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2759

ENVIRONMENTAL TERATOGENS OF MAN

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The search for environmental factors responsible in whole or in part for congenital malformations must be almost as old as man himself. It had little or no scientific basis before Gregg's discovery of the teratogenic properties of the rubella virus (Gregg, 1941), and it received tremendous impetus from the thalidomide experience. Attention has been focused principally on drugs, but the possibility of teratogenic factors in air, water and food has also attracted recent interest.

There are many difficulties that lie in the way of proving beyond reasonable doubt that a particular environmental agent has teratogenic potential: (i) the more widely used a drug or food-stuff and the more common a malformation, the more often will they be associated by chance and the more difficult it is to establish a causal relation; (ii) a factor that predisposes to malformation is less easy to identify than one that invariably causes malformation; (iii) the "me-too" phenomenon (see section 3) is as capable of confirming a myth as a truth; (iv) retrospective studies have a major limitation in that the parents of malformed infants tend to give more frequent positive histories of almost anything than do the ents of healthy controls. Prospective studies with objective evidence of the factor under study are more tedious but more informative; (v) controls, in the sense of individuals differing from the study group only in respect of the factor studied, do not exist amongst human beings.

In a recent review of teratogenic drugs in man, Wilson (1973) found only three for which there was convincing evidence of teratogenicity—thalidomide, steroid hormones (virilization) and folate antagonists. These three are not considered in the present paper, but a critical review is made of nine other possible environmental teratogens.

1. Alcohol

Jones, Smith, Ulleland & Streissguth (1973) described 8 children born to chronic alcoholic mothers, who showed a number of features in common, and suggested that they might represent a recognizable syndrome. They later reported 3 additional cases (Jones & Smith, 1973), and further examples were described by others (Ferrier, Nicod & Ferrier, 1973; Hall & Orenstein, 1974). Pre- and post-natal growth deficiency and developmental delay were invariable, and all children but one were microcephalic. Short palpebral fissures (canthus to canthus) and maxillary hypoplasia were almost constant; abnormal palmar creases, joint anomalies and congenital heart disease were present in most, and epicanthic folds in 4, of the 11 infants. Necropsy performed on one infant revealed abnormalities of the brain, including absence of the corpus callosum.

In an attempt to determine the size of the risk to the children of alcoholic mothers, Jones, Smith, Streissguth & Myrianthopoulos (1974) identified 23 offspring of such mothers. The perinatal mortality rate was 17%, and 44% of survivors had intelligence quotients of less than 80%.

As alcohol is known to depress folate levels in both normal and alcoholic subjects (Eichner & Hillman, 1973), it is tempting to consider folate deficiency as a possible mechanism. However, Jones & Smith (1973) were able to study the nutrition of one alcoholic mother at the end of the first trimester, and found iron-deficiency anaemia but normal values for vitamin A, vitamin C and folate.

2. Anticonvulsants

Janz & Fuchs (1964) reported the outcome of 358 pregnancies in epileptic women, of whom 225 took anticonvulsants during pregnancy and 133 did not. The 5 observed congenital malformations, including 3 with cleft palate and one with congenital heart disease, all occurred in the offspring of mothers taking anticonvulsants. However, the authors concluded that there was no significant difference between the two groups.

In 1968, Meadow reported 6 infants with cleft lip and palate born to mothers who had taken anticonvulsants in pregnancy. Four of the babies had other defects, including congenital heart disease. Since then many reports have appeared of associations between anticonvulsants and congenital malformations. A number of studies, so far all retrospective, have attempted to find answers to some of the following questions: (i) Is this association real? (ii) If so, is it the epilepsy, the anticonvulsant drugs, or both, that are involved? (iii) If drugs, are some anticonvulsants more teratogenic than others? (iv) Is any specific malformation pattern associated with anticonvulsants? (v) If these drugs are teratogenic, what is the mode of action?

Table I summarizes the main surveys so far published, and provides reasonably clear answers to the first two questions. The total incidence of malformations in 2403 children born to epileptic women was 5.4%. The choice of controls is always difficult, but in the 6 studies in which local population incidence was known it ranged from 2.2% to 3.5%, figures which are in accord with numerous epidemiological studies. The over-all rate for the offspring of epileptics is therefore about twice as high as that expected.

If those taking anticonvulsants in pregnancy are separated from those not doing so, the malformation rates are respectively 6.0% and 1.4%. The latter figure suggests incomplete ascertainment in some studies. If this is equally true of mothers taking anticonvulsants, the risk of malformation in the infants of epileptics taking these drugs is probably about 3 times the incidence in the population. In the study of Fedrick (1973) a number of conditions have been included as congenital defects

TABLE I. Studies on anticonvulsants administered to epileptics and the occurrence of malformations, as compared with occurrence of malformations in controls

References	Controls			Epileptics taking anticonvulsants			Epileptics not taking anticonvulsants			All epileptics		
	Total births	Malformations		Total births	Malformations		Total births	Malformations		Total births	Malformations	
		Number	%		Number	%		Number	%		Number	%
Janz & Fuchs (1964)				225	5	2.2	133	0	0	358	5	1.4
Elshove & van Eck (1971)	12051	231	1.9	65	10	15.4						
Watson & Spellacy (1971)	50	0	0	51	3	5.9						
South (1972)				22	2	9.0	9	0	0	31	2	6.5
Speidel & Meadow (1972)	448	7	1.6	329	17	5.1	59	0	0	388	17	4.3
Koppe, Bosman, Oppers, Spaans & Kloosterman (1973)	12300	426	3.5	125	11	8.8	67	2	3.0	192	13	6.8
Lowe (1973)	31877	877	2.8	134	9	6.7	111	3	2.7	245	12	4.9
Millar & Nevin (1973)	32227	1235	3.8	110	7	6.4						
Niswander & Wertelecki (1973)	347097	(9372)*	2.7							413	17	4.1
Starreveld-Zimmerman, van der Kolk, Meinardi & Elshove (1973)				297†	22	7.4						
Bjerkedal & Bahna (1973)	112328	(2471)*	2.2	(378)*	17	4.5						
Monson, Rosenberg, Hartz, Shapiro, Heinonen & Slone (1973)	50897	1254	2.5							306	14	4.6
Fedrick (1973)	649	36	5.6							217	30	13.8
Annegers, Elveback, Hauser & Kurland (1974)	84‡	0	0	141	10	7.1	56	1	1.8	197	11	5.6
Biale, Lewenthal & Aderet (1975)										56	8	14.3
Total	600008	15909	2.7	1877	113	6.0	435	6	1.4	2403	129	5.4

* Calculated
† All but six mothers taking anticonvulsants
‡ Controls were past or future epileptics

which would not normally be so classified (e.g. squint, mental retardation, tyrosinosis, rectal prolapse), and the malformation rates for both epileptics and controls are consequently high (13.8% and 5.6%), but the risk to epileptics is still approximately 3-fold.

It is probable that, in some surveys at least, the epileptic mothers no longer taking drugs have less severe epilepsy than those taking anticonvulsants. Nevertheless, the evidence in favour of a teratogenic action of anticonvulsants is strong. With regard to individual drugs, most authors suggest that phenytoin is more teratogenic than phenobarbitone and that the two combined are more teratogenic than either alone. Primidone is largely converted to phenobarbitone in the body and probably has a similar effect. Fedrick (1973) suggests that there may be a dose–response relation with phenobarbitone but not with phenytoin.

Congenital defects have also been reported in association with sulthiame, phensuximide, pheneturide, diazepam, trimethadione (troxidone), paramethadione, ethosuximide and carbamazepine (Speidel & Meadow, 1974).

Do anticonvulsants cause any recognizable pattern of congenital malformation? Congenital heart disease and clefts of lip and palate have been commented upon in most studies, and when the available data are summated (Table II) the figures confirm the impression that the incidence of heart lesions is about 3 times, and of cleft lip and palate about 12 times, the incidence in the population. Fedrick (1973) found only 2 cases of congenital heart disease and one of cleft lip and palate in 217 births to epileptics.

Loughnan, Gold & Vance (1973) reported 7 cases of hypoplasia of the terminal phalanges in the offspring of epileptics. The fingers were worse affected than the toes, the ulnar fingers more than the radial, and the thumbs were normal. All had other defects. All mothers had taken phenytoin and a barbiturate. Barry & Danks (1974) reported 7 cases of digital hypoplasia among 62 infants born to mothers taking phenytoin with or without other drugs, one case of mild digital hypoplasia among 20 babies born to epileptics no longer taking drugs and 11 to mothers taking anticonvulsants other than phenytoin. Barr, Poznanski & Schmickel (1974) reported 3 cases of digital hypoplasia, in 2 of which the thumbs were normal.

Diaphragmatic hernia affected 2 of the 62 infants described by Barry & Danks (1974), and inguinal hernias are conspicuous in several reports.

In summary, it appears that cleft lip and palate, congenital heart disease and digital hypoplasia are conspicuous amongst a wide spectrum of malformations associated with anticonvulsants.

As regards the mode of action, the most attractive hypothesis is that of folate deficiency[1]. Many anticonvulsants,

[1] See Hibbard & Hibbard, *Br. Med. Bull.* 1968, 24, 10–14.—ED.

TABLE II. Studies on anticonvulsants administered to epileptics and the occurrence of congenital heart disease and cleft lip and/or cleft palate in their infants

References	Total births to epileptic women taking anticonvulsants	Number of infants with congenital heart disease	Number of infants with cleft lip and/or cleft palate
Janz & Fuchs (1964)	225	1	3
Elshove & van Eck (1971)	65	2	5
Watson & Spellacy (1971)	51	1	0
South (1972)	22	0	2
Speidel & Meadow (1972)	329	6	3
Koppe, Bosman, Oppers, Spaans & Kloosterman (1973)	125	4	1
Lowe (1973)	134	1	1
Millar & Nevin (1973)	110	0	2
Starreveld-Zimmerman, van der Kolk, Meinardi & Elshove (1973)	297	7	9
Annegers, Elveback, Hauser & Kurland (1974)	141	6	3
Total	1499	28 (1.9%)	29 (1.9%)

especially phenytoin, are known to cause folate deficiency, even to the stage of frank megaloblastic anaemia. Folate deficiency and folate antagonists are teratogenic in animals. Folate deficiency may be teratogenic in man and folate antagonists certainly are.

Can anything be done to diminish the risks involved in the use of anticonvulsants? Two proposals have been made: (i) stop the drugs in pregnancy, and (ii) give folate supplements. The first is bad advice, the second probably good. Knight & Rhind (1975) studied the course of epilepsy in 153 pregnancies in 59 women. In 50% of pregnancies the severity of the epilepsy was unchanged; in 5% it improved; in 45% it got worse. Stopping medication is therefore likely to be associated with increasing frequency and severity of seizures. Folate supplementation has not yet been shown to reduce the teratogenic effect of anticonvulsants, but it is unlikely to do harm. However, to be of value it would need to be started before conception or very early in pregnancy.

TABLE III. Congenital abnormalities among offspring of mothers who took lysergide (LSD)

Time at which mothers took LSD	Total births	Number of offspring who had abnormalities, and type of defect	Number of offspring with no birth defect
Before conception only	119	8 with feet turned in, feet turned out, or tibial torsion 5 (1 each of: D/D translocation; cystic fibrosis; pyloric stenosis; rubella syndrome; crimped ureter)	106
B. Before and during pregnancy	23	4 (1 each of: absent hand; absent finger and toe; bilateral cleft foot and absent fingers; bladder extrophy)	19
C. During pregnancy only	19	4 (1 each of: absent fibula, short femur and congenital heart disease; talipes, webbed toes and absent fingers; megacolon; spondylothoracic dysplasia)	15

3. Lysergide

Considerable interest and discussion has centred round the possibility that lysergide (lysergic acid diethylamide; LSD) might be capable of acting as a mutagen, a teratogen, or both. The first possibility is beyond the scope of this paper. The second is not easy to answer. Long (1972) reviewed the then available evidence relating LSD to malformations and concluded that there was ". . . little evidence at present that LSD has teratogenic effects in human beings." Wilson (1973) took a similar view. However, the reports that Long (1972) assembled deserve close scrutiny and are summarized in Table III. If groups B and C in Table III, comprising the offspring of all mothers taking LSD in pregnancy, are considered together, there were 42 children of whom 5 had congenital absence of extremities. Similar defects were not seen amongst 119 children in group A. The difficulty in interpreting these remarkable figures stems from what might be called the "me-too" phenomenon. The first association between LSD and "congenital amputations" was reported by Zellweger, McDonald & Abbo (1967). After the publication of such a report, the presentation of an infant with a similar lesion automatically prompts a search for a history of LSD, just as reduction deformities of the limbs prompted a search for a history of thalidomide in times past. Furthermore, cases with positive histories are more likely to be reported than those with negative histories. The risk of terminal defects in the offspring of mothers taking LSD is therefore likely to be much lower than the 12% suggested by the published cases, but the remarkable frequency of this type of defect cannot be altogether ignored.

Torpin (1968) has adduced good evidence that terminal defects (congenital amputations) are caused by amniotic bands, but the cause of the bands is unknown. It is possible that LSD somehow predisposes to such bands (Blanc, Mattison, Kane & Chauhan, 1971).

A prospective study of an unselected series of pregnancies in women taking LSD would provide some definitive answers. Until then the Scottish verdict of "not proven" may be more appropriate than an acquittal.

4. Sex Hormones

If the general term "sex hormones" is used to include androgens, oestrogens and progestogens, the developing embryo may be exposed to exogenous sex hormones in three

quite different ways: (i) Hormones, usually progestogens, may be prescribed with the intention of discouraging spontaneous abortion. Evidence that they are capable of doing so is not strong, but their use for this purpose continues. This form of therapy exposes the embryo to exogenous hormone for the greater part of the period of organogenesis and in relatively large doses. The importance of this lies in the fact that smaller doses given for shorter periods are unlikely to be more teratogenic, unless it is accepted that the larger, prolonged doses actually induce abortion. (ii) Oral contraceptives, which combine progestogen with oestrogen, may continue to be taken through the early stages of an unrecognized pregnancy, or may even be started after conception has taken place. (iii) Pregnancy-test drugs, which combine androgen and oestrogen, have been widely used in the UK until recently, but their use has been discontinued on the grounds that they may have a teratogenic effect. These tablets are designed to be taken for 2 or 3 days only.

The ability of some progestogens, notably ethisterone and norethisterone, to masculinize a female fetus is well documented (Wilkins, Jones, Holman & Stempfel, 1958). This is not teratogenesis in the usual sense. Masculinization may also occur with androgens (Black & Bentley, 1959) and possibly with some other hormones (Fine, Levin & McConnell, 1963). There is little evidence that the administration of these drugs causes malformations other than masculinization. There is indeed some evidence to the contrary (Spira, Goujard, Huel & Rumeau-Rouquette, 1972). Levy, Cohen & Fraser (1973), however, found that, of 76 mothers of infants with transposition of the great vessels, 6 had received hormones for threatened abortion.

There is as yet no satisfactory study of the outcome of pregnancies in the early part of which oral contraceptives have been taken. There have been several reports of normal infants born after exposure to contraceptive pills (Lind, 1965; Rice-Wray, Márquez-Monter & Gorodovsky, 1970; Spira *et al.* 1972), but the numbers are small. Pregnancy-test tablets and most contraceptive pills are combinations of progestogen and oestrogen. A surprisingly high frequency of intake of these preparations has been reported amongst mothers of children with congenital heart disease, DiGeorge syndrome (Nora & Nora, 1973) and the VACTERL anomaly (vertebral, anal, cardiac, tracheoesophageal, renal, limb) (Nora & Nora, 1975). There was a positive history in 20 of 224 mothers of infants with congenital heart disease, but in only 4 of 262 controls. In 19 cases of VACTERL anomaly, 13 mothers had taken progestogen–oestrogen compounds during the estimated vulnerable period.

Pregnancy-test drugs are currently under consideration as possible teratogens. I identified, from prescriptions, 189 pregnancies in which pregnancy-test tablets had been dispensed in the first trimester (Smithells, 1965). The only congenital defects identified in the infants were patent ductus arteriosus in both of monozygotic twins, and a heart murmur in the baby of a mother who had been a rubella contact when 8 weeks pregnant. Laurence, Miller, Vowles, Evans & Carter (1971) found a history of hormonal pregnancy tests in 22 of 271 cases of neural tube defect and in 22 of 323 controls—an insignificant difference. Oakley, Flynt & Falek (1973) found in Atlanta, Georgia, that hormonal tests were used in 10% of all pregnancies, but without evidence of teratogenicity.

Gal, Kirman & Stern (1967) and Gal (1972) reported a significant increase in hormonal pregnancy tests in 100 mothers of infants with myelomeningocele or hydrocephalus, but the mean gestational age at which the tablets were taken was substantially later than the age of closure of the posterior neuropore (Sever, 1973). A more recent retrospective survey (Greenberg, Inman, Weatherall & Adelstein, 1975) also found a greater frequency of hormonal pregnancy tests in the mothers of 149 infants with a variety of defects (23) than in 149 controls (8).

It is important to note that the 3 prospective studies are consistent in revealing no evidence of teratogenicity, in contrast to the retrospective studies cited. Nevertheless, as hormonal pregnancy tests have no place in modern medicine, the doubts that have been raised are more than adequate as a basis for discontinuing their use. In contrast, any remaining doubts about the possible teratogenicity of hormonal contraceptives need to be clarified as quickly and as effectively as possible.

5. Warfarin

The ability of most anticoagulants (except heparin) to cross the placenta, and the consequent haemorrhage in the fetus and newborn, have been recognized for some time (Mahairas & Weingold, 1963; Bocquet, 1964; Saidi, Hoag & Aggeler, 1965). A teratogenic effect specifically attributed to warfarin sodium is a more recent development. DiSaia (1966) described the pregnancy and delivery of a woman with a mitral valve prosthesis who was maintained on warfarin throughout pregnancy. The infant had nasal hypoplasia and optic atrophy and was later described in more detail by Becker, Genieser, Finegold, Miranda & Spackman (1975). Kerber, Warr & Richardson (1968) also described a woman with a mitral valve prosthesis treated with warfarin throughout pregnancy, whose infant had nasal hypoplasia, choanal stenosis and delayed development.

Pettifor & Benson (1975) reported 3 infants whose mothers took anticoagulants (warfarin in at least 2 cases) in the first trimester. Two had marked hypoplasia of the nasal bones and stippled epiphyses; one of these was mentally retarded. The third had only mild hypoplasia of the nasal bones. Shaul, Emery & Hall (1975) described one case of chondrodysplasia punctata associated with warfarin administered to the mother and referred to 2 similar unreported cases. Becker *et al.* (1975) described 2 cases, including that of DiSaia (1966), both associated with warfarin.

Congenital stippled epiphyses, first described by Conradi (1914), comprise at least two clinical entities. Spranger, Opitz & Bidder (1971) suggest that one form typified by extreme shortening of the limbs (rhizomelic type) is due to an autosomal recessive gene, while the second variety (Conradi–Hünermann), of which a flat nasal bridge is characteristic, may be due to a dominant mutant gene or to non-genetic factors. The cases described in association with warfarin fall into the latter category.

Although the numbers are as yet small, the association of such a rare disorder with such unusual medication in pregnancy is unlikely to be coincidental. The concept of warfarin embryopathy has been accepted by at least one authority (Warkany, 1975). Whether the teratogenic effect is mediated through multiple small haemorrhages or by some other means is not yet known. The mental retardation in some cases may well be due to respiratory difficulty in the neonatal period secondary to nasal obstruction.

6. Folate Deficiency

The possible role of nutritional deficiencies in the aetiology of human malformations has been debated for a very long time. Interest in Western countries has centred on possible deficiencies of vitamins rather than of energy sources. There is ample experimental evidence that malformations can be produced in many animal species by feeding vitamin-deficient diets or vitamin antagonists in pregnancy (Kalter & Warkany, 1959). Human malformations can also result from the administration of folate antagonists to the mother (Thiersch, 1952).

Circumstantial evidence linking malformations with maternal diets that were either generally unsatisfactory or specifically lacking in vitamins has been reported by Burke, Beal, Kirkwood & Stuart (1943), Coffey & Jessop (1958), Pitt & Samson (1961), Richards (1969) and others. Biochemical evidence of folate deficiency has been linked to malformations by Hibbard & Hibbard (1963), Fraser & Watt (1964), Hibbard, Hibbard & Jeffcoate (1965), and Hibbard & Smithells (1965). Other workers, however, have been unable to demonstrate any such relation (Giles, 1966; Pritchard, Scott, Whalley & Haling, 1970; Scott, Whalley & Pritchard, 1970).

More recently a prospective study of approximately 1000 pregnancies has been reported in which certain vitamin concentrations, including folate, have been determined in the first trimester of pregnancy (Smithells, Sheppard & Schorah, 1975). The mean red-cell folate value of the mothers of 6 infants with neural tube defects was significantly lower than the mean of controls ($P < 0.001$), as was the mean leucocyte vitamin C concentration ($P < 0.05$). Concentrations of serum folate and riboflavin were also lower but not significantly so. Means for 7 mothers of infants with congenital heart disease were similar to those for controls.

It seems improbable that folate deficiency is ever an isolated cause of congenital defect in the human being, but it may prove to be one correctable factor involved in malformations of multifactorial origin.

7. Operating-Room Environment

In the last few years great interest and concern has centred round the observation of apparently impaired reproductive efficiency in medical and nursing staff working in operating theatres. The disabilities reported include increased frequencies of involuntary infertility, spontaneous abortion and congenital malformation. Of additional interest is the effect on the wives of male anaesthetists.

Vaisman (1967) surveyed the health of 303 Russian anaesthetists and noted (amongst other things) that of 31 pregnancies in female anaesthetists, 18 ended in spontaneous abortion, 2 in premature birth and one in a malformed infant. Askrog & Harvald (1970) studied by questionnaire 578 anaesthetic nurses and 174 anaesthetists (both sexes) and obtained information on 212 pregnancies started before employment in the operating theatre and on 392 pregnancies started at the time of such employment. The incidence of spontaneous abortion and premature birth was twice as high in the latter group, and this was also true of the unexposed wives of male anaesthetists. The total number of congenital malformations was too small to permit any comparison.

Cohen, Bellville & Brown (1971) reported a 29.7% spontaneous abortion rate amongst 67 operating-room nurses compared with 8.6% amongst 92 general duty nurses, and 37.8% amongst 50 female anaesthetists compared with 10.3% amongst female physicians.

Knill-Jones, Rodrigues, Moir & Spence (1972) reported a malformation rate of 6.5% amongst infants of anaesthetists working while pregnant, which was significantly higher than the rate amongst non-working anaesthetists (2.5%) but not significantly higher than that amongst controls (4.9%). The corresponding rates of spontaneous abortion were 18.2%, 13.7% and 14.7%. Unexplained infertility was significantly higher in working anaesthetists.

Corbett, Cornell, Endres & Lieding (1974) surveyed 621 nurse anaesthetists and recorded data on 434 births following pregnancies during which the mother worked and 261 in which she did not. The incidence of birth defects in the two groups was 16.4% and 5.7%, respectively ($P < 0.005$). However, the difference is largely accounted for by skin defects, principally naevi (33/434 and 5/261), inguinal hernia (14 and 2, respectively) and "other musculoskeletal anomaly" (7 and 0, respectively). Unfortunately, unspecified heart murmurs, malabsorption syndrome and mental retardation are included as birth defects. There was no significant difference between the two groups in regard to major malformations.

A large-scale national study in the USA (American Society of Anesthesiologists, 1974) compared 49585 operating-room personnel with 23911 controls. Females exposed to operating-room conditions experienced higher rates of spontaneous abortion, congenital defects, cancer and hepatic and renal disease. The increased malformation rate was shared by unexposed wives of exposed males. The increases were as follows: for nurse anaesthetists, malformations up 60% ($P < 0.01$); for female anaesthetists, malformations up 100% (not significant); for wives of male anaesthetists, malformations up 25% ($P = 0.04$). Malformations in the infants of female anaesthetists and paediatricians were as follows (skin anomalies being excluded):

Malformations	*Anaesthetists (384) (exposed)*	*Paediatricians (276) (not exposed)*
Cardiovascular *	10	0
Respiratory	2	0
Musculoskeletal†	7	2
Gastrointestinal	0	0
Central nervous system	5	1
Urogenital	3	4
Total	27	7

* It is not stated whether this includes non-specific heart murmurs
† Not further specified

From a review of these studies there seems little room for doubt regarding the true increase in spontaneous abortion rates amongst women exposed to operating-room conditions. It is widely accepted that anything capable of causing embryonic or fetal death may also be teratogenic, and a similar increase in malformation rates would not be surprising. So far the American Society of Anesthesiologists' study is the only one of any magnitude, and all are retrospective. Until definitive answers can be found there are at least good grounds for believing that there are teratogenic forces at work in operating theatres. Whether these arise from anaesthetic gases (as in generally assumed), from stress (which has been suggested) or from some other factor remains to be determined. The apparent involvement of the unexposed wives of exposed males adds an intriguing dimension to the puzzle.

8. Blighted Potatoes

In 1972, Renwick published his hypothesis that anencephaly and spina bifida (ASB) were related to the ingestion or absorption by pregnant women of teratogenic substances in potatoes, and that these teratogens developed in response to infection of the tubers by the potato blight fungus, *Phytophthora infestans*. He suggested that 95% of cases of ASB could be prevented by the total avoidance of potatoes by expectant mothers. The hypothesis met with a cool reception (*British Medical Journal*, 1972; *Lancet*, 1972) and doubts were raised about some of the basic concepts underlying the hypothesis. Correlations between severity of blight and incidence of ASB tended not to confirm the idea of a temporal relation (Masterson, Frost, Bourke, Joyce, Herity & Wilson-Davis, 1974), and retrospective studies of potato consumption revealed no differences between the mothers of ASB infants and controls (Clarke, McKendrick & Sheppard, 1973; Spiers, Pietrzyk, Piper & Glebatis, 1974).

Potato-avoidance trials were initiated in a few centres and reports began to appear of ASB infants born to mothers who had avoided potatoes (Lorber, Stewart & Ward, 1973). A prospective study in Belfast (Nevin & Merrett, 1975) has now failed to demonstrate any protective effect of short-term potato avoidance. Two of 23 viable pregnancies in which potatoes were avoided ended in the birth of ASB infants and 4 others aborted spontaneously. Two of 56 viable pregnancies in which potatoes were not avoided ended in the birth of ASB infants and 5 others aborted, including a 17-week fetus with iniencephaly. Thus the incidence of ASB was higher in the potato-avoidance group, but not significantly so.

The full results of other potato-avoidance trials will be awaited with interest, but with little doubt about the outcome.

9. Soft Water

The first suggestion that the striking geographical distribution of anencephalus in the British Isles might be related to some factor in the drinking-water is attributed to Penrose (1957). He had in mind the presence or absence of trace elements. In the British Isles, defects of the neural tube are most common in north-west England, Wales, Scotland and Ireland. These are essentially areas of mountain, old rock and soft water. In south-east England, where the incidence of neural tube defects is relatively low, the underlying ground is predominantly chalk and gravel and the water is hard with a high calcium content.

This idea was also taken up by Stocks (1970), who suggested that high calcium levels, to which high mortality from cardiovascular disease has been attributed (Crawford, Gardner & Morris, 1968a, 1968b), might somehow be contributing to the high incidence of anencephalus in the same regions. Fedrick (1970) examined the hypothesis in more detail and found significant correlations between anencephalus and the total hardness, calcium content and pH of the water supply in 10 different areas of the UK.

Lowe, Roberts & Lloyd (1971) studied these relations in 48 local authority areas of South Wales, an area of high incidence of neural tube defects. They found a significant negative correlation with total water hardness ($r = -0.40$), but concluded that the relation might well be a secondary rather than a direct one. Fielding & Smithells (1971) compared the incidence of anencephalus in two hard-water towns of south-west Lancashire with that in the neighbouring soft-water city of Liverpool and found a higher incidence in the hard-water areas. Artificial softening of the water in one town did not appear to influence the incidence of anencephalus in the short term.

Crawford, Gardner & Sedgwick (1972) found that the infant mortality rate in the regions of the UK had a significant negative correlation with total water hardness ($r = -0.55$) and total calcium ($r = -0.64$), but for anencephalus the correlations were smaller and not significant ($r = -0.22$ and -0.29, respectively). Spiers, Wright & Siegel (1974) found in the USA an insignificant positive correlation between infant mortality rates and water hardness.

There is as yet no conclusive evidence of the relation of water supply to congenital defects. Household water supplies are extremely complex to study, often derived from many sources mixed in variable proportions and changing in composition from time to time. As a potential vehicle of trace elements (for good or harm) and pollutants, tap-water is probably unrivalled, but is likely to remain a difficult subject for scientific study.

So far as neural tube defects are concerned, studies of migrants suggest that their malformation rates tend to go with them (Hobbs, 1969; Leck, 1969); this in turn suggests that in the short term the local water supply may not be important.

10. Conclusion

Present evidence suggests that, in addition to thalidomide, steroid hormones and folate antagonists, alcohol, anticonvulsants, warfarin and some factor relating to work in operating theatres should be accepted as environmental teratogens in man. LSD and folate deficiency may be. Sex hormones, blighted potatoes and factors associated with soft water are probably not.

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