# CONGENITAL TOXOPLASMOSIS SIMULATING HAEMOLYTIC DISEASE OF THE NEWBORN

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FOETAL hydrops suggests haemolytic disease of the newborn. There are, however, other, less common, causes, among these toxoplasmosis.

The purpose of this paper is to report three cases of congenital toxoplasmosis which at first gave rise to suspicions of haemolytic disease.

*Case 1.* Baby D. was born on 8th July, 1954.

Abnormalities noted during this, the mother's first pregnancy, were: excessive gain in weight, hydramnios, frequency of micturition and profuse vaginal discharge. Labour lasted 16 hours. Foetal heart sounds ceased 10 minutes before delivery.

The baby was stillborn, severely hydropic and weighed 4 pounds 13¾ ounces. The placenta was unduly large, fleshy pink in colour, friable and oedematous.

## POST-MORTEM EXAMINATION

When the skull was opened numerous small whitish-yellow, necrotic areas were seen beneath the pia-arachnoid on the surfaces of both cerebral hemispheres. During the removal of the brain yellowish fluid escaped in quantity suggesting hydrocephalus. Multiple soft, yellowish, necrotic areas were found throughout both cerebral hemispheres, particularly around the lateral ventricles. The hind brain showed no apparent lesion, but its softness precluded detailed examination.

The serous sacs contained much fluid. Nothing of note was found in the heart and lungs.

The liver and spleen were enlarged, the latter being 4 times the usual size.

The kidneys and suprarenals did not seem unusual.

## HISTOLOGY

*Brain.* Sections showed multiple areas of necrosis and calcification. These were particularly abundant in the superficial cortical zone, and in the subependymal region. The areas of calcium deposition were generally surrounded by an intense inflammatory reaction, predominantly histiocytic, but with varying numbers of plasma cells, lymphocytes and polymorphonuclear leucocytes. Some of the blood vessels in relation to necrotic foci were involved in the inflammatory reaction. The choroid plexus was heavily infiltrated with acute and chronic inflammatory cells.

Typical toxoplasma pseudocysts were found, not in the necrotic areas, but in the adjacent apparently healthy tissue, 1–2 mm. away (Fig. 1). Among the necrotic debris were aggregations of granular material which had some resemblance to both pseudocysts and terminal colonies, but had no surrounding membrane (Figs. 2 and 3).

*Heart.* The subepicardial region and, to a

lesser extent, the myocardium were infiltrated by lymphocytes, histiocytes and plasma cells. No necrosis of the muscle fibres was present. No toxoplasma could be found.

*Liver*. Haemopoiesis was excessive, even allowing for prematurity. Much of it was of primitive type. The Prussian blue reaction was negative.

*Spleen*. There was an excess of erythropoietic cells. The Prussian blue reaction was negative.

*Kidney*. A narrow neogenic zone remained, indicative of prematurity. As in the liver, haemopoiesis was excessive even allowing for the prematurity (Fig. 4). Many of the red cells in the renal vessels were of primitive type (Fig. 5).

*Eye*. Posterior uveitis was present. There was no evidence of involvement of the optic nerve. Aggregations of bodies resembling toxoplasms were found in the disorganized retina.

*Pancreas and Suprarenal*. Nothing unusual.

*Placenta*. The villi were swollen and oedematous, as in haemolytic disease.

## Serology

*Blood Grouping*

Mother: Group A Rh. positive.

Mother's serum and baby's cells: Indirect Coombs's test negative. No abnormal antibodies found.

Father: Group B Rh. negative.

Baby: Group A Rh. positive. Direct Coombs's test negative.

Wassermann: Mother—negative.

*Toxoplasma Antibodies*

| | Dye Test | C.F.T. |
|---|---|---|
| Baby: | | |
| 12th July, 1954 | | |
| Cord Blood .. .. .. | 1/2,500 | 1/32 |
| Heart Blood .. .. .. | 1/5,750 | 1/32 |
| Mother: | | |
| 12th July, 1954 .. .. | 1/12,500 | 1/32 |
| 27th July, 1954 .. .. | 1/18,000 | 1/640 |
| 25th January, 1955 .. .. | 1/7,000 | 1/64 |
| 21st March, 1955 .. .. | 1/2,000 | 1/16 |
| 21st April, 1955 .. .. | 1/220 | 1/32 |
| 19th May, 1955 .. .. | 1/275 | 1/64 |
| 17th June, 1955 .. .. | 1/240 | 1/64 |
| 18th July, 1955 .. .. | 1/65 | 1/64 |
| 28th July, 1955 .. .. | 1/57 | 1/64 |
| Mother (*continued*): | | |
| 8th August, 1955 .. .. | 1/800 | |
| 11th August, 1955 .. .. | 1/1,500 | 1/64 |
| After birth of succeeding child: | | |
| 31st August, 1955 .. .. | 1/1,000 | 1/32 |
| Succeeding healthy baby: | | |
| 31st August, 1955 .. .. | 1/1,250 | 1/64 |
| Father: | | |
| 22nd July, 1954 .. .. | 1/4 | 1/4 |

## Isolation of Toxoplasma

At first it was thought that attempts to isolate the parasite would fail. A suspension of the brain was inoculated on 8th July, 1954 in Edinburgh into two guinea pigs intraperitoneally, two mice by the same route, and two mice intracerebrally. One of the guinea pigs was killed on 16th July, 1954, but no toxoplasms were found in smears of peritoneum, spleen, liver or brain. None the less a suspension of these tissues was inoculated into the peritoneal cavity of two guinea pigs and two mice.

Apart from one passage mouse which died of ante-partum haemorrhage nineteen days after inoculation, and the guinea pig which was killed, all the original and passage animals were still alive on 17th September, 1954. On that date one of the original mice and the surviving passage mouse were killed in Sheffield. No toxoplasms were found, but a suspension of their brains, livers, and spleens was inoculated intracerebrally and intraperitoneally into two mice. In ten days these looked ill, were killed and toxoplasms were found in their peritoneal fluids.

The rest of the original mice were killed on 27th September, 1954. Again no toxoplasms were found but combined intracerebral and intraperitoneal inoculation of a suspension of their organs into further mice produced toxoplasmosis.

Following on this success blood was taken from the remaining original and the two passage guinea pigs which had been kept in Edinburgh. High titre dye test results were obtained on their sera.

The original guinea pig was killed on the 95th day (18th October, 1954). No toxoplasms were found in it, nor did inoculation of mice with its peritoneal exudate, spleen and liver (brain was not included) produce toxoplasmosis even after four blind passages.

One of the passage guinea pigs was killed on the 74th day (28th September, 1954) after inoculation. No toxoplasms were found in it, nor did combined intracerebral and intraperitoneal inoculation of a suspension of its spleen and liver (brain was not included) produce toxoplasmosis in mice even after three blind passages. The other passage guinea pig was killed on the 250th day (18th March, 1955) and toxoplasms were isolated in the first set of mice inoculated intraperitoneally and intracerebrally with brain suspension.

This guinea pig was a virgin female at the time of inoculation on 16th July, 1954. She was caged with a boar for the last two weeks of October, 1954, and gave birth to two healthy females on 9th January, 1955.

*Case 2.* Baby T. was born on 6th December, 1954.

The mother had been subject to epileptic fits, but the last was 8 years before this pregnancy, during which she was well.

The membranes ruptured prematurely and she was admitted to hospital in labour at thirty-five and a half weeks. Labour lasted 11 hours. Presentation was breech and forceps were applied to the aftercoming head.

In spite of endotracheal oxygen, the baby gasped only a few times and died.

Apart from emphysematous swelling of the neck, no external abnormalities were noted; in particular there was no external evidence of hydrocephalus nor of oedema. The placenta was large and flabby, as in haemolytic disease.

### Post-mortem Examination

*Brain.* When the skull was opened deep yellow fluid escaped, probably from the lateral ventricles. There was considerable subdural haemorrhage with large amounts of blood clot lying on the superior surface of each half of the tentorium cerebelli and extending around the mid-brain. The pia-arachnoid was healthy and no necrosis or calcification was obvious on the surface of the brain. Section, however, showed numerous areas of necrosis and calcification, most pronounced in the walls of the greatly dilated ventricles.

*Thorax.* Bilateral pneumothorax was present, the lungs lying far back in the pleural cavities. The pericardium was healthy and the heart was of appropriate size and developmentally normal.

*Abdomen.* Both liver and spleen were enlarged, the spleen being approximately three times the usual size. The Prussian blue reaction on both organs was negative. Kidneys and suprarenals showed no pathological change.

*Eyes.* After fixation the eyes showed on section a small whitish, opaque lesion on the surface of the retina immediately posterior to the ciliary body.

### Histology

The histological features were almost the same as in Case 1. The cerebral lesions were similar. Toxoplasma pseudocysts (Fig. 6), terminal colonies (Fig. 7) and aggregations of granular material (Fig. 8), similar to those in Case 1, were found. Microscopy showed chorio-retinitis and myocarditis. The liver and spleen both showed excessive haemopoiesis much of this, in the liver, being of primitive type.

### Serology

*Blood Grouping*

Mother: Group O Rh. positive. No abnormal antibodies found.

Baby: Coombs's test negative.

A subsequent healthy baby was born in February, 1956.

*Toxoplasma Antibodies*

| | Dye Test | C.F.T. |
|---|---|---|
| Baby: | | |
| 9th December, 1954 .. .. | 1/1,300 | 1/240 |
| Mother: | | |
| 16th December, 1954 .. .. | 1/1,050 | 1/64 |
| 14th November, 1955 .. .. | 1/280 | 1/20 |
| 19th January, 1956 .. .. | 1/54 | 1/20 |
| Father: | | |
| 19th May, 1955 .. .. | 1/8 | 1/8 |

### Isolation of Toxoplasma

Suspension of brain was inoculated in Sheffield by combined intracerebral and intraperitoneal routes into six mice on 9th December, 1954. Toxoplasms were found in 5 of these mice killed between the eighth and thirteenth day after infection.

Suspension of brain, liver and spleen was inoculated intraperitoneally into eight mice in Edinburgh on 8th December, 1954. Four were taken to Sheffield. These were killed after 12, 42, 82 and 83 days. Toxoplasms were isolated from 3 in first intracerebral and intraperitoneal passage. Second passage mice were inoculated

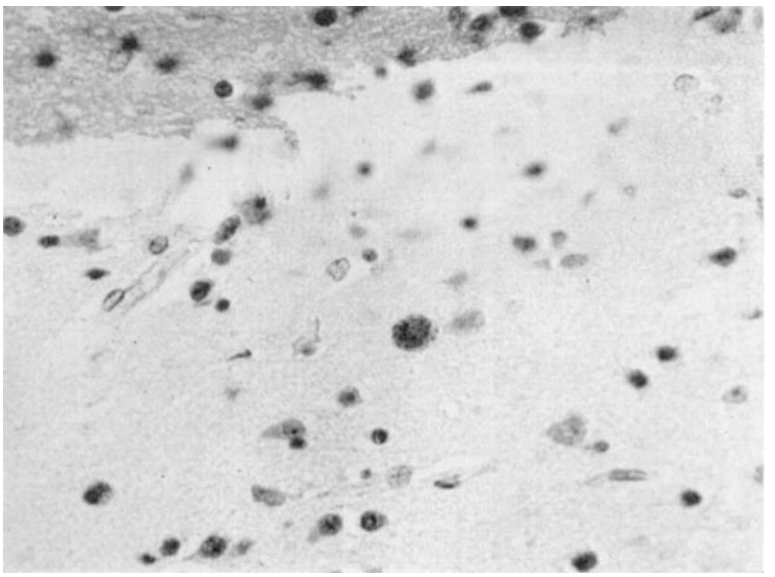

FIG. 1

Case 1. Toxoplasma pseudocysts in apparently healthy brain tissue. ×550.

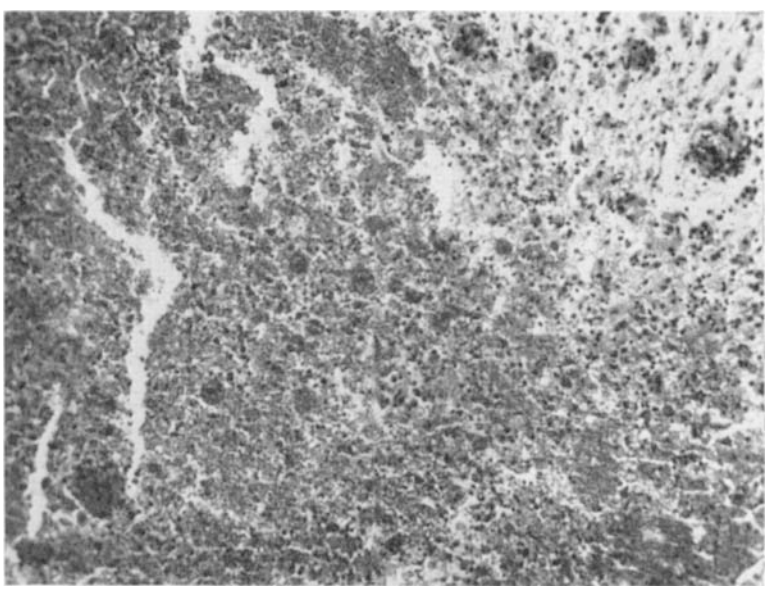

FIG. 2

Case 1. Aggregations of granular material having some resemblance to pseudocysts, but without surrounding membrane. Found in necrotic area of brain. ×125.

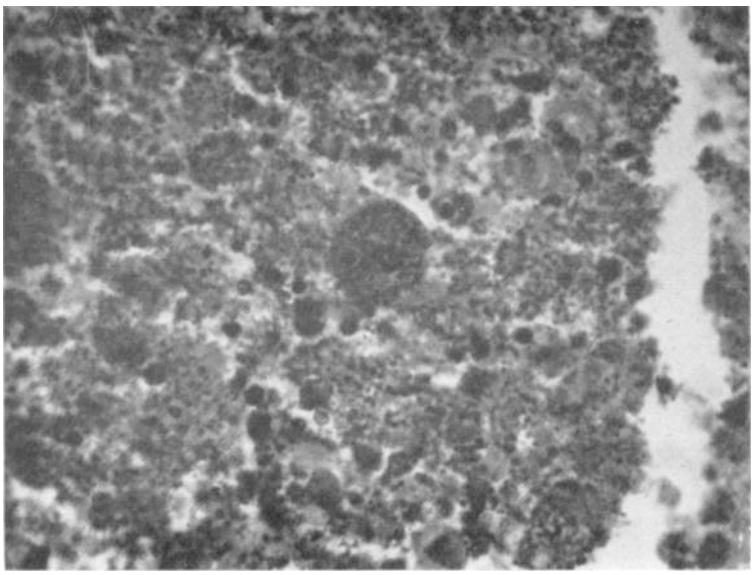

FIG. 3

Case 1. Aggregations of granular material having some resemblance to pseudocysts, but without surrounding membrane. Found in necrotic area of brain. ×600.

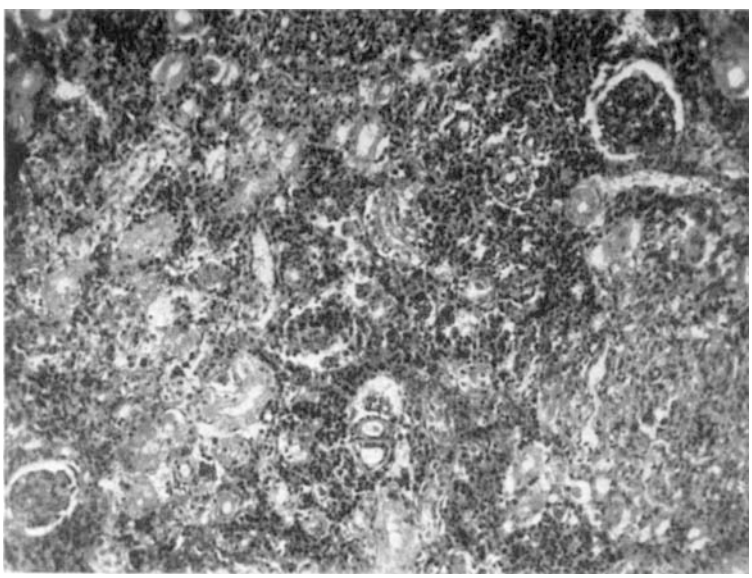

FIG. 4

Case 1. Excessive haemopoiesis in kidney. ×134.

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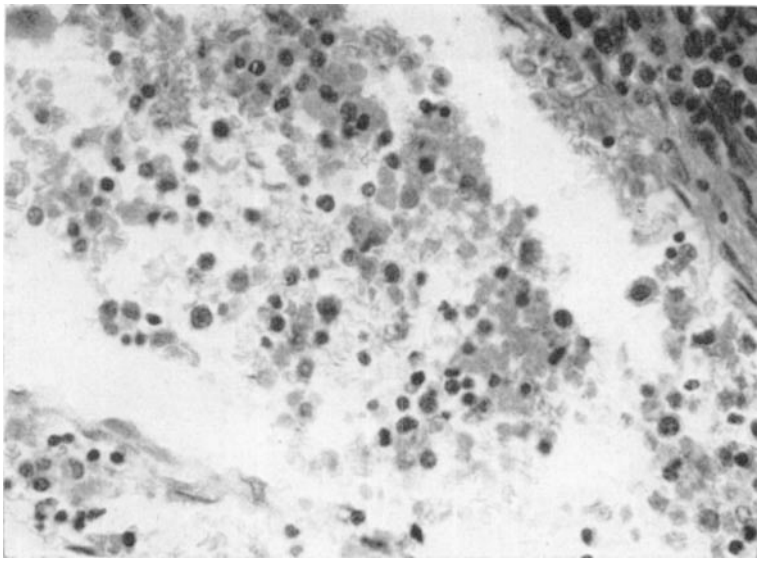

FIG. 5
Case 1. Primitive type of red cells in kidney. ×500.

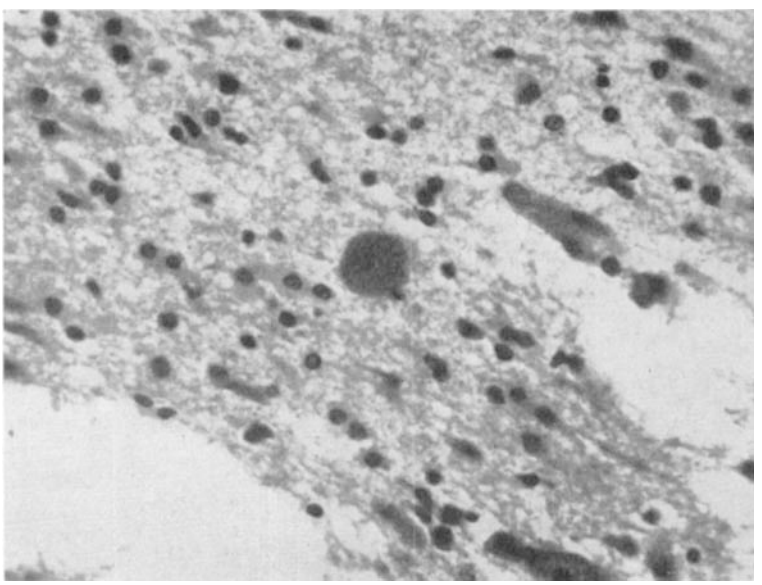

FIG. 6
Case 2. Toxoplasma pseudocysts in brain. ×550.

A.D.B., J.H.B., W.F.F., J.K.A.B., C.P.B.

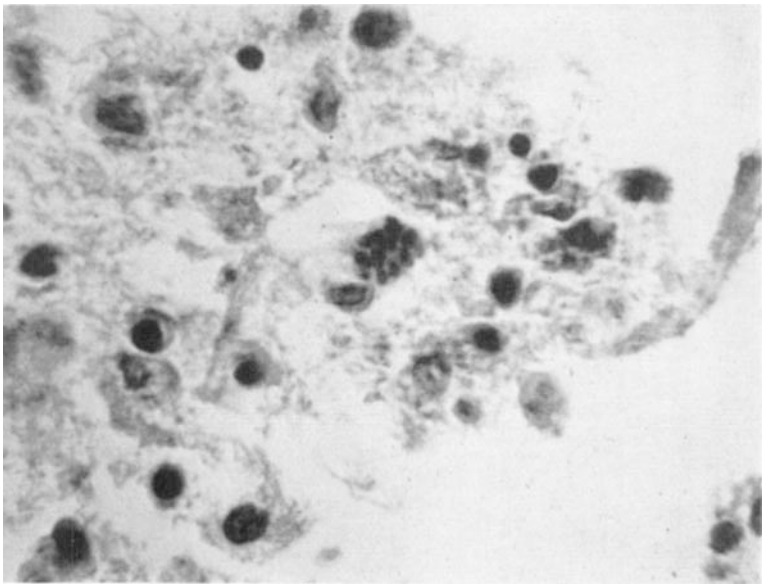

FIG. 7

Case 2. Toxoplasma terminal colony in brain. ×1,100.

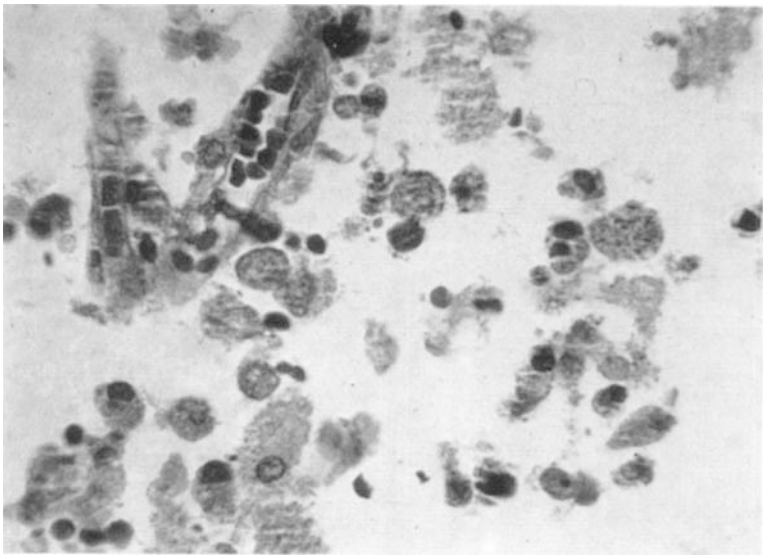

FIG. 8

Case 2. Aggregation of granular material in brain. ×600.

A.D.B., J.H.B., W.F.F., J.K.A.B., C.P.B.

and left for 102 days. Third passage from one of these resulted in death from toxoplasmosis in 10 days.

One of the original mice had a litter of four 44 days after inoculation. These were alive and apparently well 28 days later. They were then killed and one was observed to have an enlarged spleen and increased peritoneal fluid. Neither from this mouse nor its litter-mates were toxoplasms obtained.

Passage was made by the intraperitoneal route alone from the 4 mice retained in Edinburgh. Scanty toxoplasms were found in the passage mice, but two further passages were unsuccessful.

A further 3 mice were inoculated in Edinburgh on 24th December, 1954 with a suspension of the baby's brain, liver and spleen, after it had been kept at 4° C. for 16 days. Toxoplasms were found in the first passage mice inoculated from these.

Unsuccessful attempts were made to isolate toxoplasms by inoculating a suspension of the baby's brain on the chorio-allantoic membrane of fertile eggs.

*Case 3.* Baby G., born on 23rd August, 1955.

The mother's first pregnancy was in August, 1952, and resulted in abortion at 12 weeks. Her second pregnancy went to term and a normal live baby was born in February, 1954. This, her third pregnancy, resulted in the birth of a stillborn macerated foetus at 30 weeks.

Except for a slight oliguria the mother's health was good during this pregnancy.

### Post-mortem Examination

The body was severely macerated with widespread desquamation. The remaining epidermis was deep yellow, but this may have been the result of meconium staining.

When the skull was removed the underlying brain, although extremely soft and macerated, showed ill-defined, yellowish-white areas which were probably either on the surface of the brain or related to the pia-arachnoid. Nothing could be distinguished when the brain was sectioned. It was almost entirely mush. All the serous sacs contained blood-stained fluid. No abnormality was noted in the heart or lungs. The spleen, however, was found to be approximately twice the usual size.

The liver was of normal size. Neither the liver nor spleen gave the Prussian blue reaction.

No pathological changes were found in any other organ.

The placenta was not unusual in appearance.

### Histology

Advanced maceration made it difficult to detect any other change in the organs. No calcification was found in the brain.

### Serology

*Blood Grouping*

Mother: Group A Rh. negative.

Father: Group O Rh. positive (probable Rh. genotype CDe/ode).

Previous pregnancy (1954) Baby Group O, Rh. unknown. Coombs's test negative.

*Toxoplasma Antibodies*

| | Dye Test | C.F.T. |
|---|---|---|
| Mother: | | |
| 25th August, 1955 .. .. | 1/10,000 | 1/64 |
| Father: | | |
| 2nd September, 1955 .. | 1/46 | |

### Attempted Isolation of Toxoplasma

Suspensions of placenta, brain, spleen and liver were inoculated into mice and guinea pigs. Some of those inoculated with brain died a few days later of bacterial infection. The rest survived for 2 months. Their sera were then tested for toxoplasma antibodies without significant result. Failure to isolate toxoplasms is attributed to the advanced decomposition of the brain.

### Discussion

The laboratory investigations present some points of interest.

Mrs. D.'s serum dye test antibodies rose markedly in titre in the last month of her subsequent pregnancy. Vivell and Buhn (1953) claim that in 10 to 15 per cent of instances pregnancy raises an already existing titre.

The baby then born was found to have passively transferred antibodies to even higher titre than its mother, yet it was and remained perfectly well. High antibody titres alone, even if found both in mother and baby, do not necessarily indicate current toxoplasma infection.

Interesting, but not novel, is the prolonged survival of some of the inoculated animals and their giving birth to healthy offspring. One guinea pig, subsequently proved to be infected, survived for 250 days and had produced a healthy litter. So too, one of the mice had a healthy litter 44 days after inoculation, and was proved to have toxoplasmosis 39 days later. As has been shown by many workers, among them Lépine (1929) and Weinman (1943), toxoplasms may persist in mice without doing any apparent damage for long periods even for the duration of their natural lives. Still more often do they do so in the more resistant rat and guinea pig.

Surveys for antibody suggest that toxoplasma infection is not uncommon in the population of this country (Beverley, Beattie and Roseman, 1954). It is also likely that as in animals the parasite may in some cases persist for long periods. Jacobs, Fair and Bickerton (1954) isolated it from the eye of a man who gave a history of recurrent chorio-retinitis for eight and a half years. Stanton and Pinkerton (1953) found it in an enlarged cervical lymph node of a 26-year old woman who had an illness resembling toxoplasmic lymphadenopathy 5 years before. She gave birth to a healthy infant 36 weeks after the excision of the lymph node.

It would seem reasonable to expect that for a woman to infect her foetus she must have a parasitaemia while the foetus is susceptible. Generally it is assumed that this parasitaemia will be due to recent infection. Very rarely will this infection produce clinical signs in the mother. The only instance known to the authors of proven clinical toxoplasmosis in both mother and baby is reported by Alexander and Callister (1955). The mother had toxoplasmic lymphadenopathy and the baby typical congenital toxoplasmosis with hydrocephalus, enlarged spleen and liver and choroido-retinitis. In addition marked extramedullary haematopoiesis and generalized oedema were noted. Almost invariably the mother's infection will be latent. That parasitaemia can occur in latent infection has been shown by Prior, Cole, Docton, Saslaw and Chamberlain (1953), who isolated the parasite from the blood of a healthy young woman. It is, however, possible that transfer of infection to the foetus may be due not to the parasitaemia of acute infection, but to rupture of pseudocysts of chronic infection as suggested by Weinman (1952) and by Mellgren, Alm and Kjessler (1952). The difficulty in accepting the latter suggestion is that subsequent children do not have congenital toxoplasmosis.

The period during which the foetus is susceptible is probably long. It is unlikely to be in the first few weeks when the parasite would be dissolved by the enzymatic action of the trophoplast. In the case reported by Gard and Magnusson (1951) infection immediately prior to or shortly after the onset of pregnancy was followed by the birth of a healthy infant.

Infection of the mother at a somewhat later stage has led to abortion. Magnusson (1951) isolated the parasite from a foetus aborted at the third month. As the mother's dye test titre rose from 1/40 at that time to 1/250 five weeks later it is presumed that she was infected early in pregnancy. (Toxoplasmosis would not, however, appear to be a common cause of abortion. Feldman and Eichenwald (Sabin, 1953) failed to find serological evidence of current toxoplasmosis in any of 95 women who aborted.) The mother, whose case is reported by Alexander and Callister (1955) and already quoted, developed lymphadenopathy when 6-months pregnant. Heath and Zuelzer (1945) consider, on account of the nature of the eye lesions, that the twins they describe were infected not later than the seventh month of intra-uterine life. That toxoplasmosis may not manifest itself in the baby until some days or weeks after birth suggests that infection may sometimes occur in the last month of pregnancy.

There is much evidence that toxoplasma can damage the vascular and haemopoietic system, but how it does so is not clear.

Among the earliest cases reported were the 2 in adults described by Pinkerton and Henderson (1941). In these there was a rash stated to resemble that of typhus. More recently Giroud, Jadin and Reizes (1951) have produced evidence that some cases of exanthematic fever in the Congo are due to toxoplasma. In such cases, as in typhus, it is possible that toxoplasma invades the endothelial cells lining the walls of the capillaries and so produces thromboses.

Pinkerton and Henderson (1941) did, indeed, find in the brain of their cases pericapillary lesions resembling those of typhus.

In congenital cases rashes have been frequently reported: Zuelzer (1944), Callahan, Russell and Smith (1946), Wyllie, Fisher and Cathie (1950), Riley and Arneil (1950), Sabin *et al.* (1952), Hall *et al.* (1953), Magnusson and Wahlgren (1948), Beckett and Flynn (1953), and Morris, Levin and France (1955).

The rash has been variously described as purpuric, maculo-haemorrhagic, maculo-papular. Here again there may have been capillary damage or a reduction in platelets, or prothrombin deficiency. The last has been recorded by Magnusson and Wahlgren (1948) and by Gard, Magnusson, Wahlgren and Gille (1949).

Bleeding has also been reported into the skin (Smitt and Winblad, 1948), from the umbilical cord and lip (Silver and Dixon, 1954), in the stomach, intestine and lung (Callahan, Russell and Smith, 1946).

Several authors have noted a resemblance to haemolytic disease of the newborn (Callahan, Russell and Smith, 1946; Magnusson and Wahlgren, 1948; Harwin and Angrist, 1948; Neiditsch, 1951; Beckett and Flynn, 1953; Hall *et al.*, 1953), and the present authors have encountered one case the most prominent feature of which was severe thrombocytopenic purpura at one day of age.

It would be satisfactory to be able to relate this to specific damage caused by toxoplasma to the blood forming organs. The frequency of jaundice would suggest liver damage, but only rarely can evidence of this be found histologically. Nor in spite of observations of the presence of toxoplasma in bone marrow (Pinkerton and Weinman, 1940; Kabelitz, 1952; Finckh, 1954) does damage to this tissue appear to be the cause.

For the present at least it must be left as an instance (cytomegalic inclusion disease is another (Colebatch, 1955)) of extra-medullary erythropoietic activity produced by a generalized infection.

It would seem worth while to examine for toxoplasma infection cases which appear to be haemolytic disease, but in which no blood group incompatibility between mother and offspring is found. The mother's and baby's sera should be examined for toxoplasma antibodies by the dye test of Sabin and Feldman and by the complement fixation test. If the baby has died a suspension of its brain should be inoculated into mice. This should not be dismissed as impracticable because mice are not immediately available since toxoplasms survive for 16 days in brain tissue kept at 4° C.

It would be of interest and perhaps of importance to take note of any illness, however mild suffered by the mother during pregnancy. Experience at present suggests that glandular enlargement may be the commonest manifestation of acquired toxoplasmosis.

## Summary

Three cases of congenital toxoplasmosis are reported.

All three had greatly enlarged spleens; two had enlarged livers. One was macerated and another presented the picture of hydrops foetalis.

Attention is drawn to the resemblance congenital toxoplasmosis may bear to haemolytic disease of the newborn.

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## References

Alexander, C. M., and Callister, J. W. (1955): *Arch. Path.*, **60,** 563.

Beckett, R. S., and Flynn, F. J. (1953): *New Engl. J. Med.*, **249,** 345.

Beverley, J. K. A., Beattie, C. P., and Roseman, C. (1954): *J. Hyg., Camb.*, **52,** 37.

Callahan, W. P., Russell, W. O., and Smith, M. G. (1946): *Medicine*, **25,** 343.

Colebatch, J. A. (1955): *Med. J. Aust.*, **1,** 377.

Finckh, E. S. (1954): *Med. J. Aust.*, **2,** 965.

Gard, S., and Magnusson, J. H. (1951): *Acta med. scand.*, **141,** 59.

Gard, S., Magnusson, J. H., Wahlgren, P., and Gille, G. (1949): *Pediatrics*, **4,** 432.

Giroud, P., Jadin, J., and Reizes, C. (1951): *Bull. Soc. Pat. exot.*, **44,** 422.

Hall, E. G., Hay, J. D., Moss, P. D., and Ryan, M. M. P. (1953): *Arch. Dis. Childh.*, **28,** 117.
Harwin, M., and Angrist, A. (1948): *Arch. Pediat.*, **65,** 124.
Heath, P., and Zuelzer, W. W. (1945): *Arch. Ophthalmol.*, **33,** 184.
Jacobs, L., Fair, R., and Bickerton, J. H. (1954): *Arch. Ophthalmol.*, **51,** 287.
Kabelitz, H. J. (1952): *Klin. Wschr.*, **30,** 74.
Lépine, P. (1929): *C.R. Soc. Biol., Paris*, **100,** 262.
Magnusson, J. H. (1951): *Nord. Med.*, **45,** 344.
Magnusson, J. H., and Wahlgren, F. (1948): *Acta path. microbiol. scand.*, **25,** 215.
Mellgren, J., Alm, L., and Kjessler, A. (1952): *Acta path. microbiol. scand.*, **30,** 59.
Morris, D., Levin, B., and France, N. E. (1955): *Lancet*, **2,** 1172.
Neiditsch, L. (1951): *Schweiz. med. Wschr.*, **81,** 485.
Pinkerton, H., and Henderson, R. G. (1941): *J. Amer. med. Ass.*, **116,** 807.
Pinkerton, H., and Weinman, D. (1940): *Arch. Path.*, **30,** 374.
Prior, J. A., Cole, C. R., Docton, F. L., Saslaw, S., and Chamberlain, D. M. (1953): *Arch. intern. Med.*, **92,** 314.
Riley, I. D., and Arneil, G. L. (1950): *Lancet*, **2,** 564.
Sabin, A. B. (1942): *Advanc. Pediat.*, **1,** 1.
Sabin, A. B. (1953): *Amer. J. trop. Med.*, **2,** 360.
Sabin, A. B., Eichenwald, H., Feldman, H. A., and Jacobs, L. (1952): *J. Amer. med. Ass.*, **150,** 1063.
Silver, H. K., and Dixon, M. S. (1954): *Amer. J. Dis. Child.*, **88,** 84.
Smitt, O., and Winblad, S. (1948): *Acta path. microbiol. scand.*, **25,** 585.
Stanton, M., and Pinkerton, H. (1953): *Amer. J. clin. Path.*, **23,** 1199.
Vivell, O., and Buhn, W. H. (1953): *Ärztl. Forsch.*, **7,** 326.
Weinman, D. (1943): *J. infect. Dis.*, **73,** 85.
Weinman, D. (1952): *Annu. Rev. Microbiol.*, **6,** 281.
Wyllie, W. G., Fisher, H. J. W., and Cathie, I. A. B. (1950): *Quart. J. Med.*, n.s. **19,** 57.
Zuelzer, W. W. (1944): *Arch. Path.*, **38,** 1.