MATERNAL HEALTH IN EARLY PREGNANCY AND CONGENITAL DEFECT

FINAL REPORT ON A PROSPECTIVE INQUIRY

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Retrospective epidemiological studies of environmental influences upon human foetal development have so far proved to be of limited value. When routine ante-natal records were used for evidence of illness and other events in early pregnancy they were found not to contain sufficient information. Questioning mothers after delivery is unsatisfactory because their account of events in early pregnancy is liable to be coloured by the knowledge of whether or not their children are malformed. In addition, the interval between early pregnancy and delivery is too great for minor events and illnesses to be remembered accurately. A prospective survey of a large number of pregnancies was therefore undertaken to investigate associations between illnesses or other events during early pregnancy and foetal and infant death and defect.

The investigation was begun in 1952 in Watford, where for the 3 years 1952–55 women were interviewed at their first attendance at hospital and local authority ante-natal clinics; for 6 months in 1954–5 women were similarly seen at St. Albans City Hospital. In all, 3,295 women were interviewed, 3,055 of them by the author personally and the remaining 240 by two health visitors working under the author's supervision. Particulars about marital state, employment, previous pregnancies, history of illnesses, and whether the pregnancy was wanted were noted on a standard form. A detailed history was taken of experiences during the first 12 weeks of pregnancy, including illnesses, vomiting, fainting, injury or operation, anaesthetics, vaginal bleeding, attempts to induce abortion, coitus, and severe emotional upsets. Blood pressure, Rhesus group, Wassermann reactions, Kahn test, and haemoglobin estimation were recorded. The majority of the babies born locally in hospital were examined by a consultant paediatrician. For those born at home, in nursing homes, or in other areas, reports were obtained from

health visitors about examinations made by general practitioners and clinic doctors. The results of this investigation have been published (McDonald, 1958). The main positive findings were an association, significant at a 5 per cent. level, between the maternal factors of febrile illnesses, pulmonary tuberculosis, and employment in laundries, and serious malformations in the children. Because certain defects are not always evident in the neonatal period, a further review was planned of the same children when they were older.

METHOD

The report obtained on each child in the neonatal period will be referred to as the first report. By 1959, when the children were aged 3 to 6 years, a second report was sought on each child. In getting information about defects noted in the children at this age, no reference was made either to the ante-natal record or to the first report. The school health records were inspected of all children still living in the Watford area who had been medically examined at school. Health visitors using a standard questionnaire reported on children living in the Watford and St. Albans areas who were not yet at school or who had not been medically examined. Children who had moved out of the area but whose addresses were known were also reported on by health visitors. When the address of the family was unknown, other means were used to get in touch with the mother and obtain a report from her on the child's development. Except when the child was illegitimate or adopted, letters and questionnaires were sent to mothers through appropriate local Executive Councils. When there was any doubt about a defect or the letter did not reach the mother an inquiry was made from the general practitioner with whom the child was registered.

For children who were examined by health

visitors or who were followed by means of letters to the mother, questions were asked about the age at which the child walked unsupported and made brief sentences, any history of operations or convulsions, any defect found at clinical examination, and any abnormality of gait, manipulation, speech, vision, and hearing. Further inquiries were made from school medical officers, family doctors, and consultants to obtain as much information as possible about any reported abnormalities. Certain groups of children were personally examined for evidence of mental defect, cerebral palsy, deafness, and congenital heart disease; the children selected were those who did not walk alone until after their second birthday, those with abnormalities of gait, those with marked delay in learning to speak or severe speech defects, those suspected of mental retardation, and those with heart murmurs who had not had cardiological investigations. At this stage the first reports were inspected and children who were said to have had a heart murmur in infancy were also selected for examination.

The 3,295 women originally interviewed had at the time of the first report 3,081 surviving infants about whom information was available (Table I).

TABLE I
PREGNANCIES STUDIED AND SURVIVORS TRACED

No. of Women originally interviewed		3,295
Found not to be pregnant	 17	151
Outcome of pregnancy not known	 62	
Abortion—Spontaneous	 68	
Therapeutic	 3	
Maternal and foetal death	 1	
Pregnancies of 28 weeks or more or resulting in live-born child	 3,144	3,179
Add Twins	 35	
Stillbirths	 63	98
Neonatal deaths	 35	
No. of Surviving Infants on whom a First Report was Obtained		3,081
Failure to trace	 148	175
Death	 27	
No. of Children on whom a Second Report was Obtained	<div> Health Visitor 2,258 School Records 474 Mother 89 Family Doctor 85 </div>	2,906

For 148 (4.8 per cent.) of the 3,081 survivors, no information was obtained after the neonatal period. Of these, 44 (30 per cent.) were known to have emigrated, nine (6 per cent.) to have been adopted, and one to have changed his name. In addition, 29 (20 per cent.) were illegitimate and further searching for them was undesirable. The remaining 65 (44 per cent.) had moved from the area and could not be found.

Illegitimacy was, therefore, an important reason for failure to trace children. Only 84 per cent. of the children of the 224 women who admitted to extra-marital conception were traced, compared with over 95 per cent. in the whole series. As far as the maternal factors were concerned, the proportion of children untraced was slightly, but not significantly, raised among women who were Rhesus negative, who had anaemia, and who were employed. Apart from these the proportion untraced was approximately 5 per cent. in the remainder and there was therefore little evidence of important selective factors.

Another 27 of the 3,081 surviving children had died.

Second reports were obtained from health visitors, mothers, family doctors, and school health records for 2,773 children aged 3 to 6 years, and the health visitors completed reports based on their own records for 133 children who had removed to unknown addresses after the age of one year, making a total of 2,906.

RESULTS

INCIDENCE OF FOETAL AND INFANT DEATHS

63 infants were stillborn (a stillbirth rate of 20 per thousand births) and 55 died before their first birthday (an infant mortality of 18 per thousand live births). In 1953-4 in the Borough of Watford, where over half the births in the survey took place, the stillbirth rate was 19 and the infant mortality rate 22.

About one-quarter of the infants who were stillborn or who died later had gross malformations (Table II). One-third of the infants who died in the neonatal period weighed under 3 lb. After the first 4 weeks of life infections accounted for nearly half the deaths. Two (29 per cent.) of the seven children who died after the age of one year had leukaemia, but the x-ray exposure of the mothers of these children was not known.

TABLE II
ASCIBED CAUSES OF 125 STILLBIRTHS AND DEATHS (Per cent.)

Cause	Still-birth	Death		
		First 4 wks	4 wks-1 yr	1 yr and Over
Gross Malformation	25	20	27	29
Intracranial Trauma	13	18	—	—
Rhesus Isoimmunization	13	3	—	—
Birth Weight under 3 lb. (excluding above)	10	33	—	—
Asphyxia and Atelectasis	14	15	—	—
Infection	—	10	47	42
Other	25	2	26	29
Total	Per cent.	100	100	100
	Number	63	40	7

INCIDENCE OF DEFECTS

The abnormalities noted are listed in Table III. A few groups are omitted: undescended testis, because it was not looked for systematically; speech defects, because of difficulty in definition; and mental retardation not amounting to ineducability, because

some of the children were only 3 years old and thus too young for adequate ascertainment. Other diagnostic groups such as fits, hernias, asthma, and eczema, were included because although they are not generally considered as congenital defects it seemed that ante-natal factors might play some

TABLE III
DEFECTS FOUND IN 3,179 LIVE AND STILLBORN CHILDREN

Class	Defect	Total Number of Children with Defect	Number of Children with This Defect Only	Found at First Report	Confirmed at Second Report () = died	Not Noted at Second Report	First Noted at Second Report	Total Incidence of Defect (per thousand)
A	Central Nervous System							
	Anencephalus	8	7	8	(8)	—	—	2.5
	Spina bifida	7	7	—	1 (6)	—	—	2.2
	Hydrocephalus (without spina bifida)	5	5	2	(2)	—	3	1.6
	Encephalocele	1	1	1	(1)	—	—	0.3
G	Mongolism	6	4	6	5 (1)	—	—	1.9
A	Mental Defect (ineducable) excluding Mongolism	11	4	—	—	—	11	3.5
G	Cerebral Palsy	8	5	—	—	—	8	2.5
E	One fit or more at 3 years or over, or three or more episodes under 3 years	31	24	—	—	—	31	9.8
G	Less than three episodes at under 3 years	43	40	—	—	—	43	13.5
A	Oesophageal Atresia and Tracheo-oesophageal Fistula	3	2	3	1 (2)	—	—	0.9
A	Genito-urinary Defects							
	Urethral stricture, hydronephrosis, and hydroureter	3	1	1	(1)	—	—	0.9
	Absent kidneys and ureters		—	1	(1)	—	—	
	Hydronephrosis and hydroureters		—	1	(1)	—	—	
A	Hypospadias	5	5	4	4	—	1	1.6
A	Congenital Heart Disease							
	Coarctation of aorta	1	1	1	(1)	—	—	4.7
	Atresia of aortic valve	2	1	2	(2)	—	—	
	Transposition of great vessels	1	1	1	(1)	—	—	
	Interventricular septal defect	2	—	2	(2)	—	—	
	Tetralogy of Fallot	1	—	1	1	—	—	
	Patent ductus arteriosus	1	1	—	—	—	1	
	Pulmonary and aortic stenosis, interventricular septal defect, and anomaly of great vessels	1	1	1	(1)	—	—	
	Pulmonary stenosis	1	1	—	—	—	1	
	Atrial septal defect	1	1	1	1	—	—	
	Not known (with mongolism)	2	—	2	(1)	—	—	
	Systolic murmur with clinical enlargement of heart	2	2	—	—	—	2	3.8
A	Systolic murmur only	12	9	—	3	—	9	
A	Hare Lip and Cleft Palate	3	2	3	2	1	—	1.9
	Hare lip	1	—	1	(1)	—	—	
	Cleft palate	1	—	1	(1)	—	1	
	Bifid uvula	1	1	1	1	—	—	
A	Diaphragmatic Hernia	2	1	2	(2)	—	—	0.6
A	Pyloric Stenosis	19	15	2	2	—	17	6.0
B	Musculo-skeletal Defects							
	Congenital dislocation of hip	3	3	—	—	—	3	0.9
	Talipes	7	6	—	3	3	1	2.2
	Digital defects	9	9	5	1	4	4	2.8
	Deformities of chest wall	11	8	—	—	1	10	6.6
	„ „ spinal column	2	2	—	—	—	2	
	„ „ skull	1	—	—	—	—	1	
	Hypertelorism	1	1	—	—	—	1	
	Micrognathia	1	1	—	—	—	—	
	Absent pectoralis major	2	2	—	—	2	—	
	Shortening of one lower limb	2	1	—	—	—	2	
	Tail	1	1	—	—	1	—	
	Cleido-cranial dysostosis	1	1	—	—	—	—	

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TABLE III—continued
DEFECTS FOUND IN 3,179 LIVE AND STILLBORN CHILDREN

Class	Defect	Total Number of Children with Defect	Number of Children with This Defect Only	Found at First Report	Confirmed at Second Report (=died)	Not Noted at Second Report	First Noted at Second Report	Total Incidence of Defect (per thousand)
C	Hernia Umbilical	40	37	19	2	13	21	12.6
	Inguinal	37	30	4	3	1	33	12.3
B	Naevus (more than 2 in. diam.)	29	27	—	3	11	15	9.1
A	Deafness (perceptive)	1	1	—	—	—	1	0.3
A	Eye Defects							
A	Cataract (bilateral)	1	—	—	—	—	1	0.3
A	Nystagmus	2	1	—	—	—	1	0.6
D	Squint	83	70	—	—	—	83	26.1
D	Refractive Error (without squint)	31	24	—	—	—	31	9.8
D	Ptoxis	3	1	—	—	—	3	0.9
F	Asthma or Eczema	77	63	—	—	—	77	24.2
B	Miscellaneous Defects							
	Branchial cyst	1	1	—	—	—	1	11.1
	Other cysts	11	10	—	—	3	8	
	Pilonidal sinus	5	4	—	1	3	1	
	Hiatus hernia	1	1	—	—	—	1	
	Hydrocoele	6	6	—	—	1	5	
	Tongue-tie (operation)	2	1	—	—	—	2	
	Diabetes (onset at 3 yrs)	1	1	—	—	—	—	
	Coeliac disease	1	1	—	—	—	—	
	Diverticulitis	1	1	—	—	—	—	
	Other	5	5	—	1	3	1	
Children with Single Defect		464						
Children with More than One Defect		47						
Total Children with a Defect		511						160.7

part in their aetiology. 29 children (9 per thousand total births) had malformations which resulted in death either before or after birth; the diagnosis in many of these was made or confirmed at *postmortem*. In the surviving children who were traced a comparison of findings in the first and second reports was possible.

The incidence of gross malformations of the central nervous system was 6.6 per thousand births (anencephalus 2.5, spina bifida 2.2, hydrocephalus alone 1.6). All these defects (the majority being lethal) were noted in the first report, except for three children with hydrocephalus considered to be of congenital origin which was noted only in the second report. All six (1.9 per thousand) cases of mongolism were noted in the first report. In addition to five surviving children with mongolism, eleven (3.5 per thousand) children were found at the second report to have an intelligence quotient estimated at under 50 per cent. Two of these had cerebral palsy with fits and another three had fits; two of the six remaining children were possibly psychotic rather than mentally deficient. Eight children in all (2.5 per thousand) were found to have cerebral palsy: four had spastic hemiplegia, two spastic diplegia, and two bilateral athetosis.

Nearly all children suspected of deafness or with a marked speech defect were carefully examined using a special hearing test and when necessary audiometry, but apart from a mild high-frequency deafness in a child with bilateral athetosis following kernicterus due to Rhesus isoimmunization, only one child with perceptive deafness of unknown origin was found (0.3 per thousand).

As expected many cases of congenital heart disease were missed in the first report, and in a number of children the diagnosis is still incomplete as it was not felt justifiable to suggest cardiological investigation of systolic murmurs in children without symptoms or other abnormal clinical signs, or even to inform mothers if they were unaware of them. Fifteen children (4.7 per thousand) appeared to have definite congenital heart disease, although in four (including two children with mongolism) the exact diagnosis is uncertain. In four children no abnormality had been noted in the first report. There were twelve children (3.8 per thousand) who had systolic murmurs but no symptoms or other abnormal signs; only three of these had been noted in the first report.

There were six children (1.9 per thousand) with hare lip or cleft palate of some degree. One child, stated in the first report to have a cleft palate and

hare lip, was found at the second report to be normal, the mistake having been due to the confusion of two children with the same name. Nineteen children (6.0 per thousand) were reported to have had pyloric stenosis: fifteen had been treated surgically and four medically.

Three cases of congenital dislocation of the hip (0.9 per thousand) were noted at the second report. Talipes was noted at the first report in six children, but at the second report three of these were said to be normal, the condition probably being mild or successfully treated; one additional case was found at the time of the second report making a total of seven (2.2 per thousand).

Of the five boys with hypospadias, four were noted in the first report and one later. The serious eye defects, including the one case of cataract and two of nystagmus, were all first noted in the second report. The incidence of squint was found to be 26.1 and of refractive errors without squint 9.8 per thousand births.

An umbilical hernia was noted in the first report in nineteen children but in only two of these was it also noted in the second report. In 21 children it was noted only in the second report. In all, 38 children (12.6 per thousand births) were reported to have had at some time an umbilical hernia and of these about half were treated by operation. Inguinal hernia was described in three children in the first report, and 35 in the second—a total incidence of 12.3 per thousand births. Eczema or asthma was reported in 83 children (24.2 per thousand).

The ascertainment of the more serious malformations at the time of the first report is likely to be relatively complete. As the outcome of over 98 per cent. of the pregnancies was known, the incidence found of these malformations probably gives a fairly true picture of the children of the women in the survey. Although there were many domiciliary births in the series, these were not fully represented

as far as the community was concerned, which introduces a slight bias in the series towards hospital births probably involving a small excess of primiparae and women of high parities and with previous obstetric complications. The influence of these factors on the incidence of malformations is probably small, but they would tend to raise the incidence of stillbirths and neonatal deaths.

Factors likely to influence the completeness of ascertainment of defects are the nature of the defect, age of the child and methods used. In the 133 children about whom information was obtained from existing health visitors' records, fifty per thousand were reported to have defects, whereas the incidence reported in the others was 160 per thousand. Although the overall incidence of defects and disorders reported varied little (ranging between 136 and 160 per thousand) at 3, 4, 5, and 6 years, the relative proportions of the different disorders varied at different ages (Table IV). As would be expected, visual defects and asthma were diagnosed more frequently in the older children and eczema in the younger ones, and this would lead to an underestimate of the true incidence of these troubles. Squints, hernias, and convulsions were reported at a more constant rate at different ages.

When the results of school medical inspections and general practitioners' reports combined were compared with information received through health visitors and mothers (Table V, opposite), it was evident that the incidence of asthma, eczema, convulsions, and visual defects was either understated in school medical and general practitioners' reports or over-reported by health visitors and mothers (the former would seem more probable).

Only a rough comparison with the incidence of defects found in other series can be made because of the different methods of ascertainment and criteria used. The incidence of congenital heart disease in 5,000 infants examined at the age of one year in an

TABLE IV
INCIDENCE OF VARIOUS DEFECTS FOUND AT SECOND REPORT ACCORDING TO AGE OF ASCERTAINMENT

Age (yrs)	Number of Children	Incidence per Thousand Children								
		Asthma	Eczema	Fits *	Infantile Convulsions†	Hernia		Squint	Visual Defect without Squint	Children with One or More Defect
						Umbilical	Inguinal			
3	449	4	22	11	20	7	7	20	4	136
4	908	18	14	9	12	10	11	34	5	160
5	1,262	24	13	12	13	10	10	31	18	158
6	154	26	13	19	24	6	—	20	20	149
All Ages	2,773	19	15	11	14	10	10	30	11	150

* Fits: One fit or more at 3 years or over, or three or more episodes at under 3 years.

† Infantile convulsions: less than three episodes at under 3 years.

TABLE V
INCIDENCE OF VARIOUS DEFECTS FOUND AT AGE 5 ACCORDING TO METHOD OF ASCERTAINMENT

Method of Ascertainment	Number of Children	Incidence per Thousand Children							
		Asthma	Eczema	Fits*	Infantile Convulsions†	Hernia		Squint	Visual Defect without Squint
						Umbilical	Inguinal		
Health Visitor or Mother ..	765	30	17	20	17	12	8	30	25
School Medical Examiner or General Practitioner ..	497	14	8	2	4	8	12	30	8
All Methods	1,262	24	13	12	13	10	10	31	18

* Fits: One fit or more at 3 years or over, or three or more episodes at under 3 years.

† Infantile convulsions: less than three episodes at under 3 years.

investigation in New York was 8.3 per thousand total births (Richards, Merritt, Samuels, and Langmann, 1955).

The definition used included heart murmurs heard at all examinations and considered organic. The total incidence in the present series was 4.7 per thousand, or including all persistent heart murmurs, 8.5 per thousand. A comparison with the incidence of defects found among about 1,000 children carefully followed to the age of 5 years in Newcastle-upon-Tyne (Miller, Court, Walton, and Knox, 1960) reveals a fairly similar incidence of defects. The following are the rates per thousand from Newcastle, figures from the present survey being given in brackets:

Pyloric stenosis 3 (6), mongolism 4 (2), mental defect 5 (4), squint 47 (26), hypospadias 3 (2), asthma about 20 (asthma or eczema 24), congenital heart disease 3 (5), cleft palate 1 (2), and talipes 3 (2).

RELATIONSHIP BETWEEN MATERNAL CHARACTERISTICS AND EXPERIENCES IN PREGNANCY AND DEATH AND DEFECTS IN CHILDREN

The defects found in this series are numerically too few for significant associations to be found between maternal factors and individual defects, especially as some of the maternal factors under consideration occurred infrequently. For this reason the defects are grouped into Classes A to G (Table III).

Class A comprises serious or potentially serious defects of unknown aetiology, mainly those of the central nervous system and heart, and pyloric stenosis, mental defect, hare lip or cleft palate, and hypospadias.

The majority of the defects in Class B are of the skeleton and superficial structures.

Hernias (C), eye defects (D), fits (E) defined as one

fit or more at 3 years or over or three or more episodes under 3 years, and asthma or eczema (F) are considered as separate categories.

Mongolism, because of the chromosomal anomaly which has been observed, cerebral palsy, because of its association with peri-natal events, and infantile convulsions (less than three episodes under 3 years), because of their minor nature, were placed in Class G and not analysed with the other defects.

(i) *Maternal Age*.—No statistically significant correlations with maternal age were found, but certain trends were noted.

The incidence of abortions rose with maternal age (Table VI, overleaf); this was at least partly due to a tendency for older mothers, especially those who had had previous abortions, to book early for their confinement. The incidence of stillbirths and neonatal deaths without malformations and that of asthma or eczema also tended to rise with maternal age. Among the individual defects, an association was noted with maternal age, especially in mongolism, and also in congenital heart disease excluding mongolism, hare lip or cleft palate, and cerebral palsy (Table VII, overleaf).

(ii) *Maternal Parity*.—The deaths and defects in the series were too few for separation of the effect of parity from that of age. Abortions and the group of stillbirths and neonatal deaths tended to be associated with higher parity as well as with age, and the increase in older mothers could therefore be due to either factor or to both. In the Class A defects, as no trend with parity was observed, the effect if real is probably due to age and not to parity. In asthma the incidence was lower in women of higher parity and any association thus appears to be with age rather than parity.

The well-known association of pyloric stenosis with primiparity is evident in Table VII.

TABLE VI
MATERNAL FACTORS IN RELATION TO FOETAL AND INFANT DEATH AND DEFECT

Maternal Factors		Number of Pregnancies	Incidence of Deaths and Defects (per thousand pregnancies)							
			Abortions (68 cases)	Stillbirths and Neonatal Deaths Without Defect (79 cases)	Malformations		All Hernias Class C (77 cases)	Eye Defects Class D (113 cases)	Fits Class E (31 cases)	Asthma or Eczema Class F (77 cases)
					Class A ** (90 cases)	Class B (102 cases)				
Total No. 3,251			21	24	28	31	24	35	10	24
Age (yrs)	Less than 25	1,269	13	19	29	32	23	31	8	19
	25-34	1,612	25	26	25	30	24	38	11	24
	35 and Over	370	30	35	35	32	24	35	11	38
Parity	1	1,362	21	23	32	29	26	32	9	24
	2 and 3	1,432	17	23	23	37	24	34	10	26
	4+	457	31	31	28	22	13	48	9	15
Employment—Full or Part-time Work "Heavy"		1,529 264	16 19	20 19	30 38	31 45	22 19	29 42	9 0	22 19
"Unwanted" Pregnancy		921	20	26	30	29	25	40	7	27
Extra-marital Conception		224	9	13	31	36	36	36	4	13
Attempted Abortion		168	24	18	24	42	36	30	18	24
Rhesus Negative		542	26	46†	22	26	20	31	15	22
Chronic Illness at Onset of Pregnancy ..		430	16	28	40	33	30	35	23†	35
*Hypertension (diastolic BP 90 or more)		60	33	67	17	50	17	33	0	33
‡ Anaemia (Haemoglobin less than 80 per cent.)		490	24	39†	29	33	14	41	10	20
*History of cold sores (herpes simplex)		336	27	15	24	27	18	24	0	18
History of pulmonary tuberculosis		61	33	0	98†	16	16	0	16	33
Illness, etc., during First 12 Weeks of Pregnancy	Acute Illness { Non-febrile ..	1,065	19	30	24	23	23	29	8	20
	Febrile ..	148	47†	40	61†	41	20	68†	7	61†
	Vomiting	488	20	20	27	39	35	41	10	33
	Fainting	135	22	15	15	30	22	52	15	30
	Injury or Operation	143	28	0	35	42	21	35	21	14
	Anaesthetic	63	48	32	48	32	16	95†	16	16
	Vaginal Bleeding	523	38†	36	25	34	15	38	15	21
	Anxiety or "Shock"	444	27	29	20	38	18	41	7	27

* Blood pressure was recorded in approximately 50 per cent. of pregnancies and history of cold sores in about 30 per cent.

§ Blood pressure reading and haemoglobin estimation made at first ante-natal visit.

** For defects included under Class A, etc., see Table III.

†Bold figures indicate $P \leq .05$.

(iii) *Employment.*—Nearly half the mothers were engaged in part-time or full-time work outside the home. The proportion employed depended largely upon parity and varied from 80 per cent. of women who were having their first child to 20 per cent. of women having a fourth or later child.

So far as the death or defect of their children was concerned, the experience of the women who were employed did not differ greatly from that of those who were not employed (Table VI). Allowance should be made for parity in any comparison, but the rates would not be substantially altered by this. The children of women who said their work involved heavy lifting or pulling had a raised incidence of Class A defects (38 per thousand compared with 28 per thousand in all children). This was not statistically significant, whereas neonatally an association significant at a 5 per cent. level had been observed between heavy work and serious

malformations. The defects which tended to be associated with heavy work were those of the central nervous system and heart (Table VII). In the original communication it was noted that three out of the ten women doing heavy work who had defective children worked in laundries and that out of a total of 28 women who worked full-time in laundries, four (14.3 per thousand) had children with major malformations (anencephalus, hydrocephalus, cardiac defect, and hypospadias) compared with 2.8 per thousand in all maternities. This finding was unaltered by the results of the second report and the probability of its occurring by chance is small ($\chi^2=10.2$; 1 d.f.; $P=.001$). Of the total of 15 women in the series who worked in laundries, five (33.3 per cent.) conceived out of wedlock, and fourteen (93.3 per cent.) reported an illness in the first 12 weeks of pregnancy, both rates being higher than expected. In three the illness was said to be febrile; one of

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TABLE VII
SELECTED MATERNAL FACTORS IN RELATION TO CERTAIN TYPES OF DEFECT

Maternal Factors		Number of Pregnancies	Incidence of Defects (per thousand pregnancies)								
			Class A						Class B	Class G	
			Central Nervous System (21)	Heart (15)	Hare Lip and Cleft Palate (6)	Pyloric Stenosis (19)	Hypo-spadias (5)	Mental Defect* (9)		Talipes (7)	Cerebral Palsy (8)
Total No. 3,251		7	5	2	6	2	3	2	3	2	
Age (yrs)	Less than 25	1,269	6	2	1	6	2	4	3	—	—
	25-34	1,612	8	4	2	6	1	1	1	4	2
	35 and Over	370	3	17	6	3	—	6	6	6	8
Parity	1	1,362	8	4	3	10	2	4	4	2	2
	2 and 3	1,432	6	4	1	2	2	1	1	3	1
	4+	457	7	9	2	7	—	5	2	2	7
"Heavy" work		264	15	12	4	8	4	—	12	—	4
Full-time employment in laundry		28	74	37	37	—	37	—	—	—	—
"Unwanted" pregnancy ..		921	7	8	3	9	2	4	3	4	6
Chronic Illness at Onset of Pregnancy		430	7	7	—	10	—	5	2	5	—
History of Pulmonary Tuberculosis		61	34	17	—	34	—	—	—	—	—
Illness etc. during first 12 weeks of Pregnancy	Febrile Illness	148	7	7	7	7	14	7	7	—	—
	Injury or	143	—	15	7	—	7	7	—	7	—
	Operation	63	—	—	—	17	—	17	—	—	—

* Excluding mongolism and cerebral palsy

these resulted in abortion, but the children of the other two women were normal. The defects were distributed equally among women who reported illnesses and those who reported none. There was no excess of chronic illness or of anaemia among the laundry workers.

The incidence of Class B malformations was raised, although not to a significant level, in the children of women who said their work was heavy, but three of the mothers of the seven children with talipes said their work was heavy, whereas one in twelve would have been expected.

(iv) *Rhesus Negative Blood Group.*—Of the total of 3,251 infants, 542 were born to Rhesus negative mothers. The Rhesus negative mothers had, as would be expected, more than their share of stillbirths and neonatal deaths without defect (46 compared with 24 per thousand) ($\chi^2=13.2$; 1 d.f., $P=0.03$). Ten deaths were due to Rhesus isoimmunization: eight were stillborn (five of them macerated), and of the two live births to women with raised antibody titres one infant died with tentorial tears and intracranial haemorrhage and in the other an exchange transfusion was attempted but the infant died one hour after birth. The incidence of Class A defects in the children of Rhesus negative

mothers was 22 per thousand and thus about average. Only one of the eight mothers of children with cerebral palsy was Rhesus negative. This child had double athetosis following kernicterus.

(v) *Unwanted Pregnancy and Attempts to Induce Abortion.*—A little less than one-third of all the women said their pregnancies were unwanted. There appeared to be two main reasons for this: some women, particularly the older ones, thought that they already had enough children, and others, who tended to be among the younger ones, were unmarried or living under unsatisfactory conditions. The women whose pregnancies were unwanted were asked whether they had attempted to procure an abortion; 168 women admitted to having tried, mainly by taking drugs (ranging from castor oil to special drugs thought to be abortifacient) or by vaginal douching, only a few having tried other mechanical means. Of the women who admitted to attempting to induce abortion, four actually did abort and one had a therapeutic abortion on psychiatric grounds. In the remainder, pregnancy proceeded and apart from an increased incidence which did not reach a 5 per cent. level of significance of Class B defects, hernias, and fits, their children had no more defects than the others.

(vi) *Chronic and Previous Illness.*—430 women said that they were suffering from a chronic illness at the beginning of their pregnancy. These illnesses were for the most part indefinite, the commonest being chronic coughs, catarrh and “nerves”. More serious illnesses were less frequent. Children of women with a chronic illness had a slight, but not significant, excess of Class A defects (40 per thousand compared with 28 per thousand) and a significant excess of fits (23 per thousand compared with 10 per thousand) ($\chi^2=10.9$; 1 d.f.; $P<.001$). The conditions complained of by mothers did not, however, appear to differ from the general run—four had a cough, two had catarrh, one was “run down”, one had a hydronephrosis, one pulmonary tuberculosis, and the last mitral stenosis.

HYPERTENSION.—Information about blood pressure at the first ante-natal visit was only available for 1,835 women as this observation was not made until nearly half-way through the survey. 60 women were recorded as having a diastolic pressure of 90 mm. or more at the first ante-natal examination; of these, two aborted and two had hysterotomies (one for hypertension and the other for eclampsia). The incidence among their offspring of stillbirths and neonatal deaths without defect was 67 per thousand compared with 24 per thousand total births, but the difference did not reach a 5 per cent. level of significance ($\chi^2=3.5$; 1 d.f.; $P=.06$). There was no evidence of any association of hypertension with defect, but the numbers were too small to detect any but a marked association.

ANAEMIA.—Women who were anaemic (as indicated by a haemoglobin value of less than 80 per cent. at the first ante-natal examination) had an excess of stillbirths and neonatal deaths (39 compared with 24 per thousand in all maternities ($\chi^2=4.4$; 1 d.f.; $P<.04$)). The incidence of defects among their children did not, however, differ from the children of women with haemoglobin levels of 80 per cent. or more.

SYPHILIS.—This featured insignificantly in this series. Of the nine women who had a positive Wassermann reaction or Kahn test in pregnancy, one had an infant who died neonatally with tentorial tears, one child was untraced, and the remaining seven were reported to be normal and without defect.

PULMONARY TUBERCULOSIS.—An excess of women with a history of pulmonary tuberculosis among the

mothers of children with serious defects was noted in the original analysis. An excess of children with major defects was also observed among the previous pregnancies of these women. There were in all 61 women in the series who had or had had pulmonary tuberculosis; of these, two aborted and three had stillborn infants with serious defects (two were anencephalic and one had absent kidneys and a diaphragmatic hernia). At the second report one more child of a tuberculous mother was found to have a cardiac defect and two others pyloric stenosis, making a total of six Class A defects (98 per thousand) ($\chi^2=9.2$; 1 d.f.; $P=.002$).

The women with a history of pulmonary tuberculosis were divided into two groups: those whose tuberculosis was apparently healed and who were not attending a chest clinic more often than once a year, and the remainder. All but three of the 28 children of women with healed tuberculosis were traced and none had a Class A defect. Of the 33 women in the remaining group, two aborted and six of their 31 children had a Class A defect.

HERPES SIMPLEX.—About one-third of the women were asked whether they had ever had cold sores. Roughly one-third of those asked gave a positive history. These women had rather more abortions but fewer stillbirths and neonatal deaths and in general fewer children with defects than mothers with no history of cold sores.

ASTHMA.—33 women gave a history of asthma. The 22 women who said that they had had an attack of asthma during the first 12 weeks of pregnancy had three children (14 per cent.) who were reported to have asthma. None of the eleven children of women who gave a history of asthma in the past but none during pregnancy was reported to have asthma.

(vii) *Events in Early Pregnancy*

SEVERE EMOTIONAL UPSET.—In all, 444 women said that they had suffered from severe anxiety or shocks in early pregnancy. Nearly 7 per cent. of their children were untraced, which is probably because of the greater amount of illegitimacy among the untraced children; but the children who were traced had an average incidence of defects.

Much of the excessive anxiety in early pregnancy was associated with the pregnancy itself and the women who conceived out of wedlock had a great deal of worry. There was no excess of defects among the women who conceived out of wedlock apart from hernias.

COITUS.—The children of women who continued from their first missed menstrual period to have coitus at least once a week had an average incidence of foetal and infant death and defect. The outcome of the pregnancies of 233 women who abstained from coitus between the 4th and the 13th week of pregnancy differed from this in certain respects. The rate of abortions among these women was 43 compared with 21 per thousand among all the women, ($\chi^2=4.7$; 1 d.f.; $P<0.03>0.02$) and the incidence of stillbirths and neonatal deaths was decreased, but not significantly so. There were rather fewer defects among their surviving children. The excess of abortions was mainly in women who had aborted previously, and was perhaps accounted for by their having been told to take more care next time.

ACUTE ILLNESS.—The episodes of acute illness which occurred during the first 12 weeks of pregnancy were divided into those judged at the interview to be febrile and those in which there was no evidence of fever. Among the 148 pregnancies in which the women had had a febrile illness, the incidence of stillbirths and neonatal deaths was raised but not significantly so (40 compared with 24 per thousand). The incidence of abortions was significantly increased, 47 compared with 21 per thousand in all maternities ($\chi^2=4.2$; 1 d.f., $P=0.04$). Likewise the incidence of Class A defects was significantly raised to 61 per thousand compared with 28 per thousand ($\chi^2=5.5$; 1 d.f.; $P>0.01<0.02$). Of the febrile illnesses 86 per cent. were respiratory infections and eight of the nine febrile illnesses followed by Class A defects were of this nature. Examination of the seasonal distribution of the respiratory infections showed that four-fifths occurred between October and March, and six of the eight febrile respiratory illnesses associated with these defects occurred during the 6 winter months. The two Class A defects associated with summer illnesses were tracheo-oesophageal fistula (May) and spina bifida (September). The children of mothers who reported febrile illnesses also had more than twice as much reported asthma or eczema ($\chi^2=8.1$; 1 d.f.; $P=0.004$) and twice as many eye defects as other children ($\chi^2=4.2$; 1 d.f.; $P=0.04$). The possibility that mothers of children with asthma or eczema reported more acute febrile illnesses because they booked earlier and therefore recalled better was examined but found not to be the case. These mothers did not book any earlier than the other mothers, and those who booked late gave in fact more often a history of febrile illnesses than those who booked early.

VOMITING.—The children of the 488 women who vomited during the first 12 weeks of pregnancy had an essentially average incidence of death and defect. There was a slight, but not significant, excess among them of asthma and hernias. When the group was broken down into 149 women with severe vomiting and 339 with mild vomiting, there was no suggestion that excessive vomiting was associated with any abnormality except asthma and here the association did not reach a 5 per cent. level of confidence.

FAINTING.—135 women said that they had lost consciousness at least once during the first 12 weeks of pregnancy. Among their children there was an average incidence of deaths and defects apart from a slight, but not significant, excess of eye defects.

INJURIES OR OPERATIONS.—143 women reported an injury or operation during the first 12 weeks of pregnancy. These women had slightly more than their share of abortions and defects of Class A and B (but not significantly so) but no stillbirths or neonatal deaths without defect.

About two-thirds of the injuries reported were due to falls, and about one-quarter were caused by road accidents of various sorts.

A few operations were reported during the first 12 weeks of pregnancy; two women who had had a major dental operation and a herniorrhaphy respectively had normal children, and one who had had an appendicectomy had a child with a minor visual defect. Three women with normal children had had cauterization of the cervix, but the only woman who had a tubal insufflation (done during the second week) had a child with an interventricular septal defect and cleft palate.

ANAESTHETICS.—Apart from a general anaesthetic for some of the operations mentioned above and in a few cases for reduction of fractures and excision of wounds, many dental extractions were performed under nitrous oxide anaesthesia. In all, 54 women were anaesthetized during the first 12 weeks of pregnancy. There was a slight, but not significant, excess of abortions and of Class A defects in their children and a significant excess of eye defects ($\chi^2=5.5$; 1 d.f.; $P<0.02>0.01$).

VAGINAL BLEEDING.—523 women reported bleeding from the vagina after what was considered to be the last menstrual period. Some association was observed with abortions (the bleeding was probably in some cases the first evidence of abortion) and with stillbirths and neonatal deaths without defect

($\chi^2=3.5$; 1 d.f.; $P=0.06$) but none with serious defects, and there was no suggestion of an excessive incidence in any particular group of defects.

DISCUSSION

Some caution is needed in the interpretation of the results of a survey of this type and size. The likelihood of finding by chance a statistically significant association between maternal factors and children with defects is increased when a large number of different factors and defects are examined. A greater difficulty is that, in the ascertainment of abnormalities in the children, a good deal of weight is given to what mothers report about their children, and it may be that the mothers who give the fullest history of events and illnesses in early pregnancy will also report more abnormalities in their children. At the same time, the incidence of abnormalities under consideration is so low that only a fairly definite association will reach a 5 per cent. level of significance in a survey of this size except when common maternal characteristics are examined.

As the characteristics and experiences of the mothers whose pregnancy terminated in abortion or in stillbirth or neonatal death without defect were discussed in the previous communication and the results were not affected by later findings, the present discussion will be limited to malformations and other abnormalities.

MALFORMATIONS.—The likelihood of the association found between febrile illnesses and Class A defects occurring by chance is small, but there was no evidence in this survey to suggest that febrile illness played an important part in the causation of defects. Coffey and Jessop (1959) found 2.4 times as many defects among the children of women who reported influenza in early pregnancy compared with the controls. In this survey children of women with febrile illnesses had 2.2 times as many defects as other children. If febrile illnesses were an important aetiological factor, seasonal trends and yearly fluctuations dependent upon epidemics would be expected. There is some suggestion that anencephaly, which is a lethal and obvious defect suitable for study, behaves in this way (Edwards, 1958; McKeown and Record, 1951) but the mothers of the eight anencephalic infants found in the present survey gave no history of febrile illness.

The association noted between pulmonary tuberculosis in the mother and Class A defects in the child is supported by evidence from the previous pregnancies of the women with a history of tuberculosis.

However, the total number of women in the series said to have had pulmonary tuberculosis was only 61 and more evidence on larger numbers is needed to exclude the possibility that the positive finding in this series was due to some associated variable or to chance alone. If the association were confirmed, it could be due to some constitutional factor predisposing to both tuberculosis and defective children, or it could be connected with the tuberculous infection or its treatment or conceivably to diagnostic x-rays.

The high incidence of serious malformations among the small group of women working in laundries presents a similar problem. The mothers were mostly primiparae, so that there was no evidence from the previous pregnancies. Any direct effect resulting from an occupational hazard seems unlikely. It is more probable either that these women differed from the rest in some way other than their employment or that working conditions in laundries favour some adverse environmental factor, or, of course, that it was a chance finding. Laundry workers reported more illnesses than expected in the first 12 weeks of pregnancy, but the defects were distributed equally among those who reported a febrile illness and those who reported none. The women working in laundries in this area probably came from an inferior social environment, but there was no evidence of excessive anaemia among them which might indicate a poor nutritional status.

The groups of women with children who had specific defects were numerically too small to reveal any but marked differences from the rest. In mongolism, now known to be associated with a chromosomal anomaly, the maternal age effect was noticeable. There was no indication of ill-health in the mothers which might be associated with the chromosomal anomaly.

In view of the theory of raised intra-uterine pressure perhaps associated with a strong abdominal musculature as a factor in the aetiology of talipes it is interesting to note that whereas one in twelve of all the women were employed in work which they considered heavy, three of the seven mothers of children with talipes were doing work of this nature.

EYE DEFECTS.—Although the incidence of squints reported was fairly constant at different ages and using different methods of ascertainment, a substantial proportion of refractive errors without squint was certainly missed in the younger children. As there was selective reporting it is quite possible that mothers who were more concerned about their

own health during pregnancy would be more likely to worry about their children's eyes. This might explain the excess of reported febrile illnesses and also of anaesthetics which were mainly for dental extractions, but it is perhaps equally possible that there may be some aetiological connexion, and unlikely chance findings can certainly not be eliminated.

FITS.—The mothers of the 31 children who had a convulsion at 3 years or over or three or more episodes before the age of 3 years had reported an excess of ill-health of various types at the onset of their pregnancies. There would not appear to be any direct connexion between the rather vague and common conditions of which they complained and fits in the children, but it may well be that there is some indirect connexion between the two. However, the association observed is of a low order and may have arisen by chance.

ASTHMA OR ECZEMA.—The older age but lower parity of the mothers of children with asthma or eczema is consistent with a raised incidence of these conditions in the higher socio-economic groups.

Asthma or eczema were found to occur more commonly among the children of women who reported a febrile illness during early pregnancy than among those who reported none. There was no suggestion that these mothers booked earlier and therefore recalled their illnesses better. Three of the febrile illnesses were in women booking late when it was rare for a febrile illness to be reported; furthermore, febrile illnesses were in general less frequently reported by mothers over 30 than under 30, and the mothers of asthmatic children tended to be older. Perhaps the mothers of asthmatic children recalled their illnesses better than other mothers, or perhaps there is some connexion between susceptibility to infection and allergy.

The experience of this survey suggests that it is unlikely that a prospective inquiry, even based on much larger numbers, will show any important association with any ordinary events or maternal states such as vaginal bleeding, vomiting, anaemia, emotional stresses, and chronic illness, except possibly febrile illnesses, occupation, and pulmonary tuberculosis. Prospective inquiries may well be the most satisfactory method of testing hypotheses such as the possible connexion between virus infections and malformations. Promising hypotheses are unfortunately few and in the meantime more economical though less conclusive methods of searching for clues may prove more useful.

SUMMARY

The final results are presented of a prospective survey of maternal characteristics, and illnesses and events in the first 12 weeks of pregnancy in relation to death and defect in the children.

3,278 women were interviewed at their first antenatal visit and the immediate outcome of pregnancy, including the presence of any malformations observed in the infants, was ascertained in 98 per cent. The total number of infants born alive was 3,116. Later reports were obtained on just over 95 per cent. of these children (91 per cent. were aged 3 to 6 years at the time of the report, and 4 per cent. 1 to 2 years).

The main findings were as follows:

DEATHS.—The stillbirth rate in the series was 20 per thousand total births, and the infant mortality rate 18 per thousand live births.

25 per cent. of the stillbirths, 22 per cent. of the first year deaths, and 29 per cent. of the later deaths were associated with serious malformations.

DEFECTS.—Serious malformations were found in 28 per thousand total births (neurological 12, cardiac 9, genito-urinary 3, hare lip or cleft palate 2, and pyloric stenosis 6 per thousand).

Other and for the most part less serious abnormalities were found in 96 per thousand surviving children (musculo-skeletal defects 14, hernias 26, naevi 10, eye defects 43, and miscellaneous defects 12 per thousand). In addition, 26 per thousand surviving children developed asthma or eczema and 19 per thousand convulsions or fits.

The incidence of abnormality was examined among the children of mothers with particular characteristics or experiences during pregnancy. Associations significant at a 5 per cent. level were observed as follows:

(1) *Employment.*—Of a group of 28 women working full-time in laundries, four had children with serious defects—an incidence of 143 compared with 28 per thousand in all mothers.

(2) *Febrile Illness.*—148 women reported a febrile illness in the first 12 weeks of pregnancy. They had an excess of abortions (47 compared with 21 per thousand) and children with serious defects (61 compared with 28 per thousand), eye defects (68 compared with 35 per thousand), and asthma or eczema (61 compared with 24 per thousand).

(3) *Pulmonary Tuberculosis*.—The 61 women with a history of pulmonary tuberculosis had an excess of children with serious defects (98 compared with 28 per thousand).

Malformations showed no significant association with most of the events recorded in early pregnancy, notably anaemia, vaginal bleeding, vomiting, fainting, injury or operation, anaesthetic, attempted abortion, and severe emotional upsets.

I wish to thank the Medical Officer of Health for Hertfordshire for allowing me to conduct this survey and all the health visitors who took part in it, particularly those who had a large number of children to trace. I am

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