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The epidemiology of congenital malformations

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At birth the child of today faces a world in which the prospect of postponing natural death is greater than in any previous period. After birth protection from the hazards of bacterial infection or cold is increasingly assured by the ingenuity of architects. The advances in agriculture, food preservation and transport assure adequate nutrition without reference to the lactational capacity or intention of the mother. The artificial education of immune responses protects against diseases which are now becoming obsolete and, although relatively trivial in comparison with the efforts of prevention, if illness does occur therapeutic advances have reduced its hazards. In a few hundred years death during childhood has changed from an expectation at each birth to a rarity outside the experience of the great majority of parents.

While the child is faced with an environment of increasing freedom from malnutrition or infection and now faces, and may continue to face, an environment of unprecedented safety, the environment through which the child has to pass to reach birth may be more dangerous than at any previous epoch, and these dangers are multiple, complex, and may be largely related to the agricultural and therapeutic revolution which has made the world beyond the womb one of increasing freedom from want and disease.

At conception a substantial but unknown proportion of children have been conceived through a chemical barrier designed to prevent conception, a barrier which, as constructed at present, is not known to be related to any abnormality in the resultant foetus: however there is no substantial body of relevant data. The systemic contraceptives may impose a further hazard in the future, although the limited observations available so far suggest that the hazards are not severe.

After fertilisation the zygote and embryo are exposed to an environment containing increasing varieties of insecticides, fungicides, weedkillers, steroids and antibiotics incorporated into the food chain through modern agricultural methods, to increasing amounts of detergents,

dyes and frothing agents incorporated through modern marketing, cooking, and washing techniques; and to increasing amounts of biologically active substances ingested for increasingly trivial symptoms as a result of a demand excited by advertising. A fear of cancer spread by various agencies, mostly rich, well meaning, and ill-informed, contributes to an increasing exposure to abdominal X-rays. In all, the foetus has never before been exposed to such varied insults.

Formation of the embryo is effected by differential growth, and malformations are usually the expression of variations in differential growth rates beyond the tolerance of the organism. Consequently any drug which will influence differentially the growth rates of rapidly growing tissues will influence the malformation rate: usually such influences will be adverse. An ability to influence tissue growth differentially must be regarded as implying teratogenesis. There are also other possible mechanisms of teratogenesis. One example is that of aberrations in chromosome number, as in mongolism, a condition which may well arise shortly after conception and not, as often stated, at gametogenesis. A most unfortunate effect of the disclosing of the human chromosomes has been the lack of attention to any environmental precipitants of related disorders. If mongolism were as common a hundred years ago as it is today then it is surprising that it was not recognised.

In studies of teratogenesis of the commoner malformations we must consider the type of teratogen most likely to influence embryogenesis adversely by disturbing growth rates. A simple division is into the *species specific toxins*, as antibiotics, insecticides, etc. which are lethal to species other than man in concentrations tolerated, at any rate postnatally, by man and the *tissue specific toxins*, such as barbiturates, tranquillizers, steroids, etc. which act by specifically disabling some tissue, usually predictably and reversibly.

We might suppose that if a very large number of embryos were developing in environments with very different concentrations of any toxin specific for some other species, or for some highly specialized tissue in man, then it would be unlikely that the incidence of any malformation would be wholly uninfluenced by such exposure.

Where the main influence of the toxin was known to act on some metabolic pathway unknown in man, as in penicillin on muramic acid synthesis, or to act on some tissue which is unlikely to be differentiated in the embryo, as in drugs such as thalidomide which act at the subtle level of the cerebral cortex, there is no obvious reason to expect any damage. However, one of the lessons of thalidomide is that a drug with subtle

and unexplained effects in one tissue after development may disturb growth in another tissue during development.

The toxins administered through the food chain, as in modern agriculture, will normally be distributed over large populations and show regional, secular, and usually seasonal, variations. Toxins administered to individuals, while they will usually show some regional and secular changes, will have their effects revealed most readily by associating individual presumptive toxins to abnormalities recorded at birth.

It is possible that all these hazards to which the foetus are exposed are trivial. But we are ignorant of this, and we will remain ignorant unless we study the foetal environment and relate it to foetal disease. The revolutionary changes in agriculture, the international nature of large chemical and therapeutic firms, the efficiency of modern advertising, and the rapidity with which entire communities are being subjected, unknowingly, to potentially toxic agents, makes it an urgent problem, for when uniform distribution has been achieved evidence of toxicity will no longer be available.

The genetic contribution to the commoner malformations is now known to be small in the sense that no considerable reduction in incidence could follow any attempt to impose infertility on persons liable to produce malformed children, even supposing such persons could be identified. As the recurrence rate in sibs for most of the commoner malformations runs at around 3%, a risk graver than this could hardly be predicted from any study of most prospective parents.

Consequently any reduction in the incidence of malformations must be achieved by changing the environment; this can only be done by imposing restraints, by legislation or otherwise, on various professional and commercial activities. Foetal security, like road safety, cannot be improved without action and unless this is appreciated research will be ineffective.

Studies of the factors predisposing to congenital disease may be carried out by studies of individuals, of families, and of populations. The three basic approaches are often regarded as synonymous with pathological, genetical and epidemiological studies, and these have tended to be pursued independently by different investigators. The reasons for this division have been largely unrelated to the relevance of genetical or epidemiological studies in pregnancy.

The pathological study is the most important, in that without accurate recording of data and recognition of syndromes the data are of little value, and reliable data can only be acquired from communities with high standards of morbid anatomy, paediatrics, and obstetrics. Even in

such areas the absence of any satisfactory nomenclature or classification causes difficulty and confounds comparisons between different communities. As, in the commoner malformations, comparisons within communities are more important than comparisons between communities, this absence of a consistent classification is not important.

The division between single and multiple malformations is unsatisfactory; focal and generalized would be simpler. Focal malformations are those plausibly related to a localized embryonic accident or disorder, such as anencephaly or cleft palate. Generalized malformations are those excluded above. While a simple anatomical classification covers the former, generalized malformations, which largely fall into unrecognised syndromes, are poorly charted. It is extremely important that series of focal malformations are not contaminated by the presence of generalized malformations. Almost all focal malformations are commoner in the presence of generalized malformations. For example, the inclusion of mongols in series of cases of cleft palate, spina bifida, or duodenal atresia would confuse any inferences about either aetiology or prognosis. Phenocopies of genetical diseases have been said to make these studies confusing. I do not think this is a practical problem as phenocopies are only copies and will be detected as such with increasing diagnostic standards.

The familial study is largely undertaken for primary genetical purposes and need not be considered further here, except to point out that familial concentrations of disease are found in almost all diseases, and, by themselves, cannot be regarded as implying that either a proportion of cases are genetically determined or that genetical influences are of importance in predisposition to disease. Absence of a familial trend is of importance in suggesting the possibility of a viral embryopathy.

This leaves us with the population study, usually termed epidemiology. As the suffix *epi* is both redundant and incorrect in contemporary usage I prefer to use the word demiology, leaving the words epidemiology and endemiology to refer to epidemic and endemic disease, a distinction clearly made by Hippocrates.

The data available for the study of chemical teratogenesis is limited to the knowledge of what has been ingested during pregnancy, the time and place of the birth, and the presence and nature of any malformation at birth. These data are all very difficult to acquire. Ingestion of drugs during pregnancy may be forgotten, particularly as there are no conventions of pill shape or colour and many drugs may be combined into one pill: ingestion of other biologically active chemicals is unlikely to be noticed. Any malformation present has to be noted, diagnosed, and recorded. Diagnosis is difficult, only a minority of complex malformations

being resolved into distinct syndromes; when a diagnosis has been made there are considerable difficulties in recording.

Even if we can obtain data on a large number of variables related to pregnancy and compare them with a large number of variables related to birth, as in the contingency table in Figure 1, the association of one with the other is far from simple, and the problems are not solved, although they may occasionally be simplified, by such procedures as significance testing or multiple regression. Although the interpretation of such data is difficult, its collection on a population scale is now possible by the use of conventional commercial computors for the linking of prescriptions with births. Only large samples are of any value, as is clear if it is appreciated that a population of a million will only produce a few hundred malformations a year and only a few cases of any rare type.

		Malformations							
		O	A	B	C	D	E	F	G
Drugs	P	.	.	.	.	.	.	.	.
	Q	.	.	.	.	.	.	.	.
	R	.	.	.	.	.	.	.	.
	S	.	.	.	.	.	.	.	.
	T	.	.	.	.	.	.	.	.
	U	.	.	.	.	.	.	.	.
	V	.	.	.	.	.	.	.	.

Fig. 1. Hypothetical contingency table on which any interpretations on teratogenic activity in man would have to be made.

If we consider the effects of administering various doses of a substance to a large number of pregnant women and comparing the incidence of some malformation the response may be zero, the incidence being unchanged, or it may increase with increasing doses (Fig. 2). It is only possible to obtain evidence relating to teratogens if there are data for populations exposed to different levels of dosage, and if the dose response is steep between these levels; even then the difficulties are considerable. The tragedy of thalidomide, a drug of very high specificity, was only revealed and countered after a lag period of some ten thousand catastrophies. If this drug only affected 10% of foetuses the lag period would probably have been even more costly. At present it is doubtful if the casual methods of investigation in use could reverse the commercial production of any teratogen until the cost of the necessary information was measured in thousands of malformed births. The ultimate cost of such experimentation will probably be greater with the milder teratogens. It is quite possible to impose teratogens with a 1:1000 dose response to

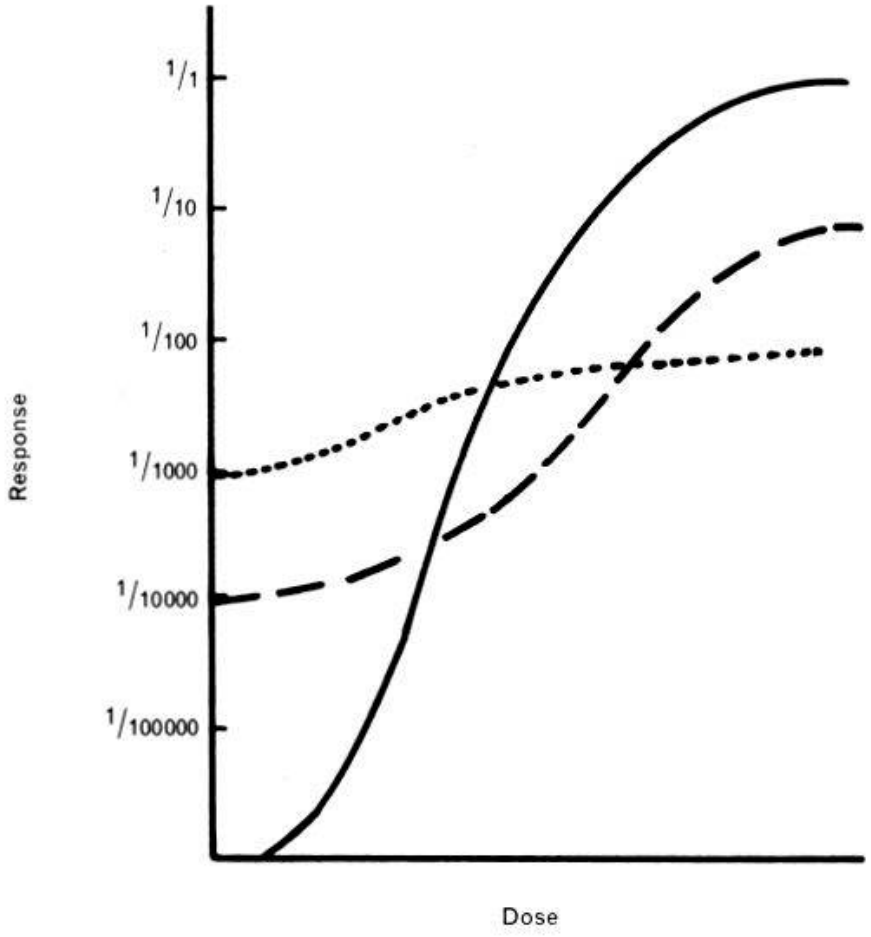

Fig. 2. Hypothetical dose response curves.

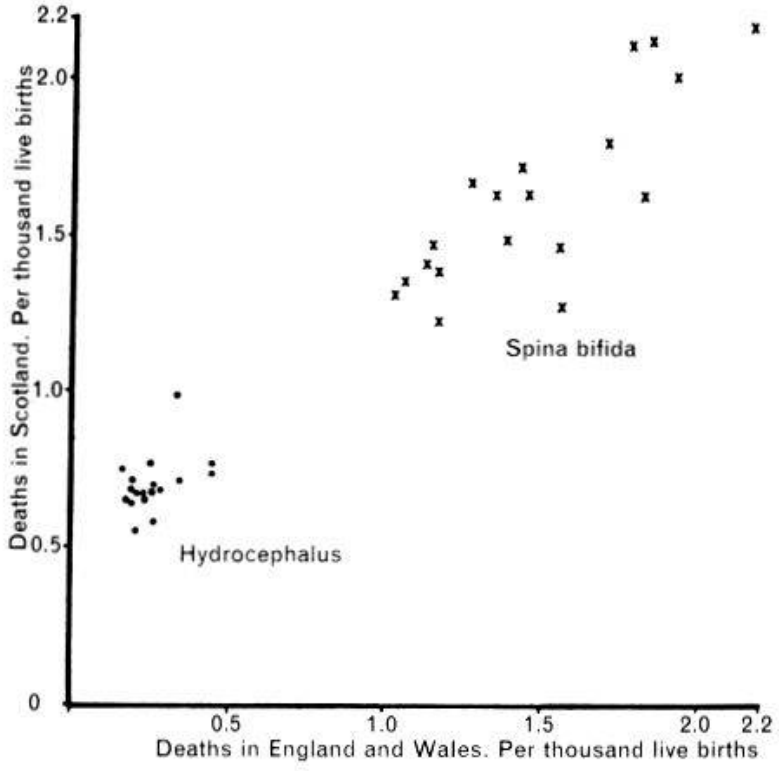

Fig. 3. The correlation of annual incidence of fatal spina bifida from year to year in Scotland and in England and Wales.

some common malformation on entire populations and yet for the association to resist discovery by the methods of detection available.

The malformations of the central nervous system due to defective fusion, of which the commonest types are anencephaly and spina bifida, are among the simplest malformations to study since diagnosis is obvious, and, since all cases must come to surgery or die early, and many do both, ascertainment is simple. The conditions are common, so that substantial data may be obtained.

Even if we examine the data available in this condition, and the reports of the Registrar General for Scotland now cover the fatal manifestations of these anomalies in over two million births, it is clear that the regional and secular variations are so great that some environmental variation must be considered to be acting with sufficient power to make these disorders largely preventable given sufficient knowledge and legislative powers. Figure 3 shows the concordant secular variation between England and Wales, and Scotland. Correlations of such magnitude imply that the greater number of these cases occurring over these years must be related to some teratogen with synchronous fluctuations between the two countries.

While it is preferable to change the environment by eliminating specific agents, as in the contemporary approach to malaria or typhus control, in the past effective control of disease has often been without any clear understanding of the mechanisms involved. In teratogenesis informed environmental control has not had, as yet, any very marked results excepting in a few specific disorders such as congenital syphilis and phocomelia; however there is sufficient knowledge of the probable effects of imposing peculiar biochemical backgrounds on developing organisms to discourage both the casual medication of any minor ailment and the planned obselescence of fashionable remedies.

Summary

A consequence of affluence is that the environment of the foetus is more variously exposed to contamination by various species-specific toxins incorporated by modern agricultural techniques and through antibiotic therapy, and by the use of tissue-specific toxins incorporated by medication, and the possible consequences, in terms of congenital malformations, are difficult to relate to these numerous, and potentially teratogenic insults.

Even if direct ascertainment of all malformations and all the associated environments were feasible, there would still be grave difficulties

in relating any teratogen to any malformation, and the cost of detection of a teratogen is likely to be numbered in thousands of casualties. The milder teratogens, since they are more difficult to detect, may be equally costly before they can be recognised.

Decisions related to legislation will have to be based on seriously limited data if the consequences of erroneously incriminating safe drugs, and of tolerating drugs suspect on limited data, are to be shared between the foetus and the drug companies.

The identification of teratogenic drugs would be greatly eased if conventions on shapes and colours of different classes of drugs were established and enforced, and the use of mixtures compounded in single pills discouraged by legislation or taxation.

Zusammenfassung

Infolge des Wohlstandes ist die Umgebung des Fetus in mannigfaltigerer Weise der Kontamination mit verschiedenen artspezifischen Giften ausgesetzt, die durch die Auswirkungen moderner landwirtschaftlicher Methoden, durch Antibioticatherapie und medikamentöse Verwendung gewebsspezifischer Toxine in den Körper gelangen; es ist schwierig, die möglichen Folgen in Form von kongenitalen Mißbildungen mit diesen zahlreichen und potentiell teratogenen Schädigungen in Zusammenhang zu bringen.

Selbst wenn die direkte Ermittlung aller Mißbildungen und der mit ihnen in Zusammenhang stehenden Umwelteinflüsse möglich wäre, so würde es immer noch große Schwierigkeiten bereiten, irgendein gegebenes teratogenes Agens mit irgendeiner gegebenen Mißbildung in Beziehung zu bringen, und bei der Berechnung des Aufwandes für die Auffindung eines Teratogens müßten Tausende von möglichen Fehlschlägen einbezogen werden. Die schwächeren Teratogene können, da sie schwieriger zu entdecken sind, gleichfalls teuer zu stehen kommen, bevor sie erkannt werden.

Entscheidungen für die Gesetzgebung müssen auf streng abgegrenzten Gegebenheiten beruhen, wenn die Konsequenzen einer irrtümlichen Beschuldigung unschädlicher Drogen und einer Duldung von begrenzt verdächtigten Drogen vom Fetus und der chemischen Industrie getragen werden müssen.

Die Identifikation teratogener Mittel würde sehr erleichtert, wenn Vereinbarungen über die Form und Farbe der verschiedenen Arten von Medikamenten getroffen und durchgesetzt würden und die Anwendung von gemischten Zusammensetzungen in Einzeltabletten durch die Gesetzgebung oder die Besteuerung erschwert würde.

Résumé

Une conséquence de la prospérité est l'exposition de l'environnement du fœtus à une contamination plus variée avec différentes toxines spécifiques pour l'espèce, qui proviennent des techniques modernes de l'agriculture, de la thérapie aux antibiotiques et de l'emploi médicamenteux de toxines spécifiques au tissu. Il est également difficile de mettre en rapport les conséquences possibles, c'est-à-dire les malformations congénitales, avec les nombreuses lésions potentiellement tératogènes.

Même si la détermination de toutes les malformations et de toutes les influences de l'environnement sur elles était faisable, il y aurait tout de même de grandes difficultés à mettre en rapport n'importe quel agent tératogène avec n'importe quelle malformation et la découverte d'un agent tératogène doit être probablement payée par des milliers d'échecs. Les agents tératogènes moins dangereux sont plus difficiles à découvrir et peuvent également coûter cher avant d'être reconnus.

Des décisions concernant la législation doivent être basées sur des données strictement limitées, si les conséquences d'une erreur dans l'incrimination de médicaments non dangereux et dans la tolérance de médicaments suspects doivent être partagées entre le fœtus et les industries chimiques.

L'identification de médicaments tératogènes serait bien facilitée si des conventions sur la forme et les couleurs des différentes classes de drogues étaient établies et imposées et si l'emploi de composés en pilules était rendu plus difficile par la législation ou la taxation.

Riassunto

Una conseguenza della prosperità, appare l'esposizione delle vicinanze del feto ad una contaminazione più variata con differenti tossine specifiche per la specie, le quali, in seguito a tecniche moderne dell'agricoltura, della terapia agli antibiotici, vengono incorporate attraverso l'uso medicamentoso di tossine specifiche per un tessuto. È ugualmente difficile stabilire un rapporto tra le possibili conseguenze in previsione di una malformazione congenita e le numerose lesioni potenziali.

Anche ammettendo che la determinazione di tutte le malformazioni e di tutti gli influssi esercitati dalle vicinanze su di esse fosse effettuabile, sorgerebbero certamente gravi difficoltà nello stabilire un rapporto tra un qualsiasi agente teratogeno e una qualsiasi malformazione, e la scoperta di un agente teratogeno dovrebbe probabilmente essere ripagata da migliaia di fallimenti. Gli agenti teratogeni meno pericolosi sono più difficili da scoprire, e possono ugualmente far pagar cara la loro scoperta.

Decisioni concernenti la legislazione devono essere basate su dati strettamente limitati, se le conseguenze di un errore nell'incriminazione di medicamenti innocui e nella tolleranza di medicamenti sospetti devono essere divise tra il feto e le industrie chimiche.

L'identificazione di medicamenti teratogeni sarebbe facilitata di molto, se fossero stabilite e imposte delle convenzioni sulla forma ed il colore delle diverse droghe, e se l'uso di composizioni in pillola fosse reso più difficile dalla legislazione o dalla tassazione.