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EXCESSIVE PERINATAL MORTALITY IN A SMALL TOWN ASSOCIATED WITH EVIDENCE OF TOXOPLASMOSIS

BY

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During the years 1956, 1957, and 1958, large and persistent differences were noted between the perinatal mortality rates for three adjacent districts in North Lincolnshire. It was found that these differences were due to variation in the stillbirth rates. The small town of Barton-on-Humber suffered a stillbirth rate of 59.6 for the triennium (see Chart). During the same period the neighbouring town of Brigg enjoyed the exceptionally favourable stillbirth rate of 9.0, while the surrounding rural district experienced a rate of 28.1. It was found that the differences in numbers of stillbirths occurring in these districts (Tables I and II) were statistically significant ($\chi^2 = 14.98$; $P < 0.001$). This paper describes the investigations which were made in an endeavour to ascertain the cause of the excess of stillbirths experienced in Barton-on-Humber.

TABLE I.—Vital Statistics for Area

	Barton-on-Humber U.D. (Pop. 6,420)			Brigg U.D. (Pop. 4,200)			Glanford Brigg R.D. (Pop. 33,200)		
	L.B.	S.B.	N.D.	L.B.	S.B.	N.D.	L.B.	S.B.	N.D.
1956 ..	101	8	3	68	1	2	493	18	7
1957 ..	104	5	3	85	1	2	535	19	6
1958 ..	95	6	0	68	0	2	563	9	9
	300	19	6	221	2	6	1,591	46	22

L.B. = Live births. S.B. = Stillbirths. N.D. = Neonatal deaths (i.e., deaths of infants during first four weeks of life).

TABLE II.—Perinatal Mortality and Stillbirth Rates (1956-8)

	Perinatal* Mortality Rate*	Stillbirth Rate
Barton-on-Humber U.D. ..	78.4	59.6
Glanford Brigg R.D. ..	41.6	28.1
Brigg U.D. ..	35.9	9.0
England and Wales (1956) ..	39.2	22.9

* Note the perinatal mortality rate used in this table is based on stillbirths and deaths below the age of 4 weeks. It differs from the perinatal mortality rate used by the Registrar-General, which only takes account of deaths in the first week of life in addition to stillbirths.

TABLE III.—Incidence of Gross Malformation and Maceration, Glanford Brigg R.D.* November, 1958-December, 1959 (Preliminary Survey). See also Table VIII.

	Grossly Malformed	Not Grossly Malformed	Total
Macerated ..	1	5	6
Not macerated ..	5	6	11
Total ..	6	11	17

* Rural district figures included, as only one stillbirth occurred in Barton-on-Humber in 1959.

By the end of 1957 it was already apparent that the excessive mortality in Barton was unlikely to be due to chance, and a preliminary survey was begun. The county medical officer of health kindly arranged for the midwives to complete a questionnaire in respect of all stillbirths and early neonatal deaths occurring in the three county districts. From these questionnaires it soon became apparent that the foetus was either malformed or macerated in almost two-thirds of all stillbirths in the area (Table II). This suggested that the factors responsible must be non-obstetric, and any inquiry must take account of possible genetic and environmental influences if it was to be successful.

Environmental Factors

Environmental factors could be chemical, physical, or biological, and the ways in which the two towns might differ in respect of such factors were considered. Both are small market towns within 11 miles (17.7 km.) of each other. Barton is situated on the Humber bank, where the salt marshes and brackish water in old clay pits provide a breeding-ground for mosquitoes, whereas Brigg is situated 10 miles (16 km.) inland on the banks of the River Ancholme—a less favourable breeding ground. Brigg is situated on two main trunk roads and has good rail connexions, whereas Barton is not on any main route. There is a hospital at Brigg, while Barton is remote from hospital facilities. The only other obvious difference between the two towns is in the nature of the local industries. The principal industries in Brigg are fruit-canning, sugar-refining, and hosiery manufacture, while the major industries in Barton are the manufacture of bicycles, chemicals, ropes, and bricks.

Physical or toxic hazards resulting from the nature of local industries might play some part in causing differences in stillbirth rates, and could be investigated by ascertaining the nature of work done during early pregnancy. Remoteness from hospital facilities could

influence stillbirths in two ways. There might be a direct effect upon obstetric care, and there could be an indirect effect if this remoteness influenced the doctors' choice of treatment for other conditions. Drugs prescribed by doctors constitute an obvious possible source of toxic chemicals, and there is some evidence to suggest that drugs in use to-day may be harmful to the developing foetus. Allison McDonald's (1958) observation that there was a significant excess of severe congenital malformation in babies born to women with active or quiescent tuberculosis as compared with babies of mothers with arrested disease might reflect a toxic effect of anti-tuberculosis drugs. McCreary's (1959) assertion that overdosage of pregnant women with vitamin B₆ and with vitamin D leads to increased incidence of congenital abnormalities, and that the administration of cortisone to pregnant experimental animals caused a vast increase in the incidence of malformations, lends further support to this hypothesis. It was felt that inquiry into all drugs prescribed during gestation might indicate if such a factor was operative. Dental anaesthesia and treatment, and exposure to x-rays, were also included for investigation.

Genetic factors are more difficult to investigate; but it was felt that, whether dominant, recessive, or multifactorial, they would result in a tendency for more than one foetus to be affected in the large families. An indication of this might therefore be gained from the obstetric histories. Stillbirths occurring in families of consanguineous parents would be suggestive of recessive inheritance. The fact that the stillbirth rate was higher in a town the size of Barton than in the surrounding small villages with their more inbred populations suggested that the cause was unlikely to be genetic.

The most hopeful line of inquiry was felt to be investigation of biological factors. Rubella and syphilis are known to be capable of harming a foetus, and Coffey and Jessop (1959) have demonstrated some correlation between history of influenza and the incidence of congenital malformation. No disease was known to be more prevalent in Barton-on-Humber than in Brigg at this time, and it seemed unlikely that any of the respiratory or E.C.H.O. virus infections could cause so localized an outbreak of such long duration. It seemed that the most probable biological agent would be an infection whose rate of spread was slow, and which was either symptomless or which produced vague or minor illness of a type seldom recognized. Brucellosis and toxoplasmosis were thought to fulfil these criteria.

Routine milk-testing had shown that cattle in the area were excreting *Brucella abortus* on a number of occasions during the years in question. Investigation of this disease was therefore deemed worth while. Toxoplasmosis had been shown by Beattie (1957) to be prevalent in Lincolnshire. His survey of blood donors in small towns and rural areas of Lincolnshire showed that in Brigg, where the stillbirth rate was 9.0, only 10% of blood donors had positive dye tests at a titre of 1/16, whereas 27% of blood donors from Brigg Rural District had positive dye tests. As the stillbirth rate for Brigg Rural District was 28.1 it appeared that stillbirths and toxoplasmosis might well be related.

On inquiry it was found that the dye-test survey had not included Barton-on-Humber, and that the specimens from Brigg rural area did not represent all parishes. Professor Beattie kindly proffered his help in investigating this problem. He offered to perform toxoplasma

dye tests on blood from mothers of stillbirths, "control" mothers of live babies, and expectant mothers. He also agreed to carry out brucella agglutination tests on these blood specimens, and to do toxoplasma dye tests on blood from donors in the Barton area. Only the retrospective part of the investigation is included in this paper.

Method and Materials

The 19 women who were resident in Barton-on-Humber and had stillborn babies during 1956, 1957, and 1958 were identified and traced. For each of these women two "control" mothers of live babies born in the same month were selected. The method of selection was to ascertain whether the stillbirth had occurred in hospital or at home, and to take the two live births which were comparable in this respect and were nearest in time to the stillbirth. Only one control was used for each stillbirth. The "spare" one was used only where the first control had left the district or gave a history of previous stillbirth. The elimination from the control group of mothers who had suffered previous stillbirth was felt to be desirable, since such stillbirths might have been caused by the same factor as those under investigation. Only one was discarded on these grounds. Since none of the women whose stillbirths were to be investigated gave a history of previous stillbirth, it was thought that this would not result in bias.

A questionnaire was designed to obtain information regarding past obstetric history, consanguinity between parents, occupation of father, and details of work outside the home, illnesses during pregnancy, dental treatment, anaesthetics, x rays, medical treatment, recreational habits, and contact with animals, in addition to details of the pregnancy under review.

Each woman was interviewed by me, and the questionnaire was completed. A specimen of 10 ml. of blood was then taken and sent in a plain tube to Professor Beattie for dye testing and brucella agglutination. Questionnaires were then sent to the general practitioners, who were asked to supply details of all drugs prescribed for these women during the period of gestation, and to give details of all diagnoses made. Details of the confinement were obtained from the midwife or doctor in attendance, or from hospital records. Records of blood-pressure readings and of urine tests during the antenatal period were obtained from both doctor and midwife independently.

Observations

The "control" and "stillbirth" groups were first compared in respect of age and parity. Concordance in these respects, though not perfect, was found to be tolerably good (Table IV).

Only two of the mothers of stillbirths undertook paid employment outside the home during the period of gestation, whereas five of the "control" mothers did so. The two who did work were a school teacher and an office worker, and both ceased work at the fourth month of pregnancy. It was possible, therefore, to eliminate industrial hazards as a cause of the high stillbirth rate.

No big discrepancies were noted between the two groups in relation to dental treatment, anaesthetics, exposure to x rays, minor illnesses, or illnesses for which the women consulted their doctors (Table V). It was found that in relationship to illnesses, however, the memories of the women proved unreliable. A number

TABLE IV.—*Maternal Age and Parity at Confinement*

	Age in Years			Parity								
	20-29	30-39	40-49	1	2	3	4	5	6	7	9	11
Stillbirths	11	7	1	4	6	4	1	2	1	—	1	—
Control	10	9	0	5	6	1	4	—	1	1	—	1

TABLE V

	Mother at Work Outside Home	Dental Treatment	Dental Anaesthetic		Exposure to X rays	No. of Mothers who had Minor Illness (Unreated)	No. of Mothers Claiming to have Received Treatment from Doctor	No. of Patients for whom Drugs were Prescribed by G.P.
			Gas	Local				
Stillbirths	2	4	2	1	2	7	8	11
Control	5	5	3	1	1	5	7	10

who were unable to remember receiving medical treatment from their general practitioner were shown, on the record of drugs administered by the doctors, to have received treatment. In the case of some others who thought the doctor had treated them, there was no entry in the medical records at the doctor's surgery to support this. It is probable that the answers to the questions on minor illnesses, insect bites, etc., are equally unreliable.

From the doctors' records of drugs prescribed it was found that of the 17 mothers of stillbirths on whom information was available, drugs had been prescribed for 11, whereas of the 17 control mothers on whom such reports were obtainable, 10 had been treated. No single drug was prescribed for more than four patients in either group. The most frequently prescribed drug was phenobarbitone, which was taken by four women in each group.

Hypnotics, alkalis, and antipyretic analgesics were prescribed more often for the mothers of stillbirths than for the control mothers (Table VI). In each case the numbers involved are small and there is no indication that any drug was the cause of stillbirth. The biggest differences were: three mothers of stillbirths took magnesium trisilicate, compared with none of the controls; three mothers of stillbirths took amylobarbitone sodium, compared with none of the control mothers. It is felt that differences in drugs prescribed are more likely to reflect the symptomatology of the disease responsible than to be the cause of the stillbirths. The excess of hypnotics and analgesics suggests that a disease causing vague symptoms for which no cause could be found, and for which a neurotic cause may have been suspected, might have been responsible.

None of the women were blood relations of their husbands, and none of the mothers of the stillbirths gave

TABLE VI

	Hypnotics				Alkalis			Antipyretic/Analgesics			
	Phenobarbitone	Amylobarbitone Sodium	Pot. Brom.	Chlorpromazine	Mag. Trisil.	Other	Total	Aspirin	A.P.C.	Pannodol	Total
Stillbirths	4	3	1	1	9	3	1	1	2	0	3
Control	4	0	0	0	4	1	4	0	0	1	1

a history of previous stillbirths. Three have a history of previous abortion, and among the control group there were two with such a history. One mother who had a stillborn baby had lost a former child seven months after birth as a result of hydrocephaly. Two of the mothers of stillbirths were sisters. Both the latter women had moderately high titres to the toxoplasma dye test, and both had titres of 1/160 to the brucella agglutination test.

The sister-in-law of these two women—wife of their brother—had produced a stillborn baby during 1955. It is therefore possible that a genetic factor might have been concerned in these instances, but the evidence is equivocal and no other evidence of a genetic cause was found.

Six of the stillbirths presented as breeches, compared with only two among the controls. One of the latter was treated by external version and delivered as a vertex. Two from the stillbirth group were "transverse lies." One was treated by internal version and delivered as a breech, the other was treated by caesarean section as labour was obstructed by a large fibromyoma which completely filled the pelvis. One of the stillbirths was the result of ante-partum haemorrhage due to marginal placenta praevia, and one of the controls was a persistent occipito-posterior which was treated by manual rotation and application of forceps. The remainder were normal deliveries.

Seven of the mothers of stillbirths had some degree of toxæmia of pregnancy, compared with four of the controls. Two of the toxæmic mothers gave birth to hydrocephalic stillborn infants.

TABLE VII.—*Incidence of Titres of Cytoplasm Modifying Toxoplasma Antibody*

Dye Test Result:	—	+1/4 —1/8	+1/8 —1/16	+1/16 —1/32	+1/32 —1/64	+1/64	Total
Stillbirths	0	1	3	2	7	6	19
Control	6	4	3	2	3	1	19

The serological findings are shown in Table VII. Regrettably, brucella agglutinations were not performed on some of the "control" bloods; but, since only two of the stillbirth group had positive tests, brucellosis can safely be eliminated as a major factor in causing the excess of stillbirths.

It can be seen from Table VII that the distribution of dye-test titres for toxoplasmosis varies greatly between the stillbirth and control groups. Most of the blood specimens from mothers of stillbirths were positive at titres above 1/32, whereas most of the "control" bloods were negative at 1/16. These differences are statistically significant. χ^2 (using Yates's correction) is 6.80 ($0.01 > P > 0.001$) when the test is done comparing the numbers giving positive and negative tests at titres of 1/16 and 1/32.

It will be seen that there is an excess of nine women with dye-test titres above 1/32 in the stillbirth group. Most of the toxoplasma-dye-test titres were very much lower than one expects to find shortly after an acute infection. As the tests were performed from one to four years after the pregnancies, during which infection was suspected, very high titres were not expected. In the stillbirth group the six highest were 1/600, 1/320, 1/110, 1/78, and two at 1/64. In the control group one woman had a titre of 1/8,000 and there were two with titres of 1/48, one of 1/32, and two of 1/18. The

woman whose titre was 1/8,000 had her blood taken for test on December 1, 1959. She had her last baby in March, 1957. Slight symptoms during the summer of 1959 may have been due to infection at this time.

Discussion

Since foetal mortality is higher in breech deliveries than in normal confinements, any series of stillbirths is likely to show a higher incidence of breech presentations than would be found in a control series. Only one of the stillborn breeches in this series was a domiciliary confinement; the rest were delivered in the same hospitals which serve the other two areas. The proportion of breeches is double that found in the series of stillbirths from the rural district on which reports were obtained. This suggests that during the years in question there was a real increase in incidence of breech presentations in women resident in Barton-on-Humber. Such an increase could be caused by any factor which altered the relative proportions of the foetal head and the available space in the maternal pelvis. Any condition which renders the foetal head larger or smaller than normal, or which causes a space-occupying lesion within the mother's pelvis, would tend to prevent "fixing" of the foetal head and predispose to malpresentation. Since congenital toxoplasmosis is stated by Feldman and Miller (1956) and Feldman (1958) to cause hydrocephaly in 22% of cases and microcephaly in a further 21%, a high incidence of malpresentation could well be caused by this condition. Three of the six breech stillbirths in this series were not due to obstetric factors, for one was both macerated and hydrocephalic, another was macerated, and the third was hydrocephalic. Such cases could well be caused by a disease such as toxoplasmosis.

In only 3 of the 19 stillbirths is it possible to state the cause with any certainty. In one case the foetal heart stopped after the mother was injured in a fall at the 27th week of pregnancy. Three weeks later she went into labour and was delivered of an immature macerated foetus. In another patient the transverse lie of the foetus was due to a large fibromyoma which filled the pelvis and to which a low-lying placenta was adherent. In this case labour was obstructed by the fibroid and caesarean section was necessary, though the baby was already dead. In a third case there was a placenta praevia and the cord encircled the baby's neck.

Though toxæmia was more frequent in the stillbirth group the difference in incidence was not significant ($\chi^2=0.50$; $0.5 > p > 0.3$). All the toxæmic mothers in both groups had positive dye tests.

The most notable difference between the two groups was in respect of toxoplasma-dye-test titres. Since this was the only difference between the groups that was statistically significant it is necessary to consider the hypothesis that some of the stillbirths might have been caused by this disease.

Though Nicolle and Manceaux (1908) described *Toxoplasma gondii* over 50 years ago, it was not until 1939 that Wolf, Cowen, and Paige proved by isolating the parasite that it caused congenital disease in man. Since then a great many cases have been described by these and other workers. Congenital toxoplasmosis may vary in severity between infections so severe as to result in stillbirth, and infections so mild that the baby appears normal at birth, but develops symptoms subsequently. Sabin (1942) described the syndrome of hydrocephaly or

TABLE VIII.—Incidence of Hydrocephaly and Maceration (Barton-on-Humber, 1956-8)

	Hydrocephaly	Not Hydrocephalic	Total
Macerated ..	2	8	10
Not macerated ..	2	7	9
Total ..	4	15	19

microcephaly, chorioretinitis, convulsions or other neurological signs, and cerebral calcifications, but any of these may occur alone, the commonest manifestation being chorioretinitis. Another manifestation of the disease is recorded by Bain *et al.* (1956), who describe three cases with features resembling haemolytic disease of the newborn. Two of these were stillborn, the third dying soon after birth.

It thus appears that stillbirth may be caused by toxoplasmosis, either primarily as a result of the infection or secondarily as a result of obstetric difficulty due to hydrocephaly or malpresentation. Consequently the finding of a significant excess of toxoplasma-dye-test titres in mothers of stillbirths (Table VII) supported by a relatively high incidence of hydrocephaly (Table VIII) suggests that toxoplasmosis may have caused a proportion of these stillbirths.

Before this hypothesis can be accepted it is necessary to consider whether the dye-test titres observed are compatible with infection at the time of the pregnancy in question. This involves consideration of: (a) the date when maternal infection must have occurred; (b) the rate of rise and fall of dye-test titres after adult infection; and (c) the interval between the confinement concerned and the taking of blood samples for testing.

It is believed that congenital toxoplasmosis results from primary maternal infection during the period of gestation. Parasites disseminated through the body by the blood form small lesions in maternal tissues. Such a locus of infection in the placenta may infect the foetus. Beckett and Flynn (1953) have demonstrated the presence of parasites in a human placenta.

Congenital toxoplasmosis is stated not to occur in Tahiti (Feldman, 1956), where the infection is so prevalent that three-quarters of the population have acquired antibodies by the age of 9 (Feldman, 1953). This suggests that only people without antibodies are at risk, and that the presence of even a low titre of antibodies to the dye test indicates safety from blood-borne dissemination and consequent foetal infection.

Maternal infection in the first trimester of pregnancy is not invariably followed by foetal infection. Gard and Magnusson (1951), Stanton and Pinkerton (1953), and Holmdahl (1953) record instances of maternal infection at this stage which did not affect the foetus. Siim (1956) and Beckett and Flynn (1953), however, record cases of maternal lymphadenopathy in the third month of pregnancy followed by foetal infection, so even as early as this maternal infections are not devoid of risk. There is no record of maternal infection during the latter six months of pregnancy, in which the foetus was not affected. It is thought, however, that for stillbirth to result the infection must have taken place at least a month prior to delivery, and the most probable date for maternal infection would lie between eight months and one month before confinement. The interval between date of confinement and date of blood-sampling in this investigation ranged from 10 to 44 months. Thus if toxoplasmosis were responsible for any of these

foetal deaths the maternal infection must have taken place from 11 to 52 months before the serological investigations.

Serial dye test estimations on women who have borne affected children, cases of active toxoplasmosis, and women found to have high titres during an antenatal survey have been recorded by Holmdahl (1953), Feldman and Miller (1956), Makstenieks and Verlinde (1957), Beverley and Beattie (1958), Beattie (1958, 1960, personal communication), and others. From these it is apparent that after infection titres rise over a period of a few months to very high levels—of the order of 1/10,000—remain there for a short time and then fall. The fall is rapid at first and then becomes much slower, low titres persisting for many years. The rate of rise and fall is very variable. Titres of from 1/128 to 1/1,024 might be expected 11 months after infection, while four years after infection they would be between 1/16 and 1/256.

The excess of titres between 1/32 and 1/600 observed in the mothers of stillbirths in this series is therefore compatible with the theory that primary maternal infection took place during the period of gestation, and some of the stillbirths could therefore have been caused by toxoplasmosis.

All the serological tests were performed during the last four months of 1959. Consequently the interval between probable date of infection and the date of testing would be longest for the 1956 stillbirths and least for the 1958 cases, if toxoplasmosis were indeed responsible. This suggests a way in which the hypothesis may be tested, for if it were correct one would expect the titres for the 1956 cases to be the lowest and the 1958 cases to be highest. Because very recent infections give rise to extremely high titres, the use of an arithmetic mean would be misleading. An infection occurring subsequent to delivery in a woman whose stillbirth was due to some other cause would seriously affect this type of average. The median, however, is free from this form of bias.

As Table IX indicates, the median dye-test titres follow the pattern which one would expect if the theory that toxoplasmosis caused a proportion of the stillbirths were correct. It is impossible, in a retrospective investigation of this kind, to prove that toxoplasmosis was responsible for any particular stillbirth in the series. A statistical association such as this could result if toxoplasmosis and the true cause of the stillbirths were both related to a third factor, such as a common means of transmission. Nevertheless, the most probable explanation of the facts observed in this investigation is that toxoplasmosis was responsible for a proportion of the stillbirths. In assessing how many of the stillbirths may have been due to this cause, one must take into account the effect of the delay between confinement and blood-sampling as well as the differences in distribution of dye-test titre. If antibodies do in fact protect against infection there will be a greater risk of infection developing subsequent to confinement in the group with the higher proportion of negative dye-test reactors. Consequently a survey done some years after confinement may underestimate the differences between the two groups.

TABLE IX

Year of occurrence of stillbirth	1956	1957	1958
Median toxoplasma-dye-test titre	1/30	1/43	1/64

This appears to have occurred in this series, for a control mother whose baby was born in 1957 was found in December, 1959, to have a dye-test titre of 1/8,000. She gave a history of vague ill-health during the summer of 1959, which may have been related to her infection. Thus, though the excess of high titres in the stillbirth group is only 9, it is likely that a difference of 10 would have been observed had the tests been carried out a year earlier.

Since high titres fall rapidly and low titres persist for years, differences between two groups in incidence of high titres would be reduced by the passage of time even if no further infections occurred. For this reason also one would expect a survey undertaken some years after the confinements to underestimate the differences. It is therefore suggested that 10 of the 19 stillbirths may well have been caused by toxoplasma infection.

It will be seen from Table X that the distribution of dye-test titres in the control group does not differ greatly from what would be expected in a rural community on the basis of Professor Beattie's survey of blood donors in Lincolnshire (Beattie, 1957, 1959). The slight excess of positive reactors as compared with that expected in an urban community is in keeping with the theory that there may have been an epidemic of toxoplasmosis in Barton-on-Humber during the three years 1956–8. The controls appear likely to be representative of the community in respect of incidence of toxoplasma antibodies. Accepting this, it was found that even if only 11 instead of 13 of the mothers of stillbirths had shown positive dye tests at 1/32, the differences between the two groups would still have been significant at the 5% level ($\chi^2=3.96$). Thus it is unlikely that the number of stillbirths due to toxoplasmosis is lower than 3.

TABLE X

Test Titre	Expected* No.		Observed No. Barton Controls
	Urban Rate	Rural Rate	
Negative at 1/8 . . .	13	10	10
Positive at 1/8, negative at 1/16 . . .	2	2	3
.. .. 1/16, 1/32	2	2	2
.. .. 1/32, 1/64	1	3	3
.. .. 1/64	1	2	1

* Derived by applying the rates observed by Beattie (1959) in blood donors in Lincolnshire to the number (19) of cases in survey and correcting to the nearest whole number.

In the past toxoplasmosis has not been regarded as a significant cause of stillbirths. None of the 633 stillbirths and neonatal deaths resulting from the 23,260 confinements investigated by Holmdahl (1953) in Goteborg between 1948 and 1951 showed evidence of toxoplasmosis, and only two cases of congenital disease were discovered. However, the perinatal mortality rate derived from Holmdahl's figures is only 27.2, compared with the figure of about 40 for England and Wales at that period. It would appear that Holmdahl was doing this work at a time when the disease was not prevalent in Goteborg. Such investigations in other areas, where the perinatal mortality rate is high, might well show a different result.

A more extensive investigation of all pregnancies occurring in the three districts of Lincolnshire during 1960 is at present in progress. It is hoped that this will prove whether toxoplasmosis is still a significant cause of stillbirths in the district. In addition, an attempt is being made to examine all the 300 children who were born in Barton-on-Humber during 1956–8, in order to

detect and treat any congenital infection. Confirmatory evidence that toxoplasmosis has been unusually prevalent in Barton-on-Humber may be obtained as a result of this work.

Conclusions

The most probable cause of the difference in incidence of stillbirths between the three districts of north Lincolnshire is infection with *Toxoplasma gondii*. Of the 19 stillbirths which occurred in Barton-on-Humber at least 3, and possibly as many as 10, are likely to have been due to toxoplasmosis. In only three cases could another cause for the stillbirth be definitely established, and the dye-test titres of two of these three mothers were among the three lowest titres observed in the series. The high incidence of malpresentation in Barton-on-Humber during this time could be due to toxoplasmosis, there being evidence in three out of the six breech presentations that the foetus was already dead or deformed prior to the onset of labour. If 10 of the 19 stillbirths were due to toxoplasmosis the remaining nine due to other causes would represent a rate of 28.2. This is still higher than the rates for England and Wales, but the difference is not significant.

Summary

Significant differences in perinatal mortality among three areas of Lincolnshire over a three year period are shown to be due to variation in stillbirth rate. Investigation of possible causes of this showed that there was a significantly higher incidence of cytoplasm-modifying antibody to *T. gondii* in the women whose babies had been stillborn, when compared with a group of mothers who had been delivered of live babies in the same month and in the same place. The two groups did not differ greatly in age, parity, or in any other respect. The hypothesis that toxoplasmosis may have been the cause of these stillbirths is discussed.

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FULMINATING ULCERATIVE COLITIS RECENT EXPERIENCE IN MANAGEMENT

BY

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During the last few years new surgical and medical measures have become available for treating very severe acute episodes of ulcerative colitis. Some experience has now been gained in the use of these measures, and the time seems opportune for a review of some of the results obtained so that recommendations can be made for the future. We have studied the results of different treatments in a group of patients with very severe acute "fulminating" colitis and have tried to answer three questions: (a) Can treatment with corticotrophin or cortisone induce a remission in a "fulminating" episode of colitis? (b) When should surgical treatment be undertaken and what operation should be performed? (c) Does previous treatment with corticotrophin or steroid drugs influence the outcome of surgical treatment in these patients? Because "fulminating" episodes of colitis are uncommon and because the early years of treatment with steroid drugs have necessarily been exploratory, some of our conclusions can only be tentative, but from them we suggest a course of action for trial in the future.

Selection of Cases

Our aim has been to study a group of the most severe cases of ulcerative colitis seen at St. Mark's and the Central Middlesex Hospitals from 1951 to 1959. As we wished to select cases of acute colitis, we have not included in the series patients ill with serious metabolic disturbance, haemorrhage, or perforation of the colon, unless these complications were preceded by a severe exacerbation of the disease. Our selection has been made on account of the severity of the illness and without reference to the treatment given or its outcome. A definition of fulminating colitis has been impossible to achieve. No group of criteria adequately defines the severity of the illness. For example, neither fever nor tachycardia is adequate as a criterion, because three of our patients were critically ill with a high fever but a pulse rate less than 120 a minute, two were apparently overwhelmed by the illness with a pulse rate consistently above 150 a minute but with slight