CONGENITAL MALFORMATIONS AND ENVIRONMENTAL INFLUENCES IN PREGNANCY

BY

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Most human congenital malformations are believed to be due to the interaction of both genetic and environmental influences. Neither retrospective enquiry (*e.g.*, Record, 1958) nor prospective study (*e.g.*, McDonald, 1961) has yet been of much value in uncovering the environmental factors responsible and, with the exception of maternal rubella infection and a small number of drugs (notably thalidomide), the nature of these influences is still not known.

In the South Wales Survey of Congenital Defects, a register has been compiled of defects occurring among all births in 1964-66 to women resident in

South Wales, *viz.*, the county boroughs of Cardiff, Swansea, Merthyr Tydfil, and Newport, and the administrative counties of Glamorgan and Monmouthshire. As part of the epidemiological investigation of these defects, and in an attempt to identify possible aetiological factors, a retrospective study was made of 833 consecutive cases (Table I) and an equal number of matched controls—being women who had given birth to normal (*i.e.*, non-malformed) infants, matched for maternal age, parity, social class, area of residence, and date of delivery (± 2 weeks).

The interviews were conducted in the homes by health visitors and local authority assistant medical officers and usually took place in the second month after delivery. Each member of a pair (the case and its control) were questioned by the same interviewer. Because of the nature of the enquiry, interviews could not be conducted 'blind'; this being so, as much information as possible concerning the congenital defect was given to the interviewer.

The factors investigated were in four groups (Table II) and related to two periods: (*a*) the first trimester, defined as the first 16 weeks of pregnancy, and (*b*) subsequent trimesters. Whenever possible, the date of the end of the first trimester was given to the interviewer.

TABLE I
THE CASES INVESTIGATED

System	Defect	No.
Central nervous	Anencephaly	107
	Spina bifida cystica	140
	Other	32
	Total	279
Cardiovascular	Septal defect	21
	Patent ductus arteriosus	16
	Aortic defect	29
	Other	34
	Total	100
Alimentary	Cleft lip/palate	66
	Pyloric stenosis	39
	Other	68
	Total	173
Musculo-skeletal	Reduction deformity	11
	Dislocation of hip	15
	Talipes	92
	Other	34
	Total	152
Miscellaneous	Mongolism	32
	Eye, ear	16
	Urogenital	15
	Skin	46
	Other	20
	Total	129
All systems		833

TABLE II
THE FACTORS INVESTIGATED

Group A: Illnesses in the First Trimester and Concurrent Illnesses

Factors Investigated	Particulars Recorded
Nausea	Severity (mild, moderate, severe)
Vomiting	Severity (mild, moderate, severe)
Fainting	Number of episodes and stage(s) of pregnancy
Bleeding	Stage of pregnancy and whether at time of an expected period
Accidents	Stage of pregnancy and nature
Coughs and colds	Stage of pregnancy
Other febrile illnesses	Stage of pregnancy and nature
Concurrent illnesses	Stage of pregnancy (for diabetes mellitus, cardiac disease, asthma, tuberculosis, migraine, mental illness, others)

For all illnesses, the type and duration of treatment were recorded.

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TABLE II (cont.)

Group B: Drugs, etc.

Factors Investigated	Particulars Recorded
Drugs (oral therapy)	Stage of pregnancy, nature of drug, reason and duration of use (for antibiotic, sulphonamide, steroid, salicylate, sedative, iron preparation, others)
Contraceptive	Use of oral and/or chemical contraceptive in the three months before conception
General anaesthetic X-ray	Stage of pregnancy and reason Stage of pregnancy and part X-rayed (abdomen, chest or other)
Smoking	Number smoked per day, whether regularly and whether she gave up for part of pregnancy
Diet	A subjective impression by the interviewer of the adequacy of the diet during the first trimester—recorded as 'not balanced', 'doubtful' or 'normal'; details were recorded.

Group C: Employment, Accommodation, Water Supply, Height, and Weight in the First Trimester

Factors Investigated	Particulars Recorded
Employment	Nature, duration and whether sedentary or non-sedentary
Accommodation	Type (own, shared or other, e.g., caravan)
Bedroom density	Ratio bedrooms used: number of occupants
Water supply	Type of supply (tap, well, other)
Height	Mother's statement
Weight	Mother's statement of weight before pregnancy or during first trimester*

*Confirmed, whenever possible, from the mother's 'pregnancy continuity card' (this fact recorded)

Group D: Miscellaneous Factors, Some having Genetic Implications

Factors Investigated	Particulars Recorded
Area of parents' birth	County of birth
Blood group	Mother's ABO and Rhesus group from Blood Transfusion Service report, continuity card or obstetric record
Cousin marriage	First cousin marriage of child's parents
Paternal age	Age at time of child's birth
Duration of marriage	Duration at time of child's birth
Family history of congenital defect	In child's siblings and parents: nature of defect(s) recorded

For the cases and controls resident in Cardiff, hospital and local authority obstetric notes were examined, and general practitioners were invited to give particulars of illnesses in pregnancy and of treatments prescribed.

The frequency of each of the factors investigated was calculated for cases and controls—by diagnosis, by system affected, and for all defects combined. The chi-square test was then applied to determine the levels of statistical significance of the differences found.

RESULTS

A statistically significant excess among cases was found for many of the factors investigated. Those relating to the first trimester are shown in the Figure.

GROUP A

For all systems combined, there were significant differences for bleeding ($P < 0.05$), accidents ($P < 0.01$), coughs and colds ($P < 0.05$), and other febrile illnesses ($P < 0.01$).

The following significant differences were present for individual systems:

Central nervous system: accidents ($P < 0.01$)Cardiovascular system: nausea ($P < 0.05$)Alimentary tract: vomiting, bleeding, coughs and colds, other febrile illnesses (all $P < 0.05$).

Within the various systems, significant differences (all $P < 0.05$) were present for the following defects:

Anencephaly: accidents

Septal defects: febrile illnesses

Cleft lip and/or palate: nausea and vomiting

Other alimentary: nausea

Talipes: other illnesses

Skin defects: bleeding and other illnesses

The rates for accidents in the first and subsequent trimesters are shown in Table III. Significant first trimester differences have been listed above; there were none in subsequent trimesters. Although accidents of all types and degrees of severity were included, the majority of those reported were falls.

TABLE III
ACCIDENTS IN PREGNANCY
(Rates for controls are shown in parentheses)

Defect	1st Trimester		2nd and 3rd Trimesters	
	Accident (%)	Significance Level	Accident (%)	Significance Level
Central nervous	12.9 (5.0)	1%	21.1 (20.4)	
Cardio-vascular	9.0 (10.0)		17.0 (19.0)	
Alimentary	11.6 (5.8)		27.2 (20.2)	
Musculo-skeletal	7.2 (5.3)		18.4 (21.0)	
Miscellaneous	4.7 (4.7)		14.7 (22.5)	
All defects	9.8 (5.8)	1%	20.4 (20.6)	
Anencephaly	17.8 (7.5)	5%	15.0 (16.8)	

GROUP B

For all systems combined, there were significant differences for salicylates ($P < 0.001$), sedatives ($P < 0.05$), other drugs ($P < 0.001$), and dietary imbalance ($P < 0.05$).

The percentages of all cases and controls having each type of drug are shown in Table IV. An important feature of the table is the absence of

		Central nervous system	Cardio-vascular system	Alimentary tract	Musculo-skeletal system	Miscellaneous	All systems
A	Nausea	X					
	Vomiting		X				
	Fainting						
	Bleeding		X				X
	Accidents	▲					▲
	Coughs and colds		X				X
	Other febrile illnesses		X				▲
	Concurrent and other illnesses						
B	Antibiotic						
	Sulphonamide						
	Steroid						
	Salicylate	X		▲		X	○
	Sedative					X	X
	Iron						
	Other drugs		X	▲			○
	Contraceptive (oral or chemical)						
	General anaesthetic						
	X-ray						
	Smoking						
	Diet	▲					X
	C	Employment					
Accommodation : type bedroom density						▲	
Water supply							
Height							
Weight							
D	Area of parents' birth						
	Blood group						
	Cousin marriage						
	Paternal age						
	Duration of marriage						
	Family history of congenital defect—sibling	○	▲		X	▲	○
	—father						○
—mother						○	

KEY	P < 0.001	P < 0.01	P < 0.05
	○	▲	X

FIGURE.—Statistically significant differences for first trimester events

TABLE IV
DRUGS IN PREGNANCY
(Rates for controls are shown in parentheses)

Drug	1st Trimester		2nd and 3rd Trimesters	
	Took Drug (%)	Significance Level	Took Drug (%)	Significance Level
Antibiotic	5.5 (4.6)		8.3 (8.2)	
Sulphonamide	0.5 (0.7)		1.8 (1.0)	
Steroid	0.7 (0.2)		0.6 (0.4)	
Salicylate	22.3 (14.4)	0.1%	28.5 (24.2)	
Sedative	8.4 (5.3)	5%	15.0 (15.2)	
Iron	43.1 (43.0)		79.8 (80.6)	
Others	37.9 (28.9)	0.1%	47.1 (43.8)	

significant differences for drugs taken in the second and third trimesters.

The following significant differences were present for individual systems:

Central nervous system: salicylates ($P < 0.05$)
dietary imbalance ($P < 0.01$)

Cardiovascular system: other drugs ($P < 0.05$)
Alimentary tract: salicylates ($P < 0.01$)
other drugs ($P < 0.01$)

Miscellaneous defects: salicylates ($P < 0.05$)
sedatives ($P < 0.05$)

Within the various systems, the following significant differences were present:

Anencephaly: dietary imbalance ($P < 0.01$)
Spina bifida cystica: dietary imbalance ($P < 0.05$)
Aortic defects: other drugs ($P < 0.05$)
Cleft lip and/or palate: other drugs ($P < 0.001$)
Other alimentary defects: other drugs ($P < 0.05$)
dietary imbalance ($P < 0.05$)

Talipes: salicylates ($P < 0.01$)
Eye and ear defects: other drugs ($P < 0.05$)
Mongolism: sedatives ($P < 0.05$)

Tables V and VI show the rates for salicylates taken and for the group of miscellaneous drugs. These tables show those defects for which there were marked differences between the rates for cases and controls, but in some instances not sufficiently great to reach levels of statistical significance. One notable feature of these tables is the absence (with one exception) of significant differences for drugs taken in the second and third trimesters.

Among the group of miscellaneous drugs taken

TABLE V
SALICYLATES IN PREGNANCY
(Rates for controls are shown in parentheses)

Defect	1st Trimester		2nd and 3rd Trimesters	
	Took Drug (%)	Significance Level	Took Drug (%)	Significance Level
Central nervous	24.0 (16.5)	5%	31.9 (25.8)	
Cardio-vascular	13.0 (15.0)		22.0 (28.0)	
Alimentary	25.4 (13.3)	1%	27.7 (25.4)	
Musculo-skeletal	22.4 (13.8)		24.3 (23.7)	
Miscellaneous	21.7 (11.6)	5%	31.8 (17.1)	1%
All	22.3 (14.4)	0.1%	28.5 (24.2)	
Anencephaly	24.0 (16.5)		28.0 (26.2)	
Spina bifida	25.0 (17.1)		35.7 (25.0)	
Cleft lip/palate	27.3 (12.1)		31.8 (27.3)	
Pyloric stenosis	20.5 (10.3)		20.5 (23.1)	
Other alimentary	26.5 (16.2)		27.9 (25.0)	
Talipes	26.1 (14.1)	1%	23.9 (21.7)	

TABLE VI
MISCELLANEOUS DRUGS IN PREGNANCY
(Rates for controls are shown in parentheses)

Defect	1st Trimester		2nd and 3rd Trimesters	
	Took Drug (%)	Significance Level	Took Drug (%)	Significance Level
Central nervous	38.4 (32.6)		45.2 (42.3)	
Cardio-vascular	36.0 (20.0)	5%	45.0 (42.0)	
Alimentary	45.7 (31.2)	1%	50.3 (46.8)	
Musculo-skeletal	30.9 (25.0)		50.7 (42.1)	
Miscellaneous	36.4 (29.5)		44.2 (46.5)	
All	37.9 (28.9)	0.1%	47.1 (43.8)	
Septal defect	57.1 (14.3)		66.7 (38.1)	
Patent ductus	18.8 (31.3)		25.0 (43.8)	
Aortic defect	37.9 (20.7)	5%	41.4 (55.2)	
Other C.V.S.	29.4 (17.6)		44.1 (32.4)	
Cleft lip/palate	56.1 (24.2)	0.1%	47.0 (47.0)	
Pyloric stenosis	33.3 (53.8)		59.0 (66.7)	
Other alimentary	42.6 (25.0)	5%	48.5 (35.3)	
Eye, ear	62.5 (12.5)	5%	50.0 (50.0)	

by mothers giving birth to babies with cleft lip and/or palate are the anti-emetics. Vomiting in early pregnancy was reported by 27 of the 66 cases studied and by 11 of the controls; 17 of the cases took anti-emetics but only 10 of the controls (Table VII).

TABLE VII
HISTORY OF VOMITING AND USE OF ANTI-EMETICS
IN FIRST TRIMESTER

	Cases (cleft lip and/or palate)	Controls
Vomiting: no anti-emetics	10	1
anti-emetics taken	17	10
No vomiting	39	55
Total	66	66

Table VIII shows the rates for dietary standards in the first trimester for each system and for those

TABLE VIII
DIET DURING FIRST TRIMESTER
(Rates for controls are shown in parentheses)

Defect	Not 'Balanced'	Doubtful	Normal	Significance Level
Central nervous	3.2 (3.9)	17.6 (7.9)	78.5 (88.2)	1%
Cardio-vascular	6.0 (6.0)	13.0 (8.0)	82.0 (85.0)	
Alimentary	4.6 (2.9)	8.1 (6.9)	86.7 (90.2)	
Musculo-skeletal	7.2 (6.6)	9.2 (10.5)	83.6 (82.9)	
Other	4.7 (3.1)	11.6 (11.6)	83.7 (85.3)	
All systems	4.8 (4.3)	12.6 (8.8)	82.4 (87.0)	5%
Anencephaly	4.7 (5.6)	26.2 (9.3)	68.2 (85.0)	1%
Spina bifida	1.4 (2.9)	13.6 (5.0)	84.3 (92.1)	5%
Alimentary (other)	8.8 (1.5)	10.3 (4.4)	79.4 (94.1)	5%

defects showing significant differences. Differences were small for those said to have diets which were 'not balanced'—with the exception of other alimentary defects. There were, however, marked differences in diets considered 'doubtful' for most systems and for the individual defects listed.

GROUP C

The bedroom density (ratio of bedrooms: occupants) differed significantly for miscellaneous defects ($P < 0.01$), there being more cases than controls with high ratios.

For individual defects there were significant differences for the following:

Anencephaly: maternal weight—heavier than controls ($P < 0.05$)

Talipes: bedroom density—more cases with low ratios ($P < 0.05$)

GROUP D

There were no significant differences for the parents' area of birth, maternal blood group, paternal age or duration of marriage.

For all systems combined, there was a highly significant ($P < 0.001$) difference for a family history of congenital defect—both for siblings and for each parent. In siblings also, this significant excess was present for most systems, viz., central nervous ($P < 0.001$), cardiovascular ($P < 0.01$), musculo-skeletal ($P < 0.05$), and for miscellaneous defects ($P < 0.01$).

These differences were due almost entirely to a recurrence of the same or similar (*i.e.*, same system) defect. Among individual defects there were significant differences for spina bifida and for the group of other central nervous system defects (both $P < 0.05$).

DISCUSSION

The limitations of a retrospective enquiry of this kind are several and cannot be overlooked.

(1) The results may be affected by bias on the part of the interviewer or the mother, whose statements may be coloured by the knowledge that her infant is either normal or abnormal.

(2) Events may be forgotten, the nature of the drugs and dosage not known, and the timing of events inaccurate.

(3) In this study the whole of the first trimester has been considered, whereas the critical periods of development are short and occur at different times for different organs.

(4) Another difficulty in this investigation is that a large number of tests of significance were performed and many of these apparently significant differences could have arisen merely by chance (Table IX).

TABLE IX
TESTS OF STATISTICAL SIGNIFICANCE

	Tests Performed	Values of P		
		< 0.05	< 0.01	< 0.001
Individual defects	799	18 (31)	2 (7)	1 (< 1)
Individual systems	205	10 (8)	7 (2)	1 (< 1)
All systems combined	41	4 (2)	2 (< 1)	5 (< 1)
Total	1,025	32 (41)	11 (9)	7 (1)

The numbers that could have occurred merely by chance are shown in parentheses

Nevertheless, where the obstetric notes of patients have been scrutinized and general practitioner reports submitted, the author has been impressed by the accuracy of the mothers' statements. Had bias on the part of the mothers or interviewers played an important role in producing statistically significant differences for events in the first trimester, it might be expected that such differences would occur in the later trimesters also. The striking lack of such differences suggests that those found for first trimester events are real.

Interobserver differences and the possibility that positive findings are the result of observer bias are lessened by using many observers. This enquiry was conducted by 58 interviewers and this fact lends weight to the likelihood that the positive findings are real.

Among the positive findings recorded above, those of particular interest are the results for salicylate administration, for the group of miscellaneous drugs (including anti-emetics), and for diet.

SALICYLATE PREPARATIONS

The results of this investigation suggest that either salicylates have a teratogenic effect or that the conditions for which they are given have such an action. This finding is of particular interest in view of the frequency with which women of childbearing age take aspirin. Carter (1964) has estimated that perhaps as many as a half take at least one tablet containing aspirin in early pregnancy.

Salicylates produce congenital malformations in mice and rats, probably by inhibiting the synthesis of acid mucopolysaccharide (Larsson, Boström, and Ericson, 1963). Among the defects produced in rats are craniorachischisis, exencephaly, and hydrocephaly (Warkany and Takacs, 1959).

Carter and Wilson (1963) have reported an increased pregnancy wastage rate following the administration of salicylates in a small series in general practice but due entirely to abortions. In the pilot analysis of the Outcome of Pregnancy Survey conducted by the Royal College of General Practitioners, based on 1,038 pregnancies, there was no evidence of a teratogenic effect from salicylate-containing preparations (Slater, 1965). But it was shown that in order to achieve a total of 100 patients taking aspirin at some time during the first eight weeks following conception, it would be necessary to investigate about 2,500 pregnancies, and the results of the full survey of at least 10,000 cases should provide valuable evidence on this matter.

In our investigation, there was a wide range in the dosage of salicylate taken, and it is particularly interesting that, on such a crude measure of drug intake, several statistically significant differences should have been found between cases and controls. These results demand an *ad hoc* enquiry into the possible teratogenic effect of salicylates.

MISCELLANEOUS DRUGS

Prominent among this group of drugs were anti-emetics, the nature of many being unknown. One of these drugs, meclozine, has received much attention, and several studies have suggested that it has no teratogenic effect in the human (*e.g.*, Carter and Wilson, 1962; Smithells and Chinn, 1964). But Lenz (1966) has shown that, if data from 15 studies are pooled, among 3,333 infants whose mothers were given meclozine in the first trimester, 12 had a cleft lip and/or palate. This number is two to three times that expected.

The results of the investigation reported here do not permit a definite conclusion to be reached on the possible teratogenic effect of anti-emetic drugs. It is possible, of course, that vomiting in early

pregnancy or a hormonal imbalance associated with pregnancy sickness may have a teratogenic effect. The ratio of cases to controls when no anti-emetics were taken for vomiting in the first trimester (10:1) is much greater than when anti-emetics were taken (17:10), and this is evidence against a teratogenic action by anti-emetic drugs in the aetiology of cleft lip and/or palate.

DIET

Congenital malformations have been produced in experimental animals by a wide variety of deficiencies in the maternal diet. The literature on this subject was reviewed by Kalter and Warkany (1959) and among the dietary deficiencies shown to have teratogenic effects are those of vitamin A, thiamine, riboflavine, niacin, pantothenic acid, vitamin E, and folic acid. Hypervitaminosis A is also teratogenic in experimental animals, and Millen and Woollam (1958) have shown that the incidence of cleft palate in rats induced by hypervitaminosis A is much lower if the vitamins of the B group are administered at the same time. The degree of dietary deficiency needed to induce malformations in experimental animals need not be great. For example, Giroud (1960) found that a riboflavine level in the mother's liver only 20 to 30 below normal was teratogenic.

Coffey and Jessop (1958) have suggested that dietary deficiency may be an aetiological factor in anencephaly. They found evidence of a higher prevalence of defective nutrition among the mothers of anencephalics than among a control group. There was also a marked excess of unemployed fathers among the cases and they showed that in the lower income groups in Dublin the average intakes of calcium, vitamin A, riboflavine, and vitamin C were below the recommended allowance.

Burke, Beal, Kirkwood, and Stuart (1943) found that in a group of mothers, whose diet in pregnancy was classified as 'poor' or 'very poor', there was a significantly higher ($P < 0.01$) malformation rate than among those having a 'good' or 'excellent' diet.

In a blind controlled retrospective study of pregnancy diets, Pitt and Samson (1961) demonstrated the following dietary deficiencies: cleft lip and/or palate—thiamine ($P < 0.05$); congenital heart defects—protein, iron, vitamin C ($P < 0.05$), carbohydrate, and niacin ($P < 0.01$); talipes—riboflavine, niacin, vitamin C ($P < 0.05$); mongolism and spina bifida cystica—none; all malformed infants—carbohydrate, iron, thiamine, vitamin C ($P < 0.05$), and niacin ($P < 0.01$).

It has been shown that folate deficiency may

produce malformations, including central nervous system defects and cleft lip and palate, in the rat embryo (Evans, Nelson, and Asling, 1951; Nelson 1960). Studies in Liverpool suggest that there is a relationship between malformations of the fetus and defective folate metabolism based on FIGLU tests performed late in pregnancy or in the early puerperium (Hibbard and Smithells, 1965).

It is interesting, therefore, that for central nervous system defects there was a significant excess (among the cases) of diets judged to be unbalanced or doubtful. This was also true of two separate defects—*anencephaly* and *spina bifida cystica*. Although these differences could be accounted for by bias on the part of the observers, this seems unlikely as they were present in each of the six local authority areas in the investigation.

The results of this study do not permit any conclusion to be made concerning the nature of the dietary deficiencies suspected of having aetiological importance in the central nervous system malformations. In none of the defects investigated was there a significantly lower weight (pre-pregnancy or in the first trimester) among the cases, suggesting that, if dietary deficiencies play a part in the causation of congenital defects, they are not of such a nature as to produce underweight. (In fact, the mothers of *anencephalics* were significantly heavier than matched controls).

OTHER FACTORS

Defects of the central nervous system show a marked social class distribution, having a higher incidence in the lower income groups than in the upper, and this is especially true of *anencephalus* (Edwards, 1958). It has been suggested that this may be due to an increased liability to infection through overcrowding. In this study, using controls matched for several factors including social class, the only significant differences detected in standards of accommodation, judged by bedroom density, were for *talipes* (higher density among cases) and for miscellaneous defects (lower density among cases).

Anderson, Baird, and Thomson (1958), in their analysis of 37,585 single births in Aberdeen, demonstrated an excess of central nervous system malformations in small women and they suggested that this association reflected standards of childhood nutrition. In the study reported here, there was no demonstrable relationship between congenital abnormality and maternal height.

In a prospective study of 3,295 pregnancies, McDonald (1961) found an increased malformation risk in three groups—following a febrile illness in

the first trimester, in tuberculous patients, and in laundry workers. But in a study of chest clinic patients, Lowe (1964) was unable to confirm McDonald's findings of an excess of malformations in births to tuberculous patients. In the investigation reported here, the only defects in which a history of cough, cold or other febrile illness occurred significantly more often among the cases were septal defects and all alimentary tract defects combined.

SUMMARY

As part of an epidemiological study of congenital malformations in South Wales, a retrospective enquiry was made of 833 pregnancies which resulted in the birth of malformed infants and of an equal number of matched controls. Many statistically significant differences were found between cases and controls, those of greatest interest (and possible importance) being:

- (1) the taking of salicylate preparations in the first trimester (all systems, $P < 0.001$); central nervous system, $P < 0.05$; alimentary tract, $P < 0.01$; miscellaneous defects, $P < 0.05$; *talipes*, $P < 0.01$;
- (2) the taking of drugs in a miscellaneous group including anti-emetics (all systems, $P < 0.001$); cardiovascular system, $P < 0.05$; alimentary tract, $P < 0.01$; aortic defects, $P < 0.05$; cleft lip and/or palate, $P < 0.001$; other alimentary defects, $P < 0.05$; eye and ear defects, $P < 0.05$;
- (3) a diet in the first trimester considered to be 'unbalanced' or 'doubtful' (all systems, $P < 0.05$; central nervous system, $P < 0.01$; *anencephaly*, $P < 0.01$; *spina bifida cystica*, $P < 0.05$; other alimentary defects, $P < 0.05$).

Although the findings of this survey do not permit any definite conclusion to be reached regarding the nature of the environmental factors concerned in human teratogenesis, they do suggest several lines of further investigation.

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