Annotations

Drugs, infections, and congenital abnormalities

We know little of the causes of congenital abnormalities and less of their pathogenetic mechanisms. **Malformations** result from disturbances of growth during embryogenesis. Most congenital heart lesions, for example, can be understood in terms of incomplete or deviant growth of heart structures. **Deformities** result from later changes in previously normal structures by, for example, destructive pathological processes or intrauterine forces (e.g. talipes). Some defects—hydrocephalus, for example—could arise by either mechanism. Drugs can interfere with prenatal development either by disturbing embryogenesis or by exerting their pharmacological actions on developing fetal organs. Prenatal infections probably act mainly by causing inflammatory lesions in the embryo or fetus.

There is therefore a spectrum of pathogenetic mechanisms ranging from the instant teratogenesis of a single dose of thalidomide through congenital cataract caused by rubella virus in the lens, to disseminated neonatal cytomegalovirus infection in an anatomically normal baby. The identification of infective and chemical teratogens is not easy, and for two principal reasons. As regards the teratogen, in retrospective studies it may be impossible to establish with certainty that a drug was taken or an infection experienced, while prospective studies demand large numbers of pregnant women to yield sufficient malformed babies. As regards the malformation, its nature depends at least as much upon the **timing** of the teratogenic insult as upon the sensitivity of specific organs or tissues to the agent in question.

We are therefore faced not only with teratogens that can individually be responsible for a wide spectrum of defects (e.g. rubella), but also with apparently clearly defined defects that can be the end result of a dozen different pathogenetic processes (e.g. cleft palate). In practice, therefore, the recognition of a teratogen in man depends upon an astute clinician spotting an association between a drug or infection on the one hand, and a malformation or association of defects on the other. The less common the teratogen, the less common the defect, and the less variable the manifestations, the less difficult it is to notice the relationship. Gregg¹ noticed congenital cataracts and linked them with rubella. McBride² and Lenz³ both noticed phocomelia and linked it with thalidomide. If aspirin was responsible for 1% of congenital heart disease, it would be almost impossible to show.

For these reasons there are very few drugs and infections which are beyond doubt teratogenic in man. There are a few more for which the evidence is strong. Thereafter lies an exponential list of possibilities of diminishing likelihood.

**Drugs**

Table 1 lists teratogenic drugs categorised as definite, probable, and possible. This relates solely to their capacity to induce malformations. The effect of drugs in late pregnancy on neonatal metabolism, and the rather eerie possibility that antenatal drugs may affect postnatal behaviour⁴⁵ are beyond the scope of this review.

The teratogenicity of thalidomide is beyond doubt, both from the specificity of its effects and from the epidemiological data. Its mode of action is unknown, though the hypothesis of sensory neuropathy⁶ is attractive in that it offers a link between the well-known limb defects and the less well-remembered defects of ears and eyes, facial palsy, and defective eye movements. A neurogenic mechanism would also tie up with thalidomide peripheral neuropathy in adults, and might help to explain the curious excess of left limb dominance in thalidomide children.⁷

Cancer chemotherapy depends upon drugs which act upon rapidly dividing cells and therefore have the capacity to kill the cancer without killing the patient. Embryonic cells also divide rapidly, and any effective

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**Table 1**

<table>
<thead>
<tr>
<th>Drugs which cause congenital abnormalities</th>
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<tbody>
<tr>
<td><strong>Definite</strong></td>
</tr>
<tr>
<td>Thalidomide</td>
</tr>
<tr>
<td>Nor-/ethisterone</td>
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<tr>
<td>Antimitotic drugs</td>
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<tr>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Operating theatre environment (?: anaesthetics)</td>
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<tr>
<td><strong>Possible</strong></td>
</tr>
<tr>
<td>Lysergide</td>
</tr>
<tr>
<td>Sex hormones</td>
</tr>
</tbody>
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¹ Gregg
² McBride
³ Lenz
⁴ Sex hormones
⁵ Anticonvulsants
⁶ Antimitotic drugs
⁷ Operating theatre environment (?: anaesthetics)
antimitotic drug, acting by folic acid antagonism or any other way, has teratogenic potential. Potent antimitotic drugs may be embryolethal; indeed, aminopterin was once used to terminate pregnancies.\(^8\) Smaller doses may cause malformation, but normal infants have also been born after exposure to these drugs in utero.

Idoxuridine (IDU) is a DNA inhibitor used in the treatment of herpes, usually by topical application. It is teratogenic in rabbits and mice when given parenterally or into the conjunctival sac. For use on skin lesions IDU may be dissolved in dimethyl sulphoxide which penetrates the skin. Although I am aware of one healthy baby born to a mother treated with IDU in pregnancy\(^9\) the drug is better avoided if possible.

The ability of ethisterone and norethisterone to masculinise female fetuses is also beyond doubt, and is understandable in terms of the molecular similarity of these substances to testosterone. This is not teratogenesis in the thalidomide sense, but more akin to the influence of antithyroid drugs on the fetal thyroid.

Alcohol, which with gluttony and promiscuity was held responsible for all misfortunes in Victorian times, has reasserted itself as a teratogen, but only if abused. Affected infants show pre- and postnatal growth retardation, developmental delay, microcephaly, maxillary hypoplasia, congenital heart disease and joint anomalies (dislocations and subluxations), and other minor defects.\(^10\) One prospective study of 23 infants born to alcoholic mothers showed a 17% perinatal mortality rate and IQs below 80 in 44% of survivors.\(^11\)

Malformations are significantly more common among the offspring of epileptics taking anticonvulsants than in the general population or in the offspring of epileptics not taking anticonvulsants. Several anticonvulsant drugs have been incriminated but phenytoin and barbiturates, especially if taken together, appear to present the greatest hazard. Among a wide spectrum of malformations, facial clefts and congenital heart disease are the most commonly reported, and occur respectively about 12 and 3 times more often than in the general population. Anticonvulsants should not be discontinued in pregnancy if there are sound clinical indications to continue. The hypothesis that folic acid deficiency may be involved in the teratogenic action of these drugs is unproven but plausible. Folic acid supplements might help if started very early in pregnancy.

Warfarin is used especially for long-term anticoagulant treatment after heart valve replacement. The number of pregnant women on warfarin must be small, but a striking pattern of developmental anomaly has been described in several of their offspring. The most conspicuous external anomaly is hypoplasia of the nasal bones which may be severe enough to interfere with respiration and could therefore contribute to the mental retardation noted in some cases. Radiological examination of the bones shows congenital stippled epiphyses (dysplasia epiphysialis punctata) of the Conradi-Hünermann type. (It is of course important to distinguish warfarin embryopathy from the rhizomelic type of congenital stippled epiphyses which is an autosomal recessive condition.)

The adverse influence of the operating theatre environment on certain aspects of reproduction,\(^12\) including an increased incidence of malformations in the offspring of theatre personnel, seems beyond doubt, but it may be presumptuous to mention it under the generic heading 'drugs'. Volatile anaesthetic agents are regarded as the most likely culprits (and this belief underlies recent guidance from the Dept. of Health and Social Security about the ventilation of operating theatres) but this is not proven. If anaesthetics are responsible, chronic low-dose exposure appears to be more important than acute high-dose exposure. The anaesthetist is at higher risk than the patient on the table.

The possibilities that lysergide (LSD) and sex hormones might be teratogenic are as yet unresolved. Not surprisingly, data relating to LSD are somewhat haphazard. As regards sex hormones (apart from virilising hormones noted earlier), whether progestogens given for recurrent abortion, pregnancy-test drugs (now discontinued), or contraceptive pills taken in pregnancy, it is significant that the suggestions of teratogenicity all derive from retrospective studies, whereas all prospective studies published show no such effect.

The manufacturers of co-trimoxazole advise against use in pregnancy, a wise precaution as it is a folic acid antagonist, but there is as yet no clear evidence of teratogenicity. Much comfort is to be found in well-conducted prospective studies of drugs in pregnancy such as the Swedish survey of Kullander and Källén.\(^13\)–\(^16\) More than once they have provided good reason to doubt suspicions aroused by retrospection.

Infections

Table 2 lists the infections that are certainly, probably, and possibly capable of causing congenital malformations. The rubella story is for the most part too well known to need repeating and has been well reviewed by Dudgeon.\(^17\) A few less widely known aspects deserve comment, and some useful lessons
Definite
Rubella
Cytomegalovirus
Toxoplasmosis

Probable
Herpesvirus hominis
Varicella/zoster

Possible
Mumps
Influenza

Table 2 Infections which cause congenital abnormalities

are being learned from the National Congenital Rubella Surveillance Programme. The most important clinical fact is that congenital rubella is a progressive disease. Live virus can be isolated long after birth, and chronic inflammatory changes continue for some time. Deafness may not be evident until several years after birth, and successful performance in screening tests in infancy only means 'so far, so good'. It is clear that there is often a conductive element in rubella deafness in addition to sensorineural loss. The later development of diabetes mellitus in a significant minority is also indicative of chronic disease.

Fewer than 50% of mothers of rubella-affected babies have a history of rubella with rash, and 25% have no history of any significant illness or contact. Often therefore suspicion depends upon the clinical features and confirmation depends upon the laboratory. Maternal IgG rubella antibody may persist in the baby up to 8 months. The presence of specific rubella IgM is helpful in diagnosis if determined in an experienced laboratory. The suggestion that maternal rubella in later pregnancy may be associated with neurodevelopmental disorders in the offspring requires further study.

Cytomegalovirus (CMV) almost certainly affects more unborn babies than does rubella virus. CMV and herpes virus, both DNA viruses, cause similar illnesses. Low birthweight is common (as it is with rubella) and there may be a viraeic picture at birth with hepatosplenomegaly, jaundice, purpura, pneumonitis, and encephalitis. Survivors show extensive neurological damage with microcephaly, mental retardation, cerebral palsy, deafness, epilepsy, and cerebral calcification. These permanent defects may also follow trivial neonatal illness or infection which is initially asymptomatic.

Intrauterine infection with the varicella/zoster viruses can certainly produce a similar neonatal viraemic picture, but whether they are truly teratogenic is still debated. Perhaps the debate is really about the meaning of 'teratogenic'. These viruses can certainly damage unborn babies. A number of children have been described who had skin lesions or scars at birth associated with hypoplasia of underlying tissues. Involvement of the nervous system, including the eye, is common. The role of mumps, Coxsackie, influenza, and other viruses is far from clear and further work is needed.

In addition to viruses, congenital toxoplasmosis can also cause widespread damage to the brain and eye. Hydrocephalus, microcephaly, or chorioretinitis may be evident at birth, but infected infants asymptomatic at birth may have cerebrospinal fluid changes indicative of a chronic meningoencephalitis and show mental retardation and other neurological problems thereafter.

Prevention

Only a tiny minority of congenital abnormalities can be attributed exclusively to either drugs or infections. It is less easy to say what part they may play in the causation of malformations of multifactorial origin. Certainly it is worth taking what action is possible to prevent the adverse effects of drugs and infections on the embryo and fetus. This includes: (1) The intelligent and discriminate use of drugs at all times, but especially in women of child-bearing age; (2) the reporting of possible associations between drugs and malformations to the Committee on Safety of Medicines; (3) wider use of rubella vaccine; (4) possibly in the future, vaccines against CMV and toxoplasmosis.

I thank Dr Sheila Sheppard for constructive criticism and Miss Hilary Davies for impeccable secretarial help.

References

Role of circulating soluble immune complexes in disease

A wide variety of chronically disabling diseases are thought to be caused by circulating soluble immune complexes. These include collagen vascular diseases, rheumatoid arthritis, glomerulonephritis, and possibly chronic inflammatory bowel diseases. Antigen-antibody complexes are deposited in the blood vessels of affected organs and initiate damage by activation of the complement system, eliciting an inflammatory response.

The evidence for this damaging role of complexes comes largely from animal studies, in particular those in which chronic glomerulonephritis is induced by repeated antigen administration. The similarity of immunoglobulin deposition shown by immunofluorescence in human nephritis and in the animal experimental disease suggests that circulating complexes play a role in both. Only a few animals acquire chronic nephritis as a result of repeated antigen dosage, and they respond with predominantly nonprecipitating antibody which is inefficient at antigen elimination. In man, the rare complement deficiencies, in particular homozygous C1r and C2 are associated with immune complex syndromes. Antibody, complement, and phagocytes are all involved in antigen clearance and a fundamental defect in their function may underlie immune complex disease. However, in the majority of patients with such diseases the immunodeficiency is probably only relative and therefore difficult to detect.

Recently, methods have been developed for the detection of circulating soluble immune complexes in sera and their presence has been confirmed in a variety of diseases. However, mere detection is insufficient proof of pathogenicity, for it is probable that not all immune complexes are damaging, and sensitive methods detect low levels in healthy individuals. Similarly, raised levels are found in pregnancy which fall after delivery, suggesting that certain types of complex may modulate the immune response in an advantageous manner, thus possibly preventing maternal rejection of that mosaic of foreign antigens, the fetus. Facilitation or enhancement of malignant tumour growth may also be due to certain types of immune complexes.

Antigens involved in immune complex diseases may be of either exogenous or endogenous origin. Exogenous antigens include administered therapeutic agents producing serum sickness, inhaled and ingested antigens, and microbial and parasitic products derived from invading organisms. In diseases initiated primarily by exogenous antigens, the inflammatory process may release endogenous antigens which perpetuate the disease. Similarly cross-reaction of endogenous antigens with antibodies formed towards exogenous antigens may be another mechanism leading to persistent inflammation. This mechanism probably applies in poststreptococcal glomerulonephritis; in systemic lupus erythematosus...
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