in adult males than in females. In those over the age of 40, these differences are greater than one would expect as a result of chance. This might well be due to the increased opportunity to acquire infection of those men who go out to work on farms each day, and as mongols and epileptics tend to be unsuitable for outside employment this would also explain the lower incidence found in these groups.

Table 5. *Dye tests of special groups*

		Mongols			Epileptics			Others		
Age groups		No.	No. +ve	% +ve	No.	No. +ve	% +ve	No.	No. +ve	% +ve
1–19	Male	20	5	27·6	27	6	23·1	78	19	25·2
	Female	9	3		12	3		29	8	
20–39	Male	5	1	25	34	8	25·6	112	46	42
	Female	7	2		9	3		55	24	
40+	Male	5	0	38·5	26	9	39·6	168	110	62·4
	Female	8	5		22	10		81	45	
	Total	54	16	29·6	130	39	30	523	252	48·2

Three patients who were both mongol and epileptic are included in both columns.

Table 6. *Dye-test result by age and sex*

	Female			Male			Combined		
Age groups	No.	No. +1/8	% +1/8	No.	No. +1/8	% +1/8	No.	No. +1/8	% +1/8
1–9	13	4	30·8	34	7	20·6	47	11	23·4
10–19	34	8	23·5	89	22	24·7	123	30	24·4
20–29	37	12	32·5	79	30	38	116	42	36·2
30–39	20	6	30	71	25	35·3	91	31	34·1
40–49	35	12	34·3	81	37	45·7	116	49	42·2
50–59	26	12	46·2	74	53	71·6	100	65	65
60+	18	7	38·9	44	29	66	62	36	58
Total	183	61	33·3	472	203	43	655	264	40·3

Skin-test results

There are no adequate figures available for the incidence of skin-test positivity in the general population of Lincolnshire. The test has not been widely used in England, probably because antigen is not readily commercially available. Messrs

Eli Lilly manufacture antigen in the U.S.A. and were kind enough to supply me with the material used in this survey.

The skin test is simple to perform and lends itself to epidemiological surveys but, as it is unreliable in young children and, even in adults, does not become positive until many months after infection, is of only limited value to the clinician. The delay in appearance of skin sensitivity is so long that the finding of a positive skin test during an illness could almost be taken to exclude the possibility that the illness is due to toxoplasmosis.

Table 7. *Skin test: size of lesion giving best concordance with dye test*

Dye-test titres	Diameter of induration in millimetres									Total	Total concordant	Total discordant
	4 mm.	4	5	6	7	8	9	10	11+ Unsp.*			
−ve	369	5	3	1	5	1	1	3	7	1	396	378 (−)	18
1/8	42	3	—	4	12	7	13	25	28	3	137	88 (+)	49
1/32	33	5	2	5	20	16	13	16	27	6	143	98 (+)	45
1/128	4	1	2	1	3	2	1	1	2	—	17	9 (+)	8
1/256	1	—	—	—	—	—	1	—	1	—	3	2 (+)	1
1/512	1	1	—	—	—	—	—	1	—	1	4	2 (+)	2
1/1024	—	—	—	—	—	—	—	—	1	—	1	1 (+)	—
1/2048	1	—	—	—	—	—	—	—	—	—	1	—	1
1/4096	1	—	—	—	—	—	—	—	—	—	1	—	1
Total	452	15	7	11	40	26	29	46	66	11	703	578	125

* Skin test assessed positive but diameter of induration not recorded.

Although the makers recommend that induration of 10 mm. diameter be taken as the criterion of positivity, it was found that there was better concordance of dye- and skin-test results when 7 mm. was taken as the criterion.

Table 7 shows the relationship between diameter of induration and dye-test titres in 703 patients. It will be seen that, if the 10 mm. standard were adopted, dye and skin tests would be discordant in 29·3% of cases but, if the 7 mm. standard is accepted, they are only discordant in 17·75% of cases.

The 7 mm. standard was adopted in interpreting the results of skin tests in this survey.

As can be seen from Table 8, in 200 (92%) of the 218 persons whose skin tests were positive by this standard the result was confirmed by a positive dye test.

Table 9 is complementary and shows that 378 of the 485 with negative skin tests were also negative to the dye test.

Agreement between skin- and dye-test results, except in children under 10, is good in the women and in the men aged from 20 to 40. It is poor in men over the age of 50. The reason for this is obscure. The discrepancy was noted in several wards in different hospitals which were tested at different times and so is unlikely to be due to faulty technique or deterioration of antigen with storage. Although most of the women were tested before the men, a great many were tested on the same day.

Tables 10 and 11 illustrate this discrepancy.

Table 12 shows the full results of the skin-test survey. As was found in the dye-test survey, the proportion of positives rises with age up to the age of 60 and then declines slightly. The percentage of positives among children is somewhat higher than one would expect, and considerably higher than that found by Burkinshaw, Kirman & Sorsby (1953).

Table 8. *Dye tests of subnormals with positive skin tests*

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128 −1/256	+1/256 −1/512	+1/512 −1/1024	1/1024	Total	Total +ve	% +ve 1/8
1–9	2	1	1	—	1	—	—	5	3	60
10–19	1	3	7	3	—	1	—	15	14	93·3
20–29	5	12	20	1	—	—	—	38	33	87
30–39	2	12	17	—	—	1	—	32	30	93·8
40–49	4	24	17	2	—	—	1	48	44	92
50–59	2	19	27	2	—	—	—	50	48	96
60+	2	17	9	1	1	—	—	30	28	93
Total	18	88	98	9	2	2	1	218	200	92

Table 9. *Dye tests of subnormals with negative skin tests*

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128 −1/256	+1/256 −1/512	+1/512 −1/2048	+1/2048 −1/4096	1/4096	Total	Total +ve	% +ve 1/8
1–9	34	2	—	2	1	2	—	1	42	8	19
10–19	92	7	8	3	—	—	1	—	111	19	17·1
20–29	70	5	6	1	—	—	—	—	82	12	14·6
30–39	60	5	3	1	—	—	—	—	69	9	13
40–49	64	6	9	—	—	—	—	—	79	15	19
50–59	33	14	11	—	—	—	—	—	58	25	43
60+	25	10	8	1	—	—	—	—	44	19	43·2
Total	378	49	45	8	1	2	1	1	485	107	22·2

Table 10. *Females: dye test of subnormals with negative skin test*

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128 −1/256	+1/256 −1/512	+1/512	Total	Total +ve	% +ve 1/8
1–9	9	1	—	—	1	1	12	3	25
10–19	25	1	2	2	—	—	30	5	16·7
20–29	24	2	1	1	—	—	28	4	14·3
30–39	16	2	1	1	—	—	20	4	20
40–49	21	3	2	—	—	—	26	5	19·2
50–59	13	—	—	—	—	—	13	—	—
60+	11	1	—	—	—	—	12	1	8·3
Total	119	10	6	4	1	1	141	22	15·6

Table 11. *Males: dye test of subnormals with negative skin test*

Age groups	−ve	+1/8 −1/32	+1/32 −1/128	+1/128 −1/512	+1/512 −1/2048	+1/2048 −1/4096	1/4096	Total	Total +ve 1/8	% +ve 1/8
1–9	25	1	—	2	1	—	1	30	5	16·7
10–19	67	6	6	1	—	1	—	81	14	17·3
20–29	46	3	5	—	—	—	—	54	8	14·8
30–39	44	3	2	—	—	—	—	49	5	10·2
40–49	43	3	7	—	—	—	—	53	10	18·9
50–59	20	14	11	—	—	—	—	45	25	55·5
60+	14	9	8	1	—	—	—	32	18	56·25
Total	259	39	39	4	1	1	1	344	85	24·7

Table 12. *Skin-test survey of subnormals*

Age groups	Males			Females			Combined		
	Total	Total +ve	% +ve	Total	Total +ve	% +ve	Total	Total +ve	% +ve
1–9	35	4	11·4	17	2	11·8	52	6	11·5
10–19	125	10	8	57	7	12·3	182	17	9·34
20–29	80	25	31·2	65	14	21·5	145	39	26·9
30–39	71	22	31	61	12	19·7	132	34	25·8
40–49	81	28	34·5	74	23	31	155	51	32·9
50–59	74	29	39·2	67	21	31·4	141	50	35·5
60+	45	12	26·7	65	20	30·8	110	32	29·1
Total	511	130	25·4	406	99	24·4	917	229	25

DISCUSSION

In view of serological evidence that toxoplasma infection is highly prevalent in the community, congenital toxoplasmosis is surprisingly seldom diagnosed. This could be accounted for in a number of ways: maternal infection might occur without transmission to the foetus; foetal infection might occur without causing recognizable damage; or foetal damage may occur but, because of lack of the classical features, not be attributed to toxoplasmosis.

The classical syndrome of congenital toxoplasmosis is of choroidoretinitis, cerebral calcifications, mental retardation or neurological damage and hydrocephaly or microcephaly (Sabin, 1942) and, where several of these signs are present, the conditions would probably be diagnosed. For this reason, the incidence of these signs in proven cases, given by Feldman (1958), probably overestimates the frequency with which they occur in combination, and cases exhibiting only a single manifestation may well escape recognition. Thalhammer (1962) produced statistical and serological evidence to support his hypothesis that many children with unexplained congenital cerebral damage may be unrecognized cases of congenital toxoplasmosis. His figures suggest that about 20% of mentally retarded infants lacking other signs of toxoplasmosis may, in fact, be 'oligosymptomatic' cases.

Serological surveys by other workers have so far failed to confirm this opinion. Cook & Derrick (1961) in Australia found little evidence of toxoplasmosis among 342 patients in a mental hospital. Only ten out of 116 juvenile subnormals of unknown aetiology had positive dye tests and they concluded that toxoplasmosis could not have accounted for more than 7% of their cases.

Fleck (1963) found only one out of 114 sera from mental defectives under the age of 10 submitted to his laboratory by various hospitals to be positive to the dye test at a titre of 1/16 and only seven out of 93 sera from a further series of mentally retarded children were positive at a titre of 1/4. For comparison, he took sera from children not suspected of suffering from toxoplasmosis who were admitted to a children's hospital and some children undergoing a poliomyelitis antibody survey as representative of the general population. If these 'controls' were truly representative, and his figures of 16% for the incidence of positive dye test at a titre of

1/4 and 8% at a titre of 1/16 for children under 10 are correct, toxoplasmosis would not appear to be a significant cause of mental subnormality in the area served by his laboratory. It is, however, possible that, by making use of sera from children admitted to hospital, he may have overestimated the incidence in the general population.

This difficulty, in estimating the incidence of antibodies in the general population, is of considerable importance. As the incidence of toxoplasmosis may vary from year to year and from place to place, it is difficult to ensure comparability of cases and controls.

Several of the children included as controls in this survey, although dye-test negative when tested in 1962, had been reported positive to the test when their sera were tested at a different laboratory in 1960. Until the significance of these observations is known, one must view such statistical and serological evidence with some scepticism.

Despite these reservations, the excess of positivity noted in mentally defective children in hospitals in Lincolnshire is of the same order as that noted by Thalhammer in Vienna. Although the possibility that a proportion of the cases may have been due to congenital toxoplasmosis cannot be denied such a conclusion is not justified by the evidence of this investigation. If the excess of dye-test positivity in subnormal children indicated brain damage resulting from congenital toxoplasmosis one would expect that the incidence in subnormals whose condition was known not to be due to toxoplasmosis would be low. Different environments may modify the degree of exposure to risk of acquiring infection, and not only may the risk differ between hospital and home, but the quality of care provided in the home is a factor in determining which defectives are admitted to hospital.

In an attempt to eliminate these factors it was intended to compare within the hospitals a group whose condition was not due to toxoplasmosis and a group exhibiting one of the common symptoms of congenital toxoplasmosis with the rest. Mongols and epileptics were the largest readily identifiable groups suitable for this purpose. It seemed unlikely that toxoplasma infection would disturb the chromosomes of an ovum and so be a cause of mongolism. Although Ira (1960) reported a higher incidence of positive skin test in mothers of mongols than in mothers of normal children this is more probably due to the association between maternal age and mongol birth or to associated environmental factors than to a causal connexion.

Unfortunately the number of mongols in the hospitals visited proved too small for the calculation of reliable age and sex specific rates. Rates for 20-year age groups were calculated however, and these showed that below the age of 20 there was no difference in incidence between mongols, epileptics, and other subnormals. Differences found in the older groups might well be due to the fact that mongols and epileptics tend to be unsuitable for outside employment, whereas many of the other male defectives go out to work on farms.

Similarly, it is possible that environmental factors may be responsible for the high rates found in all groups of subnormal children. As a result of their condition

such children are bound to lead a very different life from that of normal controls even before their admission to hospital. Since the common mode of transmission of toxoplasma infection is not known we cannot know what environmental differences are relevant here, but it does appear that they are in the homes rather than the hospital, for although the child defectives in hospital showed an excess of dye-test positivity this became steadily less with increasing age and duration of residence in hospital, except in adult males, a number of whom worked outside the hospital. Thus, although the highly significant difference between the incidence in defective children and controls alone would suggest that toxoplasmosis might be a common cause of severe subnormality, comparison of groups within the hospital make it appear more likely that, unless toxoplasmosis is also a cause of mongolism, these differences are more probably due to postnatally acquired infections resulting from environmental factors.

Although the skin test proved far less sensitive than did the dye test, the skin-test survey showed the same trends as did the dye-test survey. Some of the discrepancies noted related to patients with high dye-test titres, suggestive of recently acquired infection which had not yet resulted in altered skin sensitivity. Many of the discrepant results, however, were in patients having only low dye-test titres. These are puzzling and suggest that skin-test sensitivity may not always be maintained for as long after infection as is the production of circulating cytoplasm modifying antibody. The fall in incidence of positivity to both tests in the oldest defectives is more probably due to a tendency for both antibody levels and dermal sensitivity to fade below the arbitrary 'threshold' at which we detect them than to higher mortality among those with positive tests. If this is the explanation, the discrepant results would be explicable on the basis of variation in the relative rates at which antibody levels and dermal sensitivity faded in different individuals whose infections had occurred many years previously.

SUMMARY

Of 918 severely subnormal patients in mental deficiency hospitals in Lincolnshire 917 were tested by the toxoplasmin skin tests, forty-nine out of 265 patients were dye tested because of a positive skin test or other indication. All patients in another group of 655 subnormals were dye tested, and comparison of these results with those of groups from the normal population showed that in children there was an excess of about 20% of dye-test positivity among the subnormals—a figure identical with that found by Thalhammer in Vienna.

The excess of positives became progressively less with increasing age and by middle age the incidence was the same in subnormals as among blood donors in the county. It is suggested that this indicates that patients in hospital are exposed to a lower risk of acquiring infection and that the higher incidence among adult males than among adult female defectives is due to the fact that more of them go out to work, many of them on farms. This factor could also explain the lower incidence of positivity in adult mongols and epileptics who are less commonly employable.

Possible explanations of the higher incidence among subnormal than among

control children are discussed. Although it is tempting to assume that it indicates that some may be cases of congenital toxoplasmosis, the lack of gradient between child mongols, child epileptics and other subnormal children does not support this hypothesis. The numbers of mongol and epileptic children were too small to give statistically significant results. It is possible that the home environments of severely subnormal children exposed them to a higher risk of infection than did the homes of the control children and that the observed excess of dye and skin-test positivity may be due to increased incidence of acquired infection before their admission to hospital.

It was found that there was reasonable concordance between the dye test at a titre of 1/8 and skin sensitivity reactions exceeding 7 mm. in diameter, but poor agreement if 10 mm. was taken as the criterion of positivity.

Despite the lesser sensitivity of the skin test, the pattern of the results was the same as that observed in the dye-test survey, and the value of the skin-test for epidemiological surveys was confirmed.

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