CONGENITAL ABNORMALITIES

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Not long ago a baby was born in a hospital in Northampton with only one eye, which was in the centre of his forehead. He had other abnormalities as well, and it was inevitable that he died within a week ; but whilst he was alive, he was of considerable interest to embryologists, and he was also a source of astonishment to many who had heard of the Cyclops only as an imaginary figure in Greek mythology.

In actual fact, of course, many of the monsters which featured in ancient myths and fairy stories owed their origins to human babies born with congenital abnormalities. It is not difficult to see how the two-headed giant of folk-lore was derived from the occasional Siamese-twin which is born with two heads and a single trunk ; and how the dwarf of mythology was based on achondroplasia. Even the idea of mermaids may have been derived originally from the rare human baby who is born with fused legs ; and numerous other examples could be quoted.

We no longer believe with Pliny that "Nature creates monsters for the purpose of astonishing us and amusing herself," for we now know that monsters are nothing more or less than Nature's mistakes. But not all of us have yet fully emerged from the twilight of folk-lore, for in country districts we still find a surprising number of superstitions and old wives' tales, and we have all come across the theory that if a pregnant woman sees a hare, her offspring will have a cleft-lip. That there are still people who believe these things is a measure of our ignorance about congenital abnormalities in general.

For a long time it has been realised that broadly speaking congenital abnormalities can be divided into two groups. In the first group are those which can be traced through several generations in a single family — the so-called hereditary abnormalities. In the second group are those which appear to arise out of the blue in families which have never previously been afflicted with them — and these are the ones which used to be attributed to all sorts of influences including witchcraft and maternal impressions, and which are nowadays described as being due to "environmental "factors. These two groups of hereditary and environmental congenital abnormalities are not always

as clear-cut as they seem, but we can conveniently consider them uder these headings.

Heredity.

Hereditary malformations depend upon inherent genetic abnormalities in the germ plasm from which the foetus develops ; and if the germ plasm (resulting from the union of the sperm and the ovum) happens to contain an abnormal gene — in single dose if the inheritance is dominant and in double dose (one from each parent) if the inheritance is recessive — then the malformation associated with that gene is bound to appear in the baby. Sometimes the malformations are physical (e.g. polydactyly), sometimes biochemical (e.g. phenylketonuria or haemophilia), but the underlying principles of their inheritance are the same. I need not elaborate this, for it has been known for a long time that certain abnormalities can run in families, and the science of genetics has even made it possible in many cases to tell parents with some precision what the mathematical chances are that their children will have the family trait. In fact a special clinic has been established at the Hospital for Sick Children, Great Ormond Street, where parents can obtain advice about the inheritance of genetically determined congenital abnormalities : and although in most cases a number of other factors have to be taken into account in addition to the hereditary one, it is in general fair to say that if the disability is inherited as a dominant trait, the chances are that 50% of the children will be affected, whereas if it is recessive the chances are only 25%. Unfortunately nobody can yet give a definite answer to the question which is uppermost in the minds of the parents, namely, "will our *next* child be affected or not?"

Many of the faulty genes which are met with today have already been handed down through countless generations : but it may not always be easy to prove this from the family trees where the inheritance is recessive, because in such cases the malformation is handed on by "symptomless carriers" and only shows up as a detectable abnormality if *both* parents happen to be carriers. Incidentally, this is more likely to happen if the parents are themselves closely related — hence the popular aversion to marriages between first cousins ; for such marriages sometimes bring to light faulty genes that have hitherto been lurking harmlessly in the family storeroom.

Mutations.

Even if due allowance is made for the difficulty of being sure about recessive genes, malformations of the hereditary type (as shown by the fact that they are subsequently inherited) do sometimes appear out of the blue in a previously blameless family tree. What has happened is that one of the previously normal genes has undergone a change or "mutation" into an abnormal one, which then remains abnormal in subsequent generations. These mutations are occurring in small numbers and quite erratically all the time, and we can do nothing about them. We can only hope that mutations for the better are occurring just as often as mutations for the worse — but this is difficult to be sure about.

What we do know is that similar mutations can also be brought about artificially by irradiating the testes or ovaries with X-rays or atomic radiation ; and this has led many people to question the wisdom of continuing atomic and hydrogen bomb tests on the present scale. But the consensus of opinion at present seems to regard this danger as remote, at any rate so far.

Environmental Factors.

In the case of the hereditary or genetically determined congenital abnormalities mentioned so far, the foetus has been inevitably affected from the moment of conception. It has never had a chance of developing normally, because its germ plasm was faulty from the start.

Not all congenital malformations are as inevitable as this. It is quite possible for an embryo to start with a normal set of genes, and still develop abnormally. Here the foetus sets off along the normal road of development, but for one reason or another is prevented from following the normal schedule in every detail ; and the result is a baby that is either unfinished or deformed. The factors concerned in such a case are not in the germ plasm, but in the environment of the developing embryo ; which means (1) that if we could discover what these factors are, we might possibly learn how to control them and so prevent this type of congenital abnormality in future, and (2) that if the baby survives, it carries a normal set of genes in spite of its deformity, and hence it does not pass on the abnormality to future generations.

There has for years been abundant evidence from animal experiments that abnormalities may be produced

by modifying the environment, but it is only recently that the part played by environmental factors in the production of human congenital abnormalities has been recognised. These environmental factors are so important that they will be considered in greater detail later on. It is essential before doing so to have a working knowledge of the various stages which the normal foetus goes through during its nine months in utero.

Normal foetal development.

There are three main stages in intrauterine development. In the first stage, the emphasis is on the development of the placenta and membranes, for without these the foetus cannot develop at all. In the second stage, which overlaps the end of the first stage to some extent, the foetus itself develops very rapidly, and all the various organs of the body differentiate in turn from what is at the start just a circular mass of cells : so that at the end of the second stage, the foetus is fully formed in every detail, and is recognisable as a miniature human baby — though still very small. In the third stage the foetus grows in size and maturity, until finally at the end of this stage it is ready to be born.

The **first stage**, or stage of placental development, lasts about 6 weeks. During this stage, growth is so rapid that the weight of the embryo increases about 25,000 times each week. It will readily be understood that any accident or insult to the embryo at this stage is likely to cause so much interference with growth that further development of the foetus is impossible — and a miscarriage results, not a deformed baby. This stage, therefore, is of little importance in the aetiology of congenital abnormalities.

The **second stage**, the stage of differentiation (also known as the organogenetic stage, because it is during this stage that the various organs of the body are developed), lasts from about the fourth to the twelfth week. It is by far the most important stage of all in the production of congenital abnormalities. During this stage, the foetus develops from something a bit reminiscent of a tiny silver fish (2 mm long) into a miniature baby complete in every detail (80 mm long.) In the rush of this complicated and delicate transformation, it is easy to understand how errors can occur : and because the timetable is a rigid one, mistakes once made cannot afterwards be rectified. In other words, if the foetus has not been properly formed during

the organogenetic stage, it never will be properly formed. If the mistake is a gross one, it will result in a miscarriage : only the minor mistakes are compatible with life.

The **third stage**, which is by far the longest stage of all, begins at the 12th week, when the differentiation of the foetus is complete, and goes on to term. During this stage the foetus goes on growing, and the various organs mature, but no fresh differentiation can occur. The growth that occurs in this stage is phenomenal, for the weight is only 20 grams at the 12th week, and it is 3,000 grams at birth.

Abnormal foetal development.

It will be realised from this brief account of foetal differentiation and growth, that most congenital abnormalities are caused by some failure of differentiation in the second or organogenetic stage. Hare-lip and cleft palate are obvious examples of an 'unfinished' type of foetus, whose development has been interfered with before differentiation was complete : and various other abnormalities — from congenital ('unfinished') hearts to congenital intestinal atresias ('unfinished' intestines) — fall into the same group. Mongols, too, are babies which have not been finished off properly, and it has been shown that their deviation from normal dates from the organogenetic stage. The list could be prolonged indefinitely, for it includes spina bifida, meningocoele, hydrocephalus, microcephalus, anencephaly, and almost all the serious forms of congenital abnormality ; and also such minor things as webbed fingers and toes, polydactyly, dermoid cysts, and various naevi. Many of thes abnormalities are clinically indistinguishable from the identical abnormalities which can be caused by heredity.

From what has been said above, it might be supposed that if a foetus manages to get through the organogenetic stage without mishap, it will be normal at birth : and this is in fact true of the majority of babies. Nevertheless, there are a few babies who acquire a congenital abnormality in the third stage of intrauterine life, the stage of general growth. These babies are perfectny formed, in the sense that all the organs are complete and properly finished off ; but some parts have become *de*formed again by mechanical factors operating during this period of rapid growth. The best known example of this is the type of club foot which arises from foetal compression in utero during the last few

months of pregnancy, when there is too little liquor for the baby to move around in and he gets caught up in a faulty position from which he cannot dislodge himself. Certain asymmetries of the skull and of the thorax are also attributable to prolonged intrauterine compression in the last months of the pregnancy.

So much for foetal development, and for some of the ways in which it can go wrong : the next step is to see if we know what it is that makes things go wrong, and whether there is anything that we can do in the way of prevention.

Factors influencing development.

Recent advances in our knowledge of congenital abnormalities have been related mainly to the organogenetic stage and have revealed a great many of the factors which have influenced development at this stage in animals. A few of these factors, such as X-rays, can be said to act directly on the cells of the developing foetus but the vast majority act indirectly by influencing the environment in which the foetus is developing. In this connection it should be realised that the environment of the foetus is not at all the same thing as the environment of the mother ; for instance, the mother may be subjected to extremes of temperature depending on local weather conditions but, for practical purposes, these extremes of temperature in the mother's environment are never passed on to the foetus. The temperature of the foetal environment is that of the mother herself. To save confusion, the foetal environment is sometimes referred to as the internal environment, contrasting with the mother's own environment which is, of course, the external environment. Throughout the rest of this account the word "environment" will be used in the sense of "internal environment."

It is immediately obvious that the environment of the human foetus is far more stable than that of many of the lower forms of life. Frogspawn in the local pond has to put up not only with wide variations in temperature, but with variations in mineral salt content of the pond water, variations in organic matter, variations in ultra-violet radiation from sunshine and so on. In the case of the human foetus the temperature range is not likely to be more than 10°F. at the most, and the composition of the blood and tissue fluids is kept reasonably constant by the various body mechanisms with which we are all familiar. More-

over, no ultra-violet radiation can reach the human foetus and, under normal conditions, no X-rays are likely to reach it either. It might well be supposed (and, indeed, it used to be taught) that with these advantages the human foetus would be able to go through the various stages of its development in complete safety, and it is only recently that convincing evidence to the contrary has been obtained.

This evidence, strangely enough, did not implicate one of the factors which was already known to cause congenital anomalies in animals, but one which had not previously been suspected at all, viz. German measles. Although, since then, German measles has been shewn to be only one of the factors which can affect the human foetus and is, in fact, one of the least important numerically, it has been written up so often in the popular Press that it has acquired quite an undeserved reputation amongst the general public. It will perhaps help to keep German measles in perspective if we consider first some of the other factors which have been shewn to be capable of producing congenital abnormalities.

Because of the obvious impossibility of carrying out experiments with humans it must be realised that practically all the work has been done with animals. How far the conclusions reached in animal experiments are applicable to man we do not yet know, but we do know that the intrauterine development of the higher mammals is along essentially similar lines to that of man and, hence, there is a strong presumption that it could be affected in essentially similar ways.

Early experiments were carried out with fish and with other creatures which lay eggs, because it is so much easier to influence the environment of a developing egg than that of a mammalian embryo. It was found, for instance, that, if magnesium chloride was added to the sea water in which eggs of a certain small fish were developing, many of the young fish on hatching out had only one eye. Similar experiments were done with other primitive organisms, adding substances like alcohol, cyanide or various alkaloids or simply applying extremes of heat or cold or ultra-violet light or X-rays to the developing embryo, and all sorts of congenital abnormalities were produced in this way: but the type of deformity produced did not always depend on the actual chemical or other agent used — it seemed rather that almost any alteration in the embryo's environment could produce abnormalities, and that the actual chemical

was of less importance than the fact that an injurious agent had been used at all. For instance, one-eyed fish could be produced equally well by adding alcohol or ether or chloretone instead of magnesium chloride to the developing eggs. Another very important discovery was that the type of deformity produced depended very largely upon the stage of development which had been reached by the embryo at the time of the "environmental insult"; for instance, a standard dose of X-rays given to pregnant mice will produce meningoceles and other brain deformities if given on the 8th day of pregnancy: but, if it is not given until a few days later (9th to 14th days) it produces deformities of the tails instead: and if given between the 15th and 17th days it produces no physical deformities, but all the male offspring are sterile.

To cut a long story short the conclusions that were reached from these and similar animal experiments were broadly these: —

a. Any severely injurious agent usually kills the embryo outright.

b. It is the milder injurious agents which (if they have any effect at all) produce the congenital abnormalities.

c. It seems likely that they do so by interfering with normal growth, because it is those organs which are most rapidly developing at the time of the injury which are most severely affected.

d. Since the various organs do not all develop simultaneously and their rates of development change in different stages, they each go through periods in which they are particularly vulnerable and periods in which they are relatively immune; hence the different results obtained when the same agent acts at different stages of pregnancy.

There is no reason to suppose that these general conclusions do not apply to the human embryo and, in fact, it would be very surprising if they did not. What we cannot at present be sure about is which of the various injurious agents which have been shewn to cause trouble in animals can really be blamed for causing congenital abnormalities in man.

It is obvious that chemical factors, in the sense of injurious chemicals deliberately added to the environment of the embryo, cannot operate in human pregnancy: but there is evidence that chemicals of another kind may possibly cause trouble. In mice and in rabbits, for instance, Cortisone treatment of the pregnant female at an early

stage of pregnancy is known to lead to a high incidence of cleft palate amongst the offspring, so it is probably not just a coincidence that a human case of cleft palate has recently been reported in which the mother had had Cortisone from the 8th to the 16th week of the pregnancy. X-ray treatment of the mother in the early months of pregnancy (e.g. for fibroids) has been shown in the past to have caused microcephaly, cataract and choroido-retinitis in the infant — a risk which is nowadays well recognised and guarded against. Atomic radiation could be equally dangerous. Vitamin deficiencies are sometimes quoted as causing congenital abnormalities but there is no good evidence that this occurs in humans. Admittedly experiments on rats have shewn that cleft palate and webbed feet can be attributed to maternal Riboflavin (Vitamin B2) deficiency, but the degree of deficiency was much more severe than anything found, even under adverse circumstances, in human beings. On the other hand, deficiency of Iodine in the mother's diet can certainly lead to cretinism in her infant so deficiencies may well play a bigger part than we think.

Of course, there must still be a great many other factors of which we are ignorant for we cannot "explain" more than a very small proportion of the human congenital abnormalities which we see. Work is, of course, still going on but we are still only exploring the fringes of the problem. It is against this background that we can now consider the role played by maternal infections in the production of foetal abnormalities.

Maternal infections.

It was an eye specialist in Australia who first called attention to an association between a certain form of congenital cataract and a maternal attack of rubella during the second or third months of pregnancy, and other workers soon found that cataracts were not the only abnormalities which could result from maternal rubella. In due course, the following were all reported as due to rebella : cataract, deaf-mutism, congenital hearts (mainly patent ductus arteriosus), defects of teeth, mental retardation. Various combinations of these things could occur together in one and the same child. In practically every case the rubella had been contracted before the 12th week of pregnancy during the organogenetic stage. Babies of mothers who contracted rubella after the 12th week of pregnancy did not show a greater incidence of congenital abnormality than would

normally be expected in the general population : in other words, an attack of rubella during the organogenetic stage can damage the developing foetus but, once the foetus is fully differentiated, an attack of rubella can do no harm.

This work immediately threw suspicion upon other infectious diseases and it was not long before isolated cases were reported of babies showing congenital abnormalities following maternal measles, poliomyelitis, influenza, mumps and almost all other infectious diseases. With the possible exception of mumps (which does seem to be suspect) and of influenza (which is borderline) these other maternal infections have not, so far, been proved to be responsible for human congenital abnormalities, and the present position is that rubella is the only infection which is really known to cause abnormalities of development.

Maternal infection after the third month of pregnancy cannot cause developmental abnormalities because, at that late stage, all the organs have been fully differentiated. In general such infections do not harm the foetus at all but there a few important exceptions. Syphilis in the mother can be, and often is, transmitted to the foetus at this stage. There are also cases on record where babies have been born with malaria, which must, therefore, have been transmitted in utera. Toxoplasmosis, a rare infection in this country, can also be transmitted from mother to foetus through the placenta, causing foetal encephalitis and resulting in post-encephalitic hydrocephaly and microcephaly associated with mental defect and with choroido-retinitis — but all these are of very rare occurrence in this country.

Prevention.

Unfortunately, in spite of all our recent knowledge about the etiology of congenital abnormalities, we are still a long way from being able to prevent their occurrence. Indeed, a moment's thought will show that in many cases the congenital abnormality may already have occurred before the mother can even be certain whether she is pregnant or not — for it is in the first 2 or 3 months that the risk to the foetus is greatest, and it is in these months that the diagnosis of pregnancy is most difficult : which means that, even if women knew what steps they ought to take during pregnancy to cut down the incidence of congenital abnormalities, they would not always realise that they were pregnant in time to take effective action. Assuming, however, that this difficulty did not exist, is there any advice that we can usefully give to women who

are pregnant, or who are contemplating pregnancy, which might prevent the incidence of abnormalities amongst their offspring?

As far as hereditary abnormalities go we can only prevent them by advising known carriers of the trait not to have children and, at best, this could only be a blunderbuss method of prevention for it would inevitably prevent normal as well as abnormal children being born to the families in question. It is not really feasible anyway, even if it were considered desirable. When it comes to "environmental" abnormalities we might hope to be able to do something better but, in fact, there is very little that we can do. The most obvious thing is to avoid pelvic X-ray therapy during pregnancy and this is already well recognised. Ordinary diagnostic X-rays do not involve a big enough dose of radiation to be dangerous. Cortisone treatment in pregnancy would seem to be highly undesirable and will doubtless be avoided when its dangers are generally known. Other hormones may be equally dangerous but, at present, we do not know enough about this aspect of the problem to be able to lay down hard and fast rules. We can also give general advice about adequate diet in pregnancy but we cannot say for certain whether this will prevent any congenital abnormalities although, of course, the advice would, in any case, be sensible.

Finally, we come to the difficult question of German measles.

As with so many other questions in medicine, the answer becomes more and more difficult as our knowledge increases: but the first thing is to get it in perspective. Even in a rubella epidemic, the number of women who actually get rubella whilst pregnant is extremely small — and the number who get it in the critical first three months of pregnancy is smaller still. In Manchester in 1952 there was an epidemic in which 8,010 cases of rubella were notified; but only 28 of these were in pregnant women, and only 13 of these were in the first three months. Even these figures are much higher than American statistics, which in one series give a mere 9 cases in the first trimester out of a total of 22,226 cases. Moreover, even in the first three months of pregnancy, there is quite a chance that an attack of rubella may not harm the foetus at all. Actual figures are difficult to come by, and estimates of the risk to the foetus vary from 80% (Australian) to 10% (Swedish), an incredibly wide divergence. Most people in this country

would not put the risk higher than about 25%, or 1 in 4, but it probably varies according to the particular strain of the virus which is prevalent at the time: and the trouble is that nobody can be sure what the risk is going to be in any given epidemic, because the epidemic is usually over before the first batch of affected babies is born. Again, even if the baby is "affected," it may not necessarily be a very serious matter: in particular, if the lesion is confined to the heart, it is almost certain to be a patent ductus arteriosus, which can be completely cured nowadays by operation. So in any series, the number of babies who are really seriously affected will be very much less than the total number of affected babies reported — and this should be more widely known.

This is not the place to go into the difficult question of the ethics of therapeutic abortion for women who actually develop rubella during the first three months: but a few words can be said about what should be done for pregnant women who become rubella contacts during that critical time. There is general agreement that such women, if they have not already had German measles, should be given prophylactic injections of gamma globulin in the hope of preventing the disease. Such injections would seem to be well worth giving on theoretical grounds, but unfortunately there are as yet no published figures to show how well they work in practice. They have in any case considerable psychological value, for any form of active treatment is preferable to doing nothing. Women who have previously had rubella (e.g., in childhood) are not usually given gamma globulin, because they are not expected to contract the disease again, and hence their babies are not considered to be at risk. Unfortunately there is some recent and very disquieting work from Sweden which seems to show that even the babies of these women, who are immune to rubella, do run an increased risk of congenital abnormalities if their mothers are exposed to rubella at the critical time, even if no clinical disease develops in the mothers after the exposure. If this work is confirmed, it means that rubella will have to be regarded as a potential hazard to every pregnant women in the first trimester: and until we know whether gamma globulin is effective or not, the only advice we can give them is to keep away from known sources of infection as far as possible — advice which it will be extremely difficult to follow during epidemics.

Conclusion.

Of every thousand babies born alive, no less than five die within the first month of severe congenital abnormalities. We can be sure that many more have died in utero without coming to term, and have been lost as miscarriages at an early stage of pregnancy. The gross wastage from congenital abnormalities must therefore be at least 1% of all pregnancies, and may well be more than this. But of more practical importance are the babies who are less severely affected, and who survive with miscellaneous abnormalities varying in severity from meningocoele and hydrocephalus on the one hand to minor naevi and dermoid cysts on the other. Surgery can fortunately patch up most of these babies, but others remain who are so abnormal that nothing can be done for them. Embryologists are at present increasing our knowledge of the mechanisms whereby these abnormalities are produced, but unfortunately they do not seem to making much progress along the road of prevention : so that at the present time it is probably true to say that it is easier to produce an abnormality than to prevent one. Is it possible that we are hoping for too much in thinking that we can improve on the natural mechanism of foetal development, and shall we perhaps find in the end that nature is so good at her job that the number of preventable abnormalities really is extremely small?

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