Teratogens in Everyday Life
The Milroy Lecture 1980

D.H.M. WOOLLAM, MA, MD, ScD, FRCP
Director, Medical Studies, Emmanuel College and Peterhouse, Cambridge
and Lecturer in Anatomy, University of Cambridge

The question I want to attempt to answer is not so much why man and other animals are born deformed, indeed that question seems rather a theological one, but simply how they come to be born deformed. I would not attempt to deny that in a large number of cases the cause is purely genetic. In perhaps the majority of cases, however, I believe that congenital malformations are caused by teratogens present in everyday life, helped on occasions by a constellation of genetic factors.

The majority of members of the medical profession have very little idea of how serious is the problem of congenital malformations. Every year in this country over 2 per cent of babies are born with severe physical and/or mental malformations. Five years' supply of seriously deformed children, if they survived for a reasonable time, would provide an average Wembley Cup Final crowd of 100,000, and they must be costing someone, probably the NHS, at least £5,000 a year each to maintain. If abnormalities at birth disappeared from the scene, there would be a very large increase in the money available for treating all kinds of diseases that we would like to subsidise more heavily.

Taking less severe malformations into account, the overall rate runs at about 6 per cent of new-born children. Only a few diseases affect 1 in 50 of the population, that is about one million, yet very little attention has been paid in the UK to the investigation of the cause of human malformations. The reason may be because teratology does not fall within the field of interest of the Royal Colleges and the Research Councils. The subject is one of extreme complexity, and it is surprising that I should be the only person in the UK with 30 years' experience of teratology who is actively engaged in research in the subject.

Until 50 years ago it was generally assumed that all malformations present in mammals at birth were due to genetic factors. Many, of course, were, but when the American veterinarian, Hale, showed in 1930 that piglets born to sows fed on a diet deficient in vitamin A had no eyeballs, the scene was set for the investigation of environmental factors in the causation of malformations. For instance, rats in a litter born to a dam submitted to a moderately severe dose of X-radiation during pregnancy have anophthalmia similar to that caused by hypovitaminosis A. Between 1940 and 1960, three small laboratories were set up and expanded. The most famous was that of the doyen of mammalian teratology, Josef Warkany, and his colleague Wilson at the Children's Hospital Research Foundation, Cincinnati, hotly pursued by Giroud and Tuchmann-Duplessis at Paris, with the laboratory set up in Cambridge by the late James Millen and myself as a modest third. The work done in these laboratories was originally largely devoted to utilising the action of teratogens in a pregnant laboratory mammal to study how abnormal and, by inference, normal development occurs, although at Cambridge we quickly embarked on the work that has dominated my personal research to the present day, namely, the attempt to identify and study agents that would either oppose, and thus produce a cure for, or enhance the action of teratogens.

The study of teratology has to take note of the fact that there is a considerable difference between various parts of the world in the incidence of malformations. We do not know whether the reason for this lies in genes or teratogens, or both; for example, congenital dislocation of the hip seems to get more frequent as one travels east from this country to Japan. On the other hand, anencephaly is uncommon in Japan and extremely common in the British Isles, reaching its peak incidence on the west coast of Ireland. It is of interest that, in South Africa, the incidence of anencephaly in the white population is similar to that in Western Europe and that in the Kaffir community it is very much lower.

There are very few principles in teratology. The most important states that the time and dosage of the teratogen received by the mother are the most important factors and that, of these, the timing of the dose is the more significant. If a teratogen is given before the blastocyst is embedded in the uterus, it may kill the embryo, but it cannot deform it. There is another way in which time is of the essence and it is this. The dangerous period for producing malformations in the human is generally agreed to be between the 21st and 36th day of pregnancy. The 10 somite human embryo (Fig. 1), about 23 days of age, with the neural tube unclosed, is clearly wide open, in more senses than one, for a teratogen to produce spina bifida. The 32-day-old embryo (Fig. 2) is getting towards the end of the very dangerous period when the limbs, ears and palate are all at a critical stage.
of development. The embryo will remain at risk until about the 80th day, but the risk is a relatively small one. Put in the simplest way, what happens in a congenital abnormality is that something that should join up with something else fails to do so or, alternatively, something closes that should remain open. Once the right pathway in development has been taken, nothing can go wrong with a particular structure. Unfortunately, the period of maximum risk from teratogens, that is between the 21st and 36th day of pregnancy, is a time when many women will not even suspect they may be pregnant. It follows, therefore, that if possible teratogens are to be put out of the reach of pregnant women, they must be denied to all women of child-bearing age, or preferably to all women who are actively trying to have a child, or who at least are not doing anything to prevent pregnancy.

Alcohol

The first potential teratogen, to which virtually the whole public is exposed, is alcohol. It is perhaps because of the vast sums of money leached from the public in the profits of distillers and brewers and in Government taxation from the sale of alcohol, that the UK lacks understanding of the deleterious effects of alcohol consumed during pregnancy. It was not always so, for during the gin epidemic of the 1720s this College reported to Parliament that parental drinking was a cause of 'weak, feeble and distempered children'. The House of Commons itself set up a committee 110 years later which reported that infants born to alcoholic mothers had a 'starved, shrimed and imperfect look'. The problem was recognised in the Bible for, in the Book of Judges we may read: 'Behold thou shalt conceive and bear a son: and now drink no wine nor strong drink'. That this was excellent advice was shown in 1972, when Dr Christy Uleland published results of a study of infants born to chronic alcoholic mothers at Seattle's Harborian Medical Center during the nine months beginning October 1962[1]. Over the next five years Doctors Jones, Uleland, David Smith and Ann Streissguth began to set forth the blueprints of what is now known as the fetal alcohol syndrome (FAS)[2-5]. The syndrome was characterised by the infants being born underweight and continuing to be underweight for age after birth. Mental deficiency was the rule rather than the exception; Professor David Smith was later to state that FAS was the third commonest cause of mental deficiency, only exceeded by hydrocephalus with spina bifida, and Down's syndrome. In FAS the head and face showed typical abnormalities, most noticeable being an extremely small head. Short eye slits and defective development of the mid-facial tissues, inner epicanthic folds and abnormalities of the external ear were also found. In point of fact, defects of the external
ear seem to occur in association with any form of mental defect, genetic and otherwise.

There can be no doubt that FAS exists, but there are doubts whether the syndrome is invariably produced by excessive consumption of alcohol or whether other teratogens are responsible for an identical condition. There may be a possibility that genetic factors work in conjunction with alcohol to cause the syndrome.

Such evidence as we have at present suggests very strongly that FAS is a true bill. It has been claimed that a chronically alcoholic woman has one chance in three of producing a child with FAS if she gets pregnant. I am strongly attracted to the analysis of the association between intensity of alcohol consumption and effect on the fetus put forward by Dr Ruth Little of Seattle (Tables 1 and 2).[6] She has suggested that only two Martinis

drinkers or chronic alcoholics, tend to decrease their consumption of alcohol very considerably as soon as they get pregnant (Table 3). Strangely, both monkeys and
drinking beer. This is a normal, alcoholic drinking. Alcoholics

Table 1. Prevalence of problem drinking among drinkers or chronic alcoholics, tend to decrease their consumption of alcohol very considerably as soon as they get pregnant (Table 3). Strangely, both monkeys and

drinking beer. This is a normal, alcoholic drinking. Alcoholics

| Table 1. Prevalence of problem drinking among drinkers or chronic alcoholics, tend to decrease their consumption of alcohol very considerably as soon as they get pregnant (Table 3). Strangely, both monkeys and |
| Prevalence of problem drinking | 3% |
| Prevalence of 'excessive' drinking | 3% |
| 2 drinks daily | 2% |
| 5 drinks on occasion | 13% |
| Prevalence of problem drinking or 'excessive' drinking (adjusted for duplications) | 10% |
| Total pregnancies | 23,536 |
| Pregnancies at risk | 2,354 |

Table 2. Level of alcohol use and associated fetal risks. (After Ruth Little[6].)

| Regular Social Drinking (2 or more drinks daily) |
| Intrauterine growth retardation |
| Increased risk of anomalies |
| Behavioural decrements in the newborn and infant |
| Increased risk of stillbirth |
| Decreased placental weight |
| Binge Drinking (5 or more drinks on occasion) |
| Structural brain abnormalities |
| Very Heavy Drinking |
| Fetal alcohol syndrome |

consumed daily can produce a birth-weight 160 g below normal, and she goes on to associate severer degrees of alcoholism with more severe fetal deformities. An Australian authority, Dr Pirola, has claimed that six beers a day are able to create a severe risk for the unborn child. This is interesting if only because Australia must be virtually the only country in which one can imagine a woman consuming six beers a day. It was Dr David Smith who originally raised the question of 'binge' drinking, potentially the most dangerous of situations, for it would seem probable that a woman taking part in a binge party between the 21st and 35th day of pregnancy, when there was a high probability that she did not know she was pregnant, might be putting the development of the embryo she was carrying into considerable jeopardy.

One fact now well established by a number of researchers is that all women, be they trifling and casual

| Table 3. Changes in drinking habits in pregnancy. (After Ruth Little[6].) |
| Decrease (%) | Increase (%) |
| All Drinkers |
| Little et al. (1976)[7] | 90 | 6 |
| Streissguth (1977)[8] | 78 | 13 |
| Hook (1978)[9] | 25-37 | |
| Heavy Drinkers |
| Little et al. (1976)[7] | 91 | 0 |
| Streissguth (1977)[8] | 86 | 8 |
| Warner and Rosett (1975)[10] | 78 | - |
| Alcoholics |
| Little and Streissguth (1978)[6] | 51 | 15 |

It is difficult to estimate how many pregnancies are at risk of ending up with the birth of a child with part or all of the fetal alcohol syndrome. The most reliable figures suggest that about 10 per cent of pregnancies are at risk. If this is so, alcohol must be one of the most dangerous hazards faced by the embryo.

Is there anything we can do to determine the incidence of and need for treatment of FAS in this country? If research funds were available, I would take advantage of the fact that surrounding Heathrow Airport, in Birmingham, and in Manchester, there are now large centres of Moslem and Hindu culture side by side with those of English, Irish, Welsh and Scottish origin. The Moslem and Hindu women will on the whole not take alcohol, at least for several generations, whether they are pregnant or not; a considerable number of the others will. I am making alcoholometric measurements on English pregnant women at the present time. I would like to carry out this work in areas of mixed population to see the influence of maternal alcoholism on mental handicap in the child. This is a simple experiment that could be carried out in the UK at the present time with an ease with which it could not be carried out anywhere else in the world, since there is nowhere else where a large immigrant teetotal community lives in close proximity with a native alcohol-consuming population.

Obviously alcohol has to be regarded as potentially one of the most dangerous teratogens to which the pregnant woman may be exposed. To stress the apparent hopelessness of the problem it presents, let us suppose that alcohol was discovered five years ago by a pharmaceutical firm. Its evident qualities as a tranquiliser and anxiolytic would certainly encourage further investigation. In submitting an application to the Committee on Safety of Medicines, the company would be able to tell the authorities that alcohol was at times responsible for severe damage to the heart, liver and central nervous system, that it was found in excessive quantities in the bloodstream of 40 per cent of individuals killed in road traffic
accidents, that mothers who took the drug daily had a one in three chance of giving birth to a child with severe mental and physical defect, and that the drug appeared to account for one-tenth of all serious congenital malformations appearing in the population. Is it likely that it would be passed to appear in the pharmacopeia?

Drugs

The appearance of thalidomide at the end of the 1950s, with its effect of producing phocomelia (seal-limb) and complete limblessness, was sensational for two reasons. First, it produced this effect in the human child; secondly, it occurred when the mother only took a tablet or two of the drug, very often to combat morning sickness, at the critical period of pregnancy for the development of limbs, somewhere in the fifth or sixth week of pregnancy.

The existence of thalidomide with its terrible effects terrified and angered governments, people and press, and from this time forward a vast number of drugs and other agents were investigated to see whether they had teratogenic properties in the rat, mouse and rabbit and therefore might have similar properties in the human. It is interesting to note two points: first, thalidomide, although highly teratogenic to baboons, chimpanzees and men, is only mildly so to mice, rats and rabbits; secondly, thalidomide-type activity is paralleled by that of coal gas, since a number of children with absent limbs have been produced when their mothers have exposed themselves to near-fatal coal gas poisoning during pregnancy.

It is often said that the most effective device we have to diminish the teratogenic activity of drugs is a label on the outside of the bottle which says 'not to be taken by pregnant women'. This might be a good idea if women in the dangerous period of pregnancy knew they were pregnant. Two more useful guide-lines are first, drugs should be given during pregnancy only if they are absolutely necessary to the health of the mother. This means that, to give but one example, if a pregnant woman has to have anti-depressants, she ought to have a therapeutic abortion. Nothing a doctor can do is worse than to bring about the birth of a live deformed child. Secondly, the leaders of the medical profession should press the pharmaceutical industry to do two things: to arrange that drugs are only sold under one name, whichever firm sells them (thalidomide was sold under 49 different names); secondly, to stop the sale of two or more drugs in the same tablet so that, for example, what are colloquially known as 'uppers' and 'downers' are taken in the same pill, the idea presumably being to ensure that nothing whatsoever happens.

Cigarette Smoking

Cigarette smoking is widely believed to cause small underweight babies with respiratory difficulties. Not so commonly stressed is the idea that nicotine may well be a potent teratogen, although it may be some other constituent of the burnt cigarette or its enclosing paper that makes the act of smoking teratogenic. Pipe-smoking or even cigar-smoking are never considered dangerous to the development of the embryo, probably because these activities are not indulged in by women. As with alcohol, women, however addicted, actually decrease their consumption of cigarettes during pregnancy. A possible interaction between these teratogens is obviously worth looking for.

Rubella

One important teratogen which has aroused interest since 1941 is rubella or German measles. It was first associated with cataract by the Australian ophthalmologist, Gregg, and later was shown to cause a wide constellation of malformations, notably congenital heart disease, when the mother suffered from the disease during the critical period of pregnancy. Clearly, no woman should become pregnant without information as to whether she has had German measles appearing in her medical records. If she has not had it, she should be immunised against the disease. Maternal rubella is one of the most dangerous agents faced by the human embryo. The reason why enshrines perhaps the most important principle in teratology. Agents that damage the developing tissues slightly do not lead to the birth of a live deformed embryo but of a normal healthy one. Agents that damage developing tissues severely do not cause the production of a live deformed infant, they kill it at an early stage of development. Only a small number of agents that produce moderate damage during development lead to what we wish to avoid at all costs—the birth of a live deformed infant. The common cold virus will do no harm at all; on the other hand, smallpox and poliomyelitis will cause death and abortion or resorption of the fetus. The problem with rubella is that, almost uniquely among viral diseases, it lies in that narrow band of teratogenic agents whose activity is nearer the normal than the abnormal end of the spectrum, so the embryo survives their effects to become a child with one or more serious malformations. In the case of rubella, the most important of these are malformations of the lens of the eye, of the lining of the heart, and of the brain.

Diet

It is my belief that most women go into pregnancy at least half a stone too heavy. It is easy to talk about a balanced diet with plenty of essential minerals and vitamins supplemented by exercise and fresh air, but how many women in fact carry this training programme out in the important four-month period before pregnancy? It is commonplace to talk about a pregnant woman eating for two but, even at the end of pregnancy, she is not eating for two but for one and a sixteenth, and at the very beginning of pregnancy she is eating for one and a 20 millionth. Women do eat too much during pregnancy. As the American dietician said, 'Yes, madam, there is something that is making you fat and it is called food'.

A Physician's Advice

Finally, I want to consider the advice a physician should
give to a woman who is contemplating pregnancy or who is actually pregnant, considering the situation as it applies to a young intelligent recently married couple, both of whom are working.

It is not unreasonable to assume that in the majority of cases the wife will have been prescribed the contraceptive pill for a year or two before she contemplates pregnancy. There is a lot to be said in favour of the pill being taken under close medical supervision only and for the use of the pill, again on medical advice, to be abandoned in favour of male contraception for at least four months before the woman tries to get pregnant. This four-month period between abandoning the pill and attempting to become pregnant may be utilised by the physician so as to be of the greatest value to the mother, her future child and the community for, as pregnancies become fewer, healthy undeformed babies become more precious. The care and maintenance of a child with certain deformities may cost the community up to £1,000,000 during its lifetime. Those who have the care of women of child-bearing age should be highly educated in genetics and the environmental factors affecting embryonic development, that is to say those teratogens active in everyday life.

Certain teratogens can be dismissed immediately. No alcohol should be consumed during pregnancy and no alcoholic woman should become pregnant. No woman contemplating pregnancy should smoke.

Pregnancy and childbirth can be compared to a much extended version of an athletic race like the 10,000 metres, a long journey culminating in a brisk dash for the tape where delivery occurs. An athlete does not prepare for such a race by eating large numbers of chocolates, smoking 40 cigarettes a day and downing half a bottle of gin every 24 hours. Nor should a pregnant woman prepare for her race in that way. The health of the mother is the health of the fetus.

Conclusion

Finally, I must express my amazement at the lack of support in the UK for the study of the reasons why and how children are born deformed, particularly since we do not seem to be very far from an answer to this most appalling of all human problems. Perhaps our approach should be tinged with a little of the spirit Professor F.A.E. Crew showed when he wrote: 'Children yet unconceived are as much the patients of the physician as are the moribund senescents on whom he is prepared to lavish his care'.

Dr Gavin Milroy, who must be numbered among the first of the community physicians, would surely have agreed heartily with that sentiment.

References

1. Ulleland, C. N. (1972) Annals of the New York Academy of Science, 197, 167.
2. Jones, K. L. and Smith, D. W. (1975) Lancet, 2, 999.
3. Jones, K. L., Smith, D. W., Ulleland, C. N. and Streissguth, A. P. (1975) Lancet, 1, 1267.
4. Jones, K. L. and Smith, D. W. (1975) Teratology, 12, 1.
5. Streissguth, A. P. (1976) Annals of the New York Academy of Science, 273, 140.
6. Little, R. E. and Streissguth, A. P. (1978) Alcoholism: Clinical and Experimental Research, 2, 179.
7. Little, R. E., Schultz, F. A. and Mandell, W. (1976) Journal of the Study of Alcohol, 37, 375.
8. Streissguth, A. P. (1977) American Journal of Orthopsychiatry, 47, 422.
9. Hook, E. B. (1978) Birth Defects, 14, 249.
10. Warner, R. H. and Rosett, H. L. (1975) Journal of the Study of Alcohol, 36, 1995.