drugs and treats minor illnesses which are not seen by the consultant, and these are also going to play an important part in our studies. Perhaps even more important is the privilege that family doctors have in the British system of medicine of looking after a group of people through their whole life, from before conception to the terminal stages. This knowledge is being utilized in a very forceful way in the research which we are hearing about today.

THE EFFECT OF ENVIRONMENTAL FACTORS ON THE FOETUS

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Each year in England and Wales we lose by abortion a number of potential citizens at least equal to the population of Swansea. Dismay at this wastage is, however, considerably mitigated by the realization that a large proportion, perhaps one-third, of these embryos expelled at abortion are deformed, so that each year the occurrence of abortion spares us the birth of malformed babies sufficient in numbers to repopulate both Neath and Llanelly. The number of deformed children born each year is, in fact, at least equal to the population of Bridgend, so that were all the deformed to survive to the full three score years and ten, in England and Wales there would be about 1,000,000 persons suffering from a congenital malformation of one kind or another.

During the past two years we have had very much in our minds one particular major environmental factor in the causation of malformations, thalidomide, yet British women who took thalidomide during pregnancy between 1960 and 1962 gave birth to only 329 deformed children, and we mutilate that number of human beings on our roads every 24 hours. Thalidomide accounted, therefore, for only one per cent of the malformations which occurred in this country during the years 1960, 1961 and 1962. Nevertheless, for reasons that it would not be appropriate for me to go into in detail at the present time, the occurrence of the thalidomide disaster has had a profound influence on the attitude of all of us, medical and laymen alike, towards human pregnancy, and in particular towards the occurrence of congenital malformations. In the long run perhaps

the most important change will be in our attitude towards the human embryo itself. No longer will it appear as something alien and inhuman, a secure parasite immune from the stresses of the external world, born finally into that world, pristine and freshly minted, as it were, thenceforth to battle against hostile and destructive forces to which in the end it inevitably succumbs. We now feel as well as know that from the moment of implantation, if not indeed from that of fertilization, the embryo lies in an environment which possesses potentialities as dangerous to it as that which it will enter after birth, an environment whose interests are not always of necessity finely adjusted so as to be automatically compatible with its own, an environment indeed whose own well-being and comfort may demand the death and mutiliation of the embryo.

The changed attitude to research in teratology

As one who has worked for 13 years in the field of experimental mammalian teratology, that is, in studying the effects of agents introduced into the mother on the production of experimental malformations, I must confess that I have not been entirely displeased at the change in my clinical friends and colleagues, who now less frequently express their surprise that I should waste my time in studies which have no possible application to human welfare. I also find it gratifying that the anxieties of governments and drug firms are forcing millions of pounds into research on aspects of teratogenesis, research which must, if even only a small fraction of the money involved is well spent, provide as a by-product information which embryologists have needed for a very long time but have been unable to get for themselves through lack of funds. Before the thalidomide disaster, indeed, the expenditure in this country on teratological research in an average year was a little less than the cost of a few moments of advertising on commercial television. There is, however, a darker side. For years clinicians have been suspicious of too glib and easy a transference of the results of animal experiments to the human situation. Unfortunately, thalidomide has tended to produce something of a *volte-face* in this respect, so that I find somewhat to my dismay that whereas I was formerly accustomed to defend myself from the clinical gibe that the proper study of mankind is man, I now spend more time than I would wish trying to convince enthusiasts that just because a drug produces malformations in the rat, it does not follow that it will have a similar effect in the human. Nevertheless, I believe that when the pendulum has taken another swing or two, it will be seen that there have been advantages in the direction of attention away from man and towards other animals, if only for the reason that man is perhaps the least suitable of all animals for research into problems of

development. Who would seriously consider setting up a colony for breeding experiments with an animal which has to be kept for 20 years before mating takes place, an animal whose pedigree more than two or three generations back is generally a mystery, and an animal which mates with wilful capriciousness and then as a crowning insult produces litters of one or at the most two young? In the long run we can reasonably expect that a great deal of good will come out of the thalidomide disaster, in the form of increased support for and interest in research upon the basic problem of why children are born deformed. But there are thalidomide-induced dangers in current trends of thought, and it is these dangers which I must emphasize for you today. If I were to be asked, " Do you believe that a considerable number of existing drugs possess teratogenic properties for the human foetus? ", I should answer in the negative. A similar answer would have been given 10 or 20 years ago by a teratologist to the question, " Do you consider that the discovery of the teratogenic role of rubella indicates that infection with viruses is responsible for the causation of the majority of human malformations? "

The detailed reason for these answers lies in the principles of teratogenicity which I shall be dealing with later. If, however, I suggest that the whole atmosphere of this field of research seems to show that no very large proportion of the 14,000 malformations arising annually is to be attributed to single *aetiological* factors, I by no means intend to rule out the possibility that a single *prophylactic* agent may be discovered. After all, it is only 30 years since Hale, an American veterinary surgeon, found that piglets born to sows maintained on a diet deficient in vitamin A had no eyeballs and thus set in motion this new discipline of experimental mammalian teratology. Since that time, information about teratogenic agents and their effects on pregnant laboratory animals has come in from workers from a wide variety of disciplines, who have produced malformations by accident in the course of studies quite unrelated to teratology. This situation, of course, closely parallels the manner in which the few agents known to operate in human pregnancy have been discovered.

I have found myself drawn to support, albeit because of its pessimistic implications a trifle reluctantly, the dictum of F. Clarke Fraser that " a minority of congenital malformations have a major environmental cause; a minority of congenital malformations have a major genetic cause; and most malformations probably result from complicated interactions between genetic predispositions and subtle factors in the intrauterine environment ". I would therefore argue that, just as the first harvest following the introduction of new cytogenetic techniques was brilliant and abundant, including the

great discovery of autosomal trisomy in mongolism, so no one today seriously expects the application of the same techniques to produce more than scanty gleanings; on the same basis I would argue that we ought not to look to environmental factors, such as drugs and maternal diet, for the explanation of any but a very small fraction of human malformations. I believe that the best places to look for the truth about the aetiology of congenital malformations are those points where the gene meets the environment, that is, where the mother meets her surroundings, where the foetus meets the placenta and the placenta the uterus, where the developing embryonic cell meets its neighbours, and (perhaps in the last analysis of most importance) at the nuclear membrane where the nucleus of the embryonic cell meets its cytoplasm.

Teratogenic agents in the laboratory mammal

I want now to give a short description of the present state of knowledge of environmental factors operating in the laboratory mammal. I have tried to set out in order the agents thus far identified which can be applied to the pregnant laboratory animal with the purpose of producing deformed young. The first group are those known to operate in normal metabolism, and I want to draw particular attention to the importance of vitamins, hormones and their antagonists, in the first place because of the known significance of vitamins and hormones at the cellular level, and secondly because nutritional and hormonal disturbance may be very prominent in early pregnancy in all mammals. From the standpoint of the developing cell, the real distinction between a vitamin and a hormone is that, although a small number of the total cells in the body have the power of manufacturing hormones, none can make vitamins; but of course to the developing cell situated in the brain, kidney, palate, or limbs, for example, both vitamins and hormones come from somewhere else. Indeed the foetus as a whole is dependent on the mother for both during the greater and critical part of pregnancy.

The second group consists of a number of chemical agents, including thalidomide, which are not involved in normal mammalian metabolism; all of these presumably could be classified as antagonists to the first group if we knew enough about their activity. It has been suggested, for example, that both thalidomide and tetracycline owe their teratogenic activity to interference with the metabolic role of various members of the B group of vitamins.

The third group involves exposure to physical agents, for a variety of insults of a physical nature have the same kind of deleterious effect on embryonic development as do chemical substances. These include x-radiation, decompression, hypothermia and hyperthermia,

amniotic sac puncture and noise. Noise appears to require the mother as an intermediary. Aspects of teratogenesis which as yet have received little attention are the interaction of teratogenic agents with one another, and the possibility of sensitizing the embryo to or protecting it from the noxious effects of a given agent. It is not altogether surprising that these aspects should have been neglected, for they require experimentation which is extremely costly, both in time and money, and the results in most cases must inevitably be negative.

That there is extremely complex interaction between vitamins and hormones in teratogenesis can be shown by the following example. Dr Millen and I studied the ways in which the power of massive does of vitamin A to produce deformity in the rat—we used exencephaly and cleft palate as a yardstick—could be affected by the simultaneous administration of other substances. A number of these either increased or decreased the incidence of the deformity. Cortisone and methylthiouracil aggravate the effects of hypervitaminosis–A and insulin alleviates the situation, while the activity of vitamin A in this regard can be virtually abolished by members of the B group of vitamins and thyroxine. Now that the thalidomide disaster has brought the research departments of drug firms, with their vast financial resources, into the field of experimental mammalian teratology, I hope that it will not be long before a great deal more information is available on the modification of the effects of teratogenic agents. It would appear that this aspect of the field does represent a useful point of departure in the attempt to obtain prophylactic techniques for dealing with congenital malformations.

Principles of teratogenesis

From work carried out with a variety of agents in the last 10 years, it has become possible to put forward certain general principles which *appear* to govern teratogenesis. The most important principle that has appeared is the following: When a pregnant mammal is exposed to the effects of a teratogenic agent, the type of malformation produced and the incidence of that malformation are determined by two major factors, the timing and the intensity of dosage. It is generally accepted that of these two the timing is the more important.

Teratogenic agents cannot produce congenital malformations when they are administered before the implantation of the blastocyst. They may kill the embryo but they cannot as far as we know deform it. Again, after the initial period of morphogenesis of an organ is completed, the structural changes which we see in malformations cannot be produced in that organ by teratogenic agents. This is really fairly obvious. Once the septum of the heart is closed, or the two halves of the palate joined, no known agent can produce a cleft

in either. Since in the rat, for example, embedding of the embryo does not occur until the seventh or eighth day and the development of all the significant structures is completed at least 48 hours before birth, which usually occurs at the 20th or 21st day, there is a strictly limited period during which any organ is potentially vulnerable to the effects of a teratogenic agent. Within this period of limited vulnerability, there is a shorter critical period, varying from organ to organ, of intense susceptibility to the effects of the agent. In the rat, exposure of the dam to the effects of x-radiation on the eleventh day of pregnancy produces a high incidence of deformity of the kidney in the young, whereas the critical period for the heart is two days later, on the 13th day. As far as we know at present, the critical period for an organ depends on the degree of differentiation of that organ and an organ is most vulnerable to the effects of a teratogenic agent when it shows the greatest mitotic activity. At any other period of pregnancy, the cells of that organ are no more at risk than are any other cells in the embryo. The time of administration of a teratogen does not, of course, automatically coincide with the time that it has its effects. Although x-radiation and hypervitaminosis–A probably work almost immediately, inducing vitamin A deficiency is a relatively long-term process, and to produce malformations in the young the mother must be deprived of the vitamin well before the onset of pregnancy.

With all the teratogenic agents, the intensity or level of dosage is of importance, and only at certain intensities can malformations be produced. If administration of the agent is too vigorous, all the young will die *in utero* and be absorbed. If, on the other hand, it is given in too small doses it will fail to influence embryonic development and the young will be born in the normal healthy state. A teratogen is therefore effective in producing malformations only within a narrow dosage range. Once this level has been established, and provided animals of similar genetic constitution are used, it is possible to produce a deformity repeatedly with a remarkable constancy of incidence. Generally, we find that malformations result from a dosage just in excess of that without effect on the embryo, but far below that which will kill the dam. Since even in the most bizarre of monsters careful examination reveals a great excess of normal over abnormal development, it has rightly been said that the occurrence of a congenital malformation represents, from the purely biological point of view, not a reproductive disaster but really a reproductive near-success. While the type and incidence of deformity produced by a given teratogenic agent depend more on the time at which it was administered than on the level of dosage or any other single factor, there is nevertheless a wide variation

between teratogenic agents in the spectrum of malformations produced.

A question which will have to be answered is whether these differences depend mainly on factors such as rate of absorption of the teratogen, which really worked by altering the timing and intensity of dosage, or whether they represent the results of teratogens having many different and distinct effects on metabolism at the cellular level. The effect of thalidomide in the human is a classic example of this particular problem. The three environmental factors now known to produce deformed babies—rubella, thalidomide and aminopterine—produce very different malformations. It is obvious that to some extent this could be due to timing. It may be that thalidomide was not consumed by expectant mothers entirely without relationship to the period of pregnancy, but possibly in many cases specifically for morning sickness. The critical period for anencephaly, which has been caused by the administration of aminopterine in an attempt to procure abortion, is the 16th to the 24th day. That is rather before the time when morning sickness might be expected to occur, and it is interesting that anencephaly has not been reported following thalidomide intake. On the other hand, the critical period for the development of phocomelia is from the 27th to the 44th day, just the time when morning sickness tends to be prevalent. Rubella seems to produce a syndrome whose critical period is later, possibly because when it operates earlier it kills the embryo. Nevertheless, after we have taken into account the importance of timing and also the fact that deformities other than phocomelia have been reported after ingestion of thalidomide, there does seem to be a predilection of this drug for interference with the development of long bones.

Deformities produced are not specific. The typical deformity of hydrocephalus in rabbits may be due to vitamin A deficiency, for example, but this condition can also be produced by riboflavin deficiency or folic acid deficiency. In young rats whose mother was x-irradiated during pregnancy various deformities of the eye, such as coloboma or microphthalmia, can be produced, though the development of the lacrimal apparatus has not been interfered with, and the external eye muscles may develop normally in the absence of the eye. These deformities, again, could have been produced by actinomycin D, or by pteroylglutamic acid deficiency. Exencephaly can be produced by giving the dam massive injections of vitamin A. If you looked quickly at a coronal section in such a case, you might think that the ventricles had burst and thrown the choroid plexus on to the surface, but actually the basal layer of the skin can be traced straight into the choroid plexus. So this is not just a rupture but an abnormal feature of development. Again, this deformity, complex as

it appears to be, is not a peculiarity of vitamin A action, because it can be produced by mercaptopurine, or by instituting pteroylglutamic acid deficiency.

Characteristic thalidomide deformities very much resemble those produced in a child whose mother was accidentally poisoned by carbon monoxide at about the sixth week of pregnancy. Experimentally, over 30 teratogens mimic the effects of thalidomide on the development of the limbs, ranging from vitamins, amino-acid and nucleic acid antagonists to alkylating agents, antibiotics, caffeine, salicylates and nicotine. It would seem logical, therefore, to assume that the truth lies somewhere between two extremes. On the one extreme the activity of all teratogenic agents manifests itself through a final common path, and on the other each teratogenic agent has its own individual and idosyncratic pattern of effect on the enzymatic processes of the cell. The genotype of both mother and foetus is of considerable importance in determining the vulnerability of a foetus to a given teratogenic agent, and there is some evidence that the hormonal balance of the mother can influence the incidence of genetically determined deformities in the young. There is also some evidence suggesting that maternal age, the number of young in the litter, the position in the uterus which the foetus occupies relative to its siblings, and even the sex of the foetus may be significant in determining whether or not it falls victim to the effects of a teratogenic agent. At present we can only speculate on how these factors may modify the activity of teratogenic agents, for the good reason that at present we can do no more than propose mechanisms by which teratogenic agents may exert their deleterious effects. It is going to be very difficult indeed in the presence of the current interest in the chemistry of the genetic apparatus to avoid rushing straight to the cellular level and suggesting that the effects of teratogenic agents are to inactivate or replace some part of the DNA molecule, or to interfere with the production of ' messenger RNA ', or indeed to avoid putting forward one of a multitude of possible theories of this kind. However attractive such theories may be, it is important not to lose sight of the fact that even if we agree that the prime effect of a teratogenic agent must be on a DNA molecule, we still need to know where that molecule is situated.

The possible sites of primary action of both teratogens and genetic factors (for in the last analysis there can be no reason to postulate separate sites of activity for teratogen and gene) can be divided into sites in the maternal tissues, in the placenta, and in the embryo. Clearly it is not going to be enough merely to identify a teratogenic agent as present in large quantities in a foetus to establish that its action must be a direct one on the foetus, although the converse is presumably true, for if the substance or one of its metabolites

is not to be found in the foetus, there must be some intermediate step in teratogenesis involving the mother, the placenta or both.

Human teratogenesis

In view of the large number of agents shown to be teratogenic in the laboratory, it is really remarkable that relatively few environmental factors have been identified as responsible for the occurrence of human malformations. Occasional cases have been reported which suggest that the administration of cortisone or large quantities of vitamin A, or a state of deficiency of that vitamin, has resulted in the birth of a deformed child. At one time, pregnant women treated with radium for carcinoma of the cervix occasionally gave birth to malformed children, and microcephaly was reported following the atomic explosions at Hiroshima and Nagosaki, but since the incidence of congenital malformation is around two per cent, one has to be very careful not to overlook the possibility that associations such as these are due to coincidence. A few malformations have been attributed to maternal anoxia occurring at a critical period of development, but until the thalidomide tragedy rubella remained the only environmental factor of real importance whose teratogenic activity had been unequivocally demonstrated. Why should this have been? The major reason would appear to be the fact that in everyday life pregnant women are just not exposed to teratogenic agents under conditions anything like as rigorous as those maintained in animal teratogenic experiment. The equivalent in human terms of the degree of anoxia which we use to produce malformations in the mouse would be to take a woman five or six weeks pregnant to the top of Mount Everest and leave her there without oxygen equipment for five or six hours. This sort of thing does not normally happen. Again, on a weight for weight basis compared with the rodent, the teratogenic dose of vitamin A for the human would be four thousand times the amount generally recommended for the daily diet of a pregnant woman. There is one factor, the dose of which for the production of experimental malformations is not widely different from that to which the pregnant woman may be exposed, and that factor is x-radiation. The dose of x-radiation corresponding to the teratogenic dose for the rat is only, in fact, four or five times that to which a patient is exposed if a thorough radioscopic examination of the intestinal tract is carried out. A straight x-ray of the abdomen in early pregnancy provides, however, only about a twenty-fifth part of the dosage equivalent to the minimal teratogenic dose in the rodent, and of course the dangerous potentialities of radiation in early pregnancy have been well recognized for some time.

While it is only right to stress that the teratogenic agents I have mentioned act in concentrations far in excess of those liable to occur

under the conditions of human life, there is always the possibility that a pregnant woman may be much more sensitive to a given teratogen than is the laboratory mammal. Thalidomide is perhaps an example of such an agent. Again, we ought not to put out of our minds the possibility of individual as well as species variation. Some women have apparently taken quite large amounts of thalidomide during pregnancy without deforming their children, while others seem to have produced malformed babies after only two or three tablets. These individual variations may be due to the concurrent activity of factors which we are inclined to lump together under the heading 'genetic', largely because their complexity defies present analysis. Alternatively, they may be due to the summation of a number of teratogenic effects of agents, each of which itself is present in sub-teratogenic concentration. It may be, for example, that the woman who is especially vulnerable to the effects of thalidomide is the one whose nutritional level or hormonal balance is precarious. Again, factors operating in the environment may tip the balance in favour of the expression of a latent inborn or genetic tendency to malformation. The fact remains, however, that thalidomide and rubella are the only major environmental factors which have been implicated in the aetiology of congenital malformations with a certainty comparable to that which has associated cigarette smoking with lung cancer.

Significance of social and psychological factors

Public health studies on the incidence of malformations have already produced interesting findings, but I would like to comment on two factors only, maternal psychological make-up and social class. It has long been a belief, widely held but never scientifically proven, that an unsettled way of life is associated with the production of deformed offspring. Combining the results of some studies in this field might lead to the suggestion that the ideal prescription for a congenital malformation is to be born out of wedlock to a young working-class mother of short stature and low intelligence, living in squalid conditions on a poor diet in a large European city which has recently been subjected to heavy bombardment from the air. While such conditions would undoubtedly mean that the mother was subjected to severe psychological stress in early pregnancy, they would also expose her foetus to all the dangers of malnutrition, hormonal disturbance and infection. Not unnaturally, there has been considerable disagreement amongst highly competent authorities as to the precise significance of social class and psychological factors in the causation of malformations. It would appear that the operation of these factors, if indeed they operate at all, is more likely to be secondary, sensitizing the embryo to the activity of other

primary agents. In the long run the most valuable lesson that has emerged from the thalidomide tragedy must surely be the stress we now lay on the necessity for both caution and scepticism in all matters that pertain to the welfare of the foetus, caution in prescribing to women who may be pregnant, scepticism before rushing to implicate a drug as teratogenic in the human on the basis of a small uncontrolled series of cases, or an animal experiment, and caution and scepticism above all before attributing the blame for the birth of a deformed foetus on his parents or more remote ancestors, on his mother's diet, demeanour or way of life, on the welfare services of the State, or on the shortcomings of the society into which it is born. Nevertheless, where we appear at present to be in need of the greatest care is in our whole attitude to this basic mother-foetus relationship. If we can no longer see the foetus as snugly insulated by the mother from the asperities of the environment, if we now realize that in prescribing drugs for a young woman's headache or emotional upset we may all unwittingly be prescribing lifelong suffering and mutilation for her small, unseen passenger, we must also not forget that the foetus receives from the mother not only dangerous chemical substances like thalidomide but also all the materials which bring him in nine months from a single cell to a complex, functioning, independent being of some 15,000,000,000,000 cells.

At the present time we know virtually nothing of the complex mechanisms of control required to ensure that the foetus gets what it wants from the mother at precisely the right time and in precisely the right amounts. If the results of animal experimentation have any validity for man, it would appear that a relatively wide variation in quantity of the vital materials in the supply line can exist, ranging from poverty to excess, without interfering with the minimal requirements of the foetus. The fact that it is possible, for example, to produce malformations by instituting either hyper- or hypo-vitaminosis in the dam suggests, however, that the toleration of the system which adjusts the concentration of the materials reaching the foetus from the mother, although wide, is by no means absolute. When it comes to the question of giving advice to the woman who is frightened that she might produce a deformed child, the conclusions I have drawn myself from the present state of knowledge are rather along these lines. The odds against this happening are about 50–1 anyway, and we know no way of reducing or increasing these odds at present except by genetic counselling. We must be very cautious indeed before prescribing any form of regime or diet, any form of abstinence, or any form of indulgence. We live at a time when medicine is invaded and fertilized by other sciences and vice versa, but ironically it is also a time when the public is encouraged by mass

education media to demand certainty where certainty does not exist. A clear authoritative pronouncement by a medical man will always be uncritically welcomed. I believe we must insist on the right to give a scientific reply to the basic question, " Why is a child born deformed? " and to say, " We can't answer your question; we just don't know the answer. Ask again in ten years' time and we shall probably be able to give it to you ". At the present time, therefore, I would say that when we are thinking of the welfare of the human embryo in the uterus we are best guided by a middle of the road principle of the kind somewhat surprisingly applied by Nietzsche, in a much wider context when he said:

> Of nothing is it any longer possible to say, ' This is good everywhere and always, and this is bad everywhere and always '. Good and bad must be determined afresh on every occasion, and always in relation to a definite purpose, by which alone anything can be good or bad, for only he who knows whither he saileth knoweth which is his fair wind and which is his foul wind.

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A SOCIO-GENETIC SURVEY OF THE MAJOR CENTRAL NERVOUS SYSTEM MALFORMATIONS IN SOUTH WALES

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The major central nervous system malformations, which consist mostly of the dysraphic syndromes of anencephaly, spina bifida cystica and cranium bifidum, together with certain forms of hydrocephalus, namely the aqueduct malformations and the so-called Dandy-Walker syndrome, can probably be classed together. There is some genetic and much experimental evidence that these are different end-products of the same general process for different noxious agents, such as x-rays, oxygen deprivation, chemicals, dyes and starvation may in susceptible experimental animals produce any