ON THE RELATIONSHIP BETWEEN MATERNAL CONDITIONS DURING PREGNANCY AND CONGENITAL MALFORMATIONS

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Introduction

Recently there has been an increased interest in the etiology of congenital malformations, and some fundamental clinical and experimental contributions to mammalian teratology have been made which indicate that developmental abnormalities may represent something more than unavoidable accidents of nature.

According to general theories, intra-uterine development is determined by the interaction between inherited principles in the foetus and environmental conditions which surround and act upon it. The question has repeatedly arisen as to whether congenital malformations are due mainly to inherited factors present in the germ cell or whether some of them may be considered as possible products of environmental influences. Most studies in human genetics have, until recently, not taken into consideration the full significance of environmental factors in the etiology of congenital malformations, although this question has been discussed in the past. It is thus remarkable that as long ago as 1902 Ballantyne made the following statement: 'There is good reason for believing that malformations and monstrosities are the product of morbid agents acting during the embryonic period.' Since that time considerable research has been done in this field, and we are now able to distinguish several environmental factors which, besides the genetic ones, play a certain role in the pathogenesis of congenital abnormalities.

A. Age and Parity of the Mother

These are two environmental factors which lend themselves readily to statistical investigations. For instance, it has been established by a large number of observers that mongolian idiocy is closely associated with advanced maternal age (Shuttleworth, 1909; Shrubshall, 1925; Penrose, 1932; Lahdensuu, 1937; Bleyer, 1938; Ingalls, 1947). The theory has, therefore, been advanced that

mongolism is to some extent a result of changes of foetal environment due to this state. Advanced age of the mother has also been shown to be a factor in other congenital malformations, such as anencephaly, spina bifida, and congenital hydrocephaly (Malpas, 1937; Penrose, 1946a). In one series of 570 families with children showing various congenital abnormalities, Murphy (1936) reported that the mean maternal age at the time of birth of the first malformed child was 28.4 years, the corresponding age at the birth of the first normal child being 23 years.

Some authors have noticed that certain abnormalities appear more often in the first-born than in subsequent pregnancies. Still (1927), for instance, reported the well-known fact that a large proportion of children with pyloric stenosis are first-born, and suggested that the same is probably true for some other abnormalities. Primogeniture also is shown to be of possible etiological significance with regard to anencephaly, spina bifida, and congenital hydrocephaly (Malpas, 1937; Penrose, 1946a). On the other hand, some malformations tend to occur more often in later born children than in earlier siblings. Certain forms of mental deficiency, most notably mongolian idiocy, seem to come into this category (Penrose, 1934). Malpas (1937) reported in a study of 294 children with various congenital malformations born at the Liverpool Maternity Hospital that 70 per cent. of the children with cleft palate and harelip were born to multiparae in contrast to an average of multiparae in the whole hospital population of 54 per cent. In a similar study of 582 malformed children in whom hydrocephaly and spina bifida were represented in nearly one-half of the cases, Murphy and Mazer (1935) concluded that congenital abnormalities occurred more frequently in later than in earlier pregnancies.

B. Maternal Infectious Diseases

It has long been recognized that maternal infectious diseases during pregnancy may occasionally be transmitted to the foetus. Foetal variola, for instance, had been described already in 1702 by

Düttel. Similar observations on the intra-uterine transmission of malaria, yellow fever, and relapsing fever have been made in the past by Russell (1800), Finlay (1894), and Albrecht (1884). It has also been noticed that severe maternal infections during pregnancy are likely to cause death of the foetus. Thus, observations during the severe epidemic of influenza in 1918 indicated that about 30 to 50 per cent. of the mothers who contracted this disease during pregnancy lost their babies as abortions, stillbirths, or neonatal deaths (Bland, 1919; Harris, 1919).

In the past, some authors observed that infants of women who had suffered from infectious diseases during pregnancy sometimes exhibited anomalies of structure or actual malformations. Maternal syphilis is one of the first diseases to which has been attributed a teratogenic effect on the foetus. Thus Fournier (1898), in an extensive paper on syphilis, stated that the disease in pregnant women might cause malformations of the foetus such as harelip, cleft palate, spina bifida, and congenital heart disease. In recent times, some authors, especially in France, have attributed to this 'théorie syphilitique' an important role in the etiology of congenital abnormalities (Paucot et al., 1946). They reported a series of 109 children with congenital malformations, and considered that syphilis was a causative factor in 45 per cent. of the cases. There was, however, no information as to the incidence of this disease among mothers with normal children. Several authors, on the other hand, have not been able to establish any significant relationship between syphilis and congenital malformations (Clark, 1932; Murphy, 1937; Dogramaci and Green, 1947; and others).

The rare occurrence of congenital tuberculosis has been known since Charrin (1874) first published a case. Since then some authors have described solitary cases and have pointed out a possible relationship between maternal tuberculosis and certain congenital malformations in the foetus, such as deformities of the limbs, congenital heart disease, and actual monstrosities (Sarwéy, 1892;—Hanot, 1896; Kleim, 1899; Ballantyne, 1899, 1902). In recent times Murphy (1947) reported a series, comprising 109 malformed children, among whose parents pulmonary tuberculosis was detected in sixteen instances.

A supposedly benign disease, previously considered too slight in its effect on the mother to cause any influence on foetal health, suddenly assumed a more serious significance when Gregg (1941) reported the relationship between rubella in pregnant women and congenital malformations in the foetus. As evidence accumulated, a number of defects such as microcephaly, cataract, congenital heart disease, and deafness appeared to be directly attributed to the occurrence of rubella during pregnancy. Up to the present time about six hundred cases of congenital malformations associated with maternal rubella have been published. Extensive surveys on

this subject have recently been given by Swan and Tostevin (1946), Aycock and Ingalls (1946), Murphy (1947), and Wesselhoef (1947). Swan and his collaborators stated that when a woman contracts rubella within the first two months of pregnancy the chances of her giving birth to malformed children are about 100 per cent., and in the third month they are about 50 per cent. It is still possible that the child will present abnormalities even if rubella is contracted after the first trimester of pregnancy. There are, however, several observations suggesting that rubella during pregnancy is not associated with congenital malformations of the foetus as frequently as was thought. In America, Fox and Bortin (1946) reported that among eleven women who contracted rubella during pregnancy, nine being during the first four months of gestation, only one gave birth to a malformed child. In a similar study, Aycock and Ingalls (1946) observed that one in four pregnancies resulted in a defective child. Clayton-Jones (1947) has made enquiries in schools for deaf children in Manchester and has discovered a history of maternal rubella during pregnancy in about 11 per cent. of the cases. The time of the birth of these children corresponded with the large epidemic in 1940 of rubella in Manchester. A second epidemic in 1941 did not show a corresponding rise in the incidence of congenital malformations. Recently Grönvall and Selander (1948) have collected data about the occurrence of various virus diseases during pregnancy among 24,519 women in Sweden. In twenty-six cases a history of rubella, mostly within the first four months of gestation, was obtained. However, only one mother gave birth to a malformed child.

The possibility has been discussed whether the originally reported disease in Australia really was rubella or whether it was an unusually severe form of the disease (Parsons, 1946, and others). Although no definite answer has so far been obtained upon this question, the combined observations in this field indicate that environmental factors are involved in the etiology of the prenatal 'rubella syndrome.'

The established relationship between rubella and congenital malformations has given rise to the question as to what extent acute infectious diseases in general may be a primary cause in the etiology of these abnormalities. However, investigations dealing with this subject are very few. Albaugh (1945) described a child with congenital cataract, whose mother had contracted measles during pregnancy. Solitary cases of actual malformations in association with maternal measles have been observed by Swan and Tostevin (1946) and by Dogramaci and Green (1947). The former authors also reported two cases of malformed children, whose mothers had had varicella during pregnancy. A similar case has been published by Prendergast (1946). On the other hand, Grönvall and Selander (1948) did not find malformations among thirty-one children whose mothers had suffered from measles or varicella when pregnant. Observations pointing

out a certain relationship between some other maternal virus diseases, such as poliomyelitis and mumps, and congenital malformations of the foetus, have been made by Aycock and Ingalls (1946), by Swan and Tostevin (1946), and by Grönvall and Selander (1948). Recently some authors have drawn attention to maternal toxoplasmosis as a possible cause of congenital malformations (Wolf et al., 1941; Wagener, 1944; Magnusson, 1947; Warkany, 1947).

C. Nutritional Condition of the Mother

It has long been known that foetal development in utero is particularly related to the nutritional condition of the mother. In the last world war an unusually high incidence of premature births associated with maternal starvation during pregnancy was reported by Antinov (1947) and by Smith (1947). Some authors have observed a relatively high incidence of dietary deficiency during pregnancy among mothers of malformed children (Murphy and DePlanter Bowes, 1939; Burke et al., 1943). That specific insufficiencies in maternal nutrition may produce congenital defects in the offspring is shown in the extensive experimental work by Warkany and his collaborators (1941-44). They noticed that malformations such as cleft palate and various defects of the limbs occurred frequently among the litters born to rats kept on a riboflavin-deficient diet before the first two weeks of gestation. These results have later been confirmed by Noback and Kupperman (1944). Lack of vitamin A and D in rats during pregnancy has also been associated with the occurrence of congenital malformations in their progeny (Hale, 1933, 1935; Warkany, 1943). It does not follow, however, that these experimental results obtained in animals necessarily apply to man. In fact, Brzezinski et al. (1947) did not observe an increased incidence of malformations in the children of 326 mothers who had suffered from riboflavin deficiency during pregnancy.

D. Mechanical Factors

Mechanical factors or an abnormal foetal implantation have also been suggested as possible causes of congenital malformations. von Winckel (1902) and Mall (1908) reported an unduly high incidence of malformed children in association with ectopic pregnancy. Later investigations, on the other hand, have not been able to show any significant relationship between these two conditions (Dehler, 1924; Malpas, 1937). Amniotic bands have also been considered as a cause of some congenital abnormalities (Grosser, 1938), but no satisfactory proof of their significance has been made. Browne (1934) has suggested that various congenital deformities, especially those of the limbs, could be caused by an abnormal position of the foetus in utero or by an increased intra-uterine pressure. The occasional occurrence of foetal malformations in association with placenta praevia may be of some

significance. In a survey of 4,446 children born to mothers with placenta praevia, Greenhill (1939) reported that the incidence of foetal abnormalities was approximately three times higher than under ordinary conditions. Before attaching importance to this disorder as a primary cause of congenital malformations, it is necessary to emphasize that according to Penrose (1939) hereditary factors seem to play a part in the etiology of placenta praevia.

Schröder (1938) reported that a high proportion, 27 per cent., of mothers of mongolian idiots were found to have a retroflexed or prolapsed uterus, while only 5.5 per cent. of women with normal children revealed such abnormalities. Goldstein and Murphy (1929b) on the other hand, did not observe a significant correlation between maternal pelvic disorders and foetal malformations.

E. X-ray and Radium Irradiation

In 1907 von Hippel and Pagenstecher observed that x-ray irradiation of pregnant animals could cause malformations in the offspring. Later on, x-ray and radium irradiation were used in the experimental production of malformations in animals by Hanson (1923), Bagg and Little (1924), Murphy and Renyi (1930), Hertwig (1939), Raynaud and Frilley (1943), and Warkany and Schraffenberger (1947). Two different methods have been employed. Experimental mutations can be induced by irradiating the sex glands of mature females whereupon malformations develop in the subsequent generation. Alternatively, developmental defects can be provoked by direct irradiation of the foetus itself in utero. The last method was used by Warkany and Schraffenberger in a large series of rats, and in a large proportion of the offspring marked skeletal abnormalities were found, such as cleft palate, clubbed feet, shortening of mandibles, and defects of the skull. An interesting observation was that the stage of pregnancy at which the irradiation was carried out had a decisive influence upon the type of malformation produced. Therapeutic x-ray and radium irradiation of the human pelvis are also very likely to cause malformations of the foetus (Aschenheim, 1920; Zappert, 1926; Murphy, 1928; Goldstein and Murphy, 1929a). Murphy reported a study of 106 women who had been exposed to x-ray and radium irradiation during pregnancy for various reasons; seventy-five of them gave birth to children at term, and thirty-eight of these were abnormal. Microcephaly is reported as the most usual foetal abnormality due to irradiation of the mother during pregnancy.

F. Various Foetal Environmental Factors

Our knowledge of the significance of other environmental factors in the etiology of congenital malformations is very incomplete. The dependence of reproduction upon proper co-ordinated hormonal influences has been stressed in the past. Duncan (1883) and Whitridge Williams (1909) were among

the first who noticed a high tendency of stillbirths among diabetic mothers, and a certain relationship between this disease and congenital malformations has been observed by Lecorché (1885), Skipper (1933), and by Hurwitz and Irving (1937).

The possible influence of certain chemical factors upon the reproductive ability has been discussed by various authors. For instance, frequent abortions have been noticed among women working in lead industries (Paul, 1860), and foetal malformations including skeletal deformities and heart defects have also been attributed to maternal lead poisoning (Rennert, 1881; Dogramaci and Green, 1947).

Congenital malformations have also been attributed to alcoholism in the mother (Fournier, 1898; Ballantyne, 1902; Margouliiss, 1940), but no definite proof has so far been given of such a relationship.

Finally, recent observations have shown an unusually high incidence of congenital malformations in children with erythroblastosis (Weber and Scholtz, 1939; Javert, 1942; Wiener, 1947). Javert described a series of forty-seven infants with erythroblastosis of whom ten revealed congenital malformations.

The whole matter may be summarized as follows. Various observations have shown that environmental principles play an important part in the etiology of congenital malformations. Foetal abnormalities result, but not of any characteristic type in relation to the various causes. The most important factor appears to be the stage at which foetal development is disturbed. Due to the lack of specificity of teratogenic characteristics, malformations caused by environmental agents may simulate abnormalities of genetical origin.

These observations in mammals have been supported by experiments in lower animals (Stockard, 1910, 1920) but our knowledge of the whole subject is still imperfect.

Present Investigation

The influence of maternal disorders during pregnancy on foetal development can be studied in two ways. The method usually employed is to select children with congenital malformations and to question the mothers retrospectively as to the state of their health during pregnancy. However, fallacies can easily arise in such an enquiry as it depends so largely on the subjective interpretation and memory of the mother; moreover, it lacks control.

A more reliable method is to approach the problem from the other direction with a careful review of the obstetric history of a large series of women and to follow this by a study of any foetal abnormalities which might be related.

This was the principle adopted in a recent

investigation carried out at the Obstetric Hospital and the Paediatric Department, University College Hospital in London. Its aim has been to obtain by means of comparative studies a further insight into the relationship between maternal conditions during pregnancy and congenital malformations. For this purpose data concerning the health of mothers who subsequently gave birth to malformed children have been collected from the antenatal records. This has been possible because the majority of women who attend the hospital for delivery have been followed up at the antenatal clinic from their early pregnancy. The antenatal records contain detailed information of the health of the mothers before and during pregnancy (Browne, 1946). Since 1945 the records contain a special clause referring to acute infectious diseases during pregnancy.

When interpreting the possible association between various disorders during pregnancy and congenital malformations, it has seemed necessary to investigate the occurrence of corresponding disorders under ordinary conditions. As controls 200 women were chosen at random, who during the same period gave birth to normal children in the same Department.

In comparing the results obtained in the two groups current statistical formulae have been employed (see Appendix).

Results

Information has been collected about seventy-three malformed children who were born during the years 1945-48 in this hospital. During this period the total number of deliveries amounted to 3,593, showing an incidence of children with malformations of about 2 per cent., a figure which corresponds on the whole with observations made in other hospitals (Naujoks, 1938; Malpas, 1937; Tholen, 1946).

It is well known that congenital malformations are often multiple. For the sake of clarity the cases under consideration have been classified under the chief malformations present (table 1).

It will be seen that malformations of the central nervous system were the most common (eighteen cases). Deformities of the limbs came next in frequency and consisted mainly of clubbed feet and solitary cases of anomalies of fingers and toes. A miscellaneous group has been included consisting mainly of deformities of the visceral organs and abnormalities of the skin.

Maternal age. The mean age of the mothers of malformed children was 28.6 years, the corresponding figure for the mothers in the control group being 26.5 years. The value for $t(5.0)$ gives a significantly positive correlation between advanced maternal age and the occurrence of congenital malformations in these studies.

TABLE 1

AGE AND PARITY OF SEVENTY-THREE MOTHERS WITH MALFORMED CHILDREN AND OF TWO HUNDRED MOTHERS WITH NORMAL CHILDREN

	Chief malformations of the children	No. of cases	Maternal age						Parity				
			15-19	20-24	25-29	30-34	35-39	40-44	0	1	2	3	4-5
Age and parity of 73 mothers with malformed children.	Anencephaly	12	—	4	6	2	—	—	8	2	1	—	1
	Spina bifida	6	—	1	2	2	1	—	5	—	1	—	—
	Mongolism	4	—	—	—	1	2	1	2	1	—	1	—
	Deformities of the limbs	13	—	8	1	1	3	—	10	2	—	1	—
	Congenital heart disease	11	2	1	3	2	1	2	9	—	—	1	1
	Hare lip and cleft palate	5	—	1	1	1	1	1	4	—	—	—	1
	Hypospadias	4	—	—	2	1	1	—	1	3	—	—	—
	Miscellaneous	18	1	4	5	2	6	—	13	2	1	—	2
	Total	73	3	19	20	12	15	4	52	10	3	3	5
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Age and parity of 200 mothers with normal children.	Total	200	11	83	59	34	9	4	152	40	5	1	2

Parity. Fifty-two of the seventy-three children with malformations were firstborn. Among the 200 normal children the corresponding number was one hundred and fifty-two. A comparison between these two ratios shows that there was a significantly higher incidence of multiparae among the mothers in the former group ($t = 2.5$).

Previous abortions. Fourteen (19.1 per cent.) of the mothers who gave birth to malformed children had had previous abortions. In the control group only fifteen mothers (7.5 per cent.) gave a similar history. The difference between the two ratios is significant ($\text{Chi} = 2.9$). With regard to the menstrual history no deviation from normal conditions was detected among the mothers who subsequently gave birth to malformed children.

The Health of the Mothers during Pregnancy

It has already been mentioned that the majority of the mothers have been carefully followed up at the antenatal clinic from their early pregnancy. Reference is now made to the question whether there are maternal disorders during pregnancy predisposing or at any rate preceding the occurrence of foetal malformations.

In all cases the general condition of the mothers during pregnancy was satisfactory, and no clinical signs of undernourishment or vitamin deficiency could be detected. None of the mothers revealed any sign of congenital malformations. There were no cases of psychical disturbances during pregnancy, which supports the view that the importance of these disturbances in the etiology of congenital malformations has in the past been overestimated.

Ante-partum haemorrhage. Fifteen of the mothers with malformed children (20.5 per cent.) had had

gestational bleeding, some of them on several occasions. In the control group nine mothers (4.3 per cent.) gave a history of ante-partum haemorrhage, showing a significantly higher incidence of this disturbance in the former group ($\text{Chi} = 4.4$). During the last ten years the incidence of gestational bleeding for the whole hospital population has been 3.9 per cent.

Toxaemia. In the Obstetric Hospital, University College Hospital, a blood pressure of 120/80 mm.Hg. is considered the upper limit of the normal, irrespective of the age of the patient, and a blood pressure exceeding this level is interpreted as a sign of toxæmia. Various types of toxæmia during pregnancy occurred in thirty-eight (53.6 per cent.) of the seventy-three mothers who bore children with malformations. In only one case was albumin detected in the urine. The corresponding incidence of toxæmia in the control group was slightly less (45.1 per cent.). The difference, however, is not significant ($\text{Chi} = 1.0$). During the last ten years toxæmia, according to this very strict definition, has been observed in about 50 per cent. of the whole hospital population. Thus, this disturbance does not seem to be especially commonly associated with the occurrence of foetal malformations in these studies. In this connexion it may be mentioned that Naujoks (1938) reported a relatively high incidence of toxæmia during pregnancy among mothers who subsequently gave birth to malformed children.

Various diseases during pregnancy. Detailed information on the occurrence of morbid states in the mothers has been gathered from the antenatal records. With regard to acute diseases, only those which occurred within the first five months of

TABLE 2
MORBID STATES DURING PREGNANCY OF THIRTY-THREE MOTHERS WITH MALFORMED CHILDREN

Case no.	Maternal age	Parity	Morbid state of the mother	Stage of pregnancy in weeks	Chief malformation of the children
ACUTE INFECTIOUS DISEASE :					
1	22	0	Influenza, 'cold'	8	Naevus
2	25	0	" "	9	"
3	21	0	" "	10	Congenital heart disease
4	39	3	" "	10	" " "
5	22	0	" "	11	Naevus
6	30	0	Pneumonia	12	Spina bifida
7	26	0	Sore throats	4	Naevus
8	24	1	" "	4	Clubbed feet
9	24	0	Cough (bronchitis)	4	Defect of diaphragm
10	26	0	" "	12	Anomaly of kidneys
11	29	0	" "	12	Spina bifida
12	26	0	Pyelitis	4	Congenital heart disease
CHRONIC INFECTIOUS DISEASE :					
13	37	0	Inactive pulmonary tuberculosis	See text	Naevus
14	36	0	" " "		Clubbed feet
15	23	1	" " "		Hypospadias
16	25	0	" " "		Naevus
17	36	1	Chronic bronchitis		Anomaly of kidney
MISCELLANEOUS :					
18	35	2	Jaundice	See text	Atresia of rectum
19	34	1	X-ray irradiation of pelvis		Hypospadias
20	34	1	Diabetes		Defect of hand
21	30	1	Thyrototoxicosis		Anencephaly
22	41	1	Anaemia gravis		Congenital heart disease
23	26	0	" "		Anencephaly
24	24	0	Mitral stenosis		Clubbed feet
25	18	0	" "		Congenital heart disease
26	41	0	" "		Mongolism
27	26	0	" "		"
28	30	0	" "		Cleft palate
29	40	4	Hepatomegaly		"
30	25	0	Uterus duplex		Encephalocele
31	37	3	Cervix uteri amputated		Clubbed feet
32	26	0	Cervical polyp		Spina bifida
33	23	0	Rh negative		Anencephaly

gestation have been included. According to the present state of knowledge it is very unlikely that injurious agents may cause foetal malformations after that time.

Among the seventy-three mothers of malformed children, various disorders during pregnancy were observed in thirty-three cases (45.2 per cent.). In table 2 these cases have been separated into three groups.

The first group in table 2 consists of twelve cases where the mothers had suffered from acute infectious diseases. It is noteworthy that the infections occurred in all cases within the first three months of pregnancy. In the second group are collected four cases of inactive pulmonary tuberculosis and one case of chronic bronchitis. In these the clinical findings remained on the whole unchanged throughout pregnancy. There was no case of syphilis

among the mothers. Over the same period a positive Wassermann reaction was observed in 0.97 per cent. of the whole hospital population.

The miscellaneous group consists of sixteen cases with various morbid conditions. Case 18 was that of a woman who, four weeks before conception, had had a blood transfusion to overcome anaemia caused by an abortion. In the fourth week of gestation jaundice was diagnosed. This may have been due to the transfusion (she was Rh-negative), but the possibility of the jaundice being of infectious origin cannot be excluded. One mother (No. 19) had been submitted to x-ray irradiation for amenorrhoea in another hospital on several occasions six years before the birth of her present child. One year after the last treatment she gave birth to a microcephalic child. In two cases (Nos. 22 and 23) severe anaemia was present throughout the pregnancy, haemoglobin

TABLE 3

MORBID STATES DURING PREGNANCY OF TWENTY-NINE MOTHERS WITH NORMAL CHILDREN

Morbid state of the mother	No. of cases	Stage of pregnancy in weeks
ACUTE INFECTIOUS DISEASE		
Influenza, 'cold' ..	3	15, 16, 20
Cough (bronchitis) ..	4	8, 13, 13, 16
Sore throats ..	2	4, 12
CHRONIC INFECTIOUS DISEASE		
Inactive pulmonary tuberculosis ..	6	See text
MISCELLANEOUS		
Mitral stenosis ..	7	
Placenta praevia ..	3	
Diabetes ..	1	
Thyrotoxicosis ..	1	
Ulcus duodeni ..	1	
Rh negative ..	1	
Total ..	29	

values varying between 40 and 50 per cent. In addition, two mothers revealed a slight degree of anaemia; the remainder had haemoglobin values exceeding 70 per cent. In one case (No. 33) the mother was Rh-negative, her child and husband being Rh-positive.

Five mothers had clinical signs of mitral stenosis, apparently of rheumatic origin. Hepatomegaly of uncertain origin and persisting throughout pregnancy was diagnosed in one case (No. 29). Only in three cases were abnormalities of the generative

organs observed (Nos. 30-32). There were no cases of ectopic gestation or placenta praevia among the mothers with malformed children. During the same period ectopic gestation occurred on fifteen occasions in the whole hospital population. In two cases version of the foetus was performed at the end of pregnancy; in the remaining cases the intra-uterine position of the foetus was normal. In the control group version was done in three instances.

Various types of foetal malformations were seen, and quite obviously no characteristic abnormality could be correlated with any particular group of maternal disorder. Abnormalities of the skin (naevi) seemed, however, to be confined to the group in which infections had occurred in the mother during pregnancy.

In table 3 are collected data about the corresponding occurrence of morbid states among the two hundred mothers who gave birth to normal children. Twenty-nine (14.5 per cent.) of the mothers had a history of various disorders during pregnancy. There were nine cases of acute infectious diseases but only in three mothers did these occur within the first trimester of pregnancy. The group of chronic infectious diseases comprises six cases of inactive pulmonary tuberculosis. In the third group are included seven cases of mitral stenosis, apparently of rheumatic origin. Placenta praevia occurred in three instances. No cases of ectopic gestation were observed, and no abnormalities of the generative organs. There were no cases of severe anaemia (haemoglobin value below 60 per cent.). One mother was Rh-negative, her child and husband being Rh-positive. Examination of the blood for a Rh factor was carried out in thirty-two mothers with malformed children and in 102 cases in the

TABLE 4

SEVENTY-THREE MOTHERS WITH MALFORMED CHILDREN AND TWO HUNDRED MOTHERS WITH NORMAL CHILDREN

	Morbid state of the mother during pregnancy	No. of cases	Maternal age						Parity				
			15-19	20-24	25-29	30-34	35-39	40-44	0	1	2	3	4-5
73 mothers with malformed children.	Acute infectious disease	12	—	5	5	1	1	—	10	1	—	1	—
	Chronic infectious disease	5	—	1	1	—	3	—	3	2	—	—	—
	Miscellaneous	16	1	2	4	4	2	3	9	4	1	1	1
	Disorder total	33	1	8	10	5	6	3	22	7	1	2	1
	No disorder	40	2	11	10	7	9	1	30	3	2	1	4
	Total	73	3	19	20	12	15	4	52	10	3	3	5
200 mothers with normal children.	Acute infectious disease ..	9	3	3	2	—	1	—	8	1	—	—	—
	Chronic infectious disease	6	—	4	—	1	1	—	5	1	—	—	—
	Miscellaneous	14	—	5	2	4	2	1	8	4	—	—	2
	Disorder total	29	3	12	4	5	4	1	21	6	—	—	2
	No disorder	171	8	71	55	29	5	3	131	34	5	1	—
	Total	200	11	83	59	34	9	4	152	40	5	1	2

control group. The number of Rh-positive mothers was twenty-eight and eighty-six respectively.

The main results of this investigation are compared in table 4. It will be seen that various morbid states during early pregnancy occurred more often among the mothers with malformed children. The difference between these two total ratios is highly significant ($\chi^2 = 6.3$). Taking the three groups of disorders separately, there was a positive correlation between the occurrence of acute and chronic infectious diseases during pregnancy and foetal malformations ($\chi^2 = 4.1$ and 2.2 respectively). The incidence of disorders included in the miscellaneous group was significantly higher among the mothers with malformed children ($\chi^2 = 5.4$).

The mean age was slightly higher among the mothers with malformed than among those with normal children. The difference, however, was not significant ($t = 1.4$). Also with regard to the maternal age in the three subgroups no significant difference was observed, the value for t being 0.9 , 1.6 , and 0.5 respectively. The parity of the mothers with malformed and with normal children did not show any significant difference. The value for t , calculated for the two main groups, was 0.2 .

Discussion

The investigations support the view that advanced maternal age and multiparity are two factors involved in the etiology of congenital malformations. It is difficult to interpret this relationship, but the relatively high incidence of malformed children in these cases is probably an expression of a diminished maternal reproductive ability perhaps of hormonal origin. The possibility must also be considered that this maternal disability is to some extent associated with constitutional characteristics predisposing to the production of malformed children. The high incidence of previous abortions among mothers with malformed children supports this possibility.

It is noteworthy that ante-partum haemorrhage preceded the birth of malformed children much more often than in the case of normal children. Ingalls and Davies (1947), who observed an unduly high incidence of bleeding during pregnancy in mothers who subsequently gave birth to mongolian imbeciles, considered the bleeding a causative factor of this foetal abnormality. It is, however, possible that the occurrence of ante-partum haemorrhage in association with abnormalities of the foetus is an expression of an incompatibility between mother and foetus, and this incompatibility might cause the tendency to abort. If this were true the bleeding would be a secondary phenomenon, rather than a primary cause of the foetal malformation. In this connexion it may be mentioned that Kalmus (1947) observed a positive correlation between ante-partum haemorrhage and advanced maternal age. It is, therefore, likely that the high incidence of gestational bleeding among mothers with malformed children in the present studies may be due partly to their relatively advanced age.

The observations have shown an abnormally high incidence of various morbid states during the early pregnancy among the mothers who gave birth to malformed children. The possibility must, therefore, be considered that these disorders are in some way involved in the etiology of the foetal malformations. It is noteworthy that there was no difference in age and parity in the two groups of mothers who had revealed various morbid symptoms during their pregnancy. This speaks in favour of the possibility that maternal disorders may act independently of other environmental principles that play a part in the causation of foetal abnormalities. It is significant that in the mothers with malformed children the infections occurred within the first three months of pregnancy, whereas in the control group they were generally observed after that time.

Any ideas of the mode of action of the various factors mentioned must for the moment remain entirely speculative. With regard to the teratogenic effect of certain virus diseases, such as rubella, the possibility of a direct action of the virus upon the growing embryo has been discussed (Swan and Tostevin, 1946; Morhardt, 1946; and others). This assumption is based upon the experimental observation that viruses have a special predilection for embryonic tissues.

The possibility must also be considered that an antigen-antibody reaction may have a harmful effect on the foetus. There is little doubt, for instance, that erythroblastosis foetalis is due to a blood incompatibility between the mother and her infant. The discovery of the Rh factor as a main cause of this disorder has given rise to the speculation that other abnormalities of the foetus may be connected with other incompatibilities of the blood (Penrose, 1946b, 1946c; Wiener, 1947). On the basis of this theory, it is possible that antibodies produced by various morbid states in the mother may interfere with the proper differentiation of the foetus during an early stage of pregnancy.

Summary

The aim of this work was to investigate, by means of comparative studies, the relationship between maternal conditions during pregnancy and congenital malformations of the foetus. For this purpose detailed data were collected from the antenatal records of seventy-three mothers who gave birth to malformed children at the Obstetric Hospital, University College Hospital, London, between the years 1945-48. Two hundred mothers who gave birth to normal children at the same hospital during this period were used as controls. The following main results have been obtained.

The mean age of the mothers with malformed children was significantly higher than the maternal age in the control group. There was also a positive correlation between multiparity and the occurrence of foetal malformations.

Fifteen, or 19.5 per cent., of the mothers with malformed children had had previous abortions, the corresponding incidence in the control group being 7.5 per cent.

The nutritional condition of the mothers during pregnancy was satisfactory in all cases, and no clinical signs of vitamin deficiency were observed.

Ante-partum haemorrhage occurred more often in pregnancies resulting in the birth of malformed children. The incidence of this disorder was 20.5 per cent. and 4.3 per cent. respectively in the two groups.

With regard to the occurrence of toxæmia during pregnancy, no significant difference was established between the mothers in the two groups.

Apart from ante-partum haemorrhage and toxæmia, various morbid states were observed during early pregnancy in 42.5 per cent. of the mothers who gave birth to malformed children. Acute infectious diseases occurred in twelve cases, all within the first three months of gestation. Of the mothers with normal children, a total of 14.5 per cent. had a corresponding history of various disorders during their pregnancy. There were nine cases of acute infectious diseases, of which, however, six occurred after the first three months of gestation.

The relatively high incidence of various morbid states during pregnancy among mothers with malformed children has led to the assumption that these states may be involved in the pathogenesis of foetal malformations.

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Appendix

Current statistical formulae have been employed for the interpretation of the results (Fisher, 1936).

The significance of a difference has been determined according to the following formula:

$$t = \frac{M_1 - M_2}{\sqrt{V}}$$

where M_1 and M_2 are the means of two series and V is the variance of this difference.

The value of Chi has been calculated according to the 2 by 2 tables as follows:

$$\text{Chi} = (xw - yz) \sqrt{\frac{(x + y + w + z)}{(x + z)(y + w)(x + y)(w + z)}}$$

where the numbers observed in the four classes are:

x	y
z	w

A value of t or Chi of 2.5 or more is considered statistically significant.

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