triggers required, one can not only make an early diagnosis but also prevent the condition developing at all. In looking for environmental factors one has to realize that there are only certain families at risk. The place to look for environmental factors which act as a trigger, for example to the development of hare-lip, is in familes where there is already a genetic risk, as in families where father and one child have already been born affected. This will lead to a new kind of public health, prophylaxis of disease through knowledge of particular genetic predispositions in individual families, rather than the kind of mass public health measures applied to whole populations which have been so successful in the past. Probably only the family doctor can apply these new techniques and I see preventive medicine in the next 50 years increasingly going back into the hands of the doctor who knows his individual families.

## DISCUSSION

***Question:*** What are the teratogenic potentialities of methylthiouracial?

**Dr Woollam:** The drug can be used to produce malformations in animals, and it can also be used to sensitize animals to the effect of vitamin A. I do not pay much attention to the effect of a drug on animal pregnancy as an indication of what is likely to happen in human pregnancy. I know of no recorded case of a human malformation attributed to methylthiouracil, although it has been in use for a fairly long time and quite a number of cases must have fallen within the age group in which pregnancy is likely. I should consider it like other drugs which produce malformations in animals, such as penicillin, streptomycin, and insulin, as probably not having the same effect in the human.

**Chairman:** As a corollary, I suppose it is right to recall that apart from a teratogenic effect, methylthiouracil may have an effect on the foetal thyroid, particularly in late pregnancy, but that is a different matter altogether.

***Question:*** What genetic counselling is given to epileptics?

**Dr Carter:** Obviously the first thing is to try to find the cause of the epilepsy. If it is due, say, to epiloia (tuberous sclerosis), then it is

due to a straight dominant gene. If it is idiopathic, one is much influenced by the family tree. If the family tree is fairly negative, the risk is only of the order of two or three per cent to the potential children of an adult epileptic, that is a two or three per cent risk of the child developing epilepsy; if the family history is heavily weighted in some families it looks as if a dominant gene is concerned and the risk is obviously higher. In general, though, this is one of the conditions where the layman's fears are usually unjustified.

***Question:*** A good deal of animal disease arises in some rural areas owing to mineral deficiencies. Is there any evidence that deficiencies of this sort play a part in producing human abnormalities?

**Dr Clarke:** This is the reverse side of the penny, but the only thing I can think of straight away is that Wilson's disease is very rare in areas of British Columbia where there is a copper deficiency, Wilson's disease being a disease where there is over-absorption of copper.

**Dr Watson:** This is an opportunity to expand on a subject I did not touch on this morning and that is being discussed in the research committee still, the Tamar Valley project. A number of College members live in the same area and they are all keen record keepers. It is suggested that a local water supply is causing a localized outbreak of cancer. We have had a lot of help from the Chester-Beattie Institute and from some American geologists, and a rather high-powered team is going to be matched, I think, by a high-powered team of general practitioner observers using the new College E recording book, in which everything that the general practitioner does or sees and every case is recorded in a standard fashion so that it can be used for retrospective studies. It is just possible that this sort of study might give clues. It is also possible that such a team could be recruited in Dr Laurence's area.

***Question:*** How does inter-racial marriage modify genetic susceptibilities to diseases? Do the offspring of foreigners (born in the United Kingdom) show any difference as regards genetic susceptibilities to disease?

**Dr Clarke:** In answer to the second question, I do not know. That is one of the things which it would be very interesting to find out. I think that negroes living in this country are more liable to hypertension, but they are probably more liable to hypertension in their own country. No real work has been done on it. Regarding the first question, the total gene complex of a race is adapted to its environment, and different races live in different environments and therefore will have different total gene complexes. There may be different arrangements on the chromosomes; there might be inversion so that pairing could not take place properly at meiosis.

This is well known in animals. There would be some sort of genetic imbalance between homologous chromosomes.

**Dr Carter:** One specific genetic susceptibility appearing in African children in this country is rickets. Nutritional rickets is reappearing probably because the dark skin of the African baby means that he needs more vitamin D than the ordinary English child. It has reappeared in Glasgow and in the Midlands, and perhaps here. On the purely practical side, I do not think there is really evidence that hybrids have any increased susceptibility to any particular disease. There is no danger medically from this.

***Question:*** Is there not some evidence that the Japanese who have lived from generation to generation in the United States are losing their congenital myopia?

**Dr Carter:** I know of two examples where races which have gone to live in other countries have behaved differently from the indigenous population. One which interested me particularly was to find that the spleen rate in East Africans living in Iraq was much lower, but the parasite rate was the same as in Arabians living in the same area; in other words, the bodily reaction to this amount of parasitism was less.

***Question:*** Are sulphonamides safe for the treatment of pyelitis in early pregnancy?

**Dr Woollam:** There is no evidence that they are not safe. They can be used to produce malformations in animals, and undoubtedly if they were to be introduced at the present time and subjected to the sort of tests that drugs are being subjected to now they would miserably fail. I should be guided by past experience and say that there is no evidence that they are in fact a danger.

***Question:*** Is it not true that some of these sulphonamides have been withdrawn from the market by the Ministry of Health?

**Chairman:** There are one or two very long-acting sulphonamides which are excreted very slowly and are being introduced now, in respect of which advice has been given that they should not be used in pregnant women, but I think this may be just a precaution in the climate of today.

**Dr C. A. Clarke:** Could Dr Wollam tell us what he feels about hypoxia as a teratogenic agent in man: (a) in relation to reports of different rates for patent ductus at top and bottom of the Andes; (b) in relation to chronic asthma, particularly in patients given morphine and pethidine? How good is the evidence for (a) and (b)?

**Dr Woollam:** There have been a number of cases which do suggest that hypoxia can be a teratogenic agent in man. Whether it is

responsible for any large number of cases or not we just cannot say. The situation is rather similar to that with regard to mechanical effects inside the uterus. It is quite possible that mechanical effects may be responsible for amputation of limbs. On the other hand, of course, limbs can be absent without their having been necessarily amputated *in utero*. There seems to be an association in experimental animals between runting and a poor blood supply to the placenta at the site of the runted foetus; anoxia could be the missing link here. Many teratogenic agents could act by virtue of producing anoxia, and in fact we have investigated this ourselves to some extent. It is quite possible, for example, that hypervitaminosis A, which we know affects some foetuses in the uterus according to their position more than others, could be reaching the foetuses with a better blood supply. Anoxia might work in the same way; if the blood supply were variable some foetuses would be relatively anoxic, so as well as maternal anoxia there might be local anoxia as a mechanism for action of many teratogens. As regards chronic asthma, I suspect that it is worth while investigating, but here again I hope that information will come from the valuable studies being carried out by the College at present both on these conditions and on drugs. A few cases may turn out to be due to a single cause, but I do not think we will find any vast proportion of mothers with chronic asthma, for example, bearing deformed children.

***Question:*** Should anti-D gamma globulin be given to all Rh-negative mothers for abortion, threatened or otherwise?

**Dr Clarke:** No.

**Chairman:** I noted that Dr Clarke indicated that the work was still very much experimental and I wondered what stage things were at now as regards practical application.

**Dr Clarke:** There is no doubt that we can prevent sensitization in Rh-negative men and in postmenopausal women. The question is, when does sensitization take place? If the Rh-positive cells get across at delivery the method will work but if they get across earlier on, our method will be no good. We think the evidence is rather in our favour, but six months' more work is necessary before we start a clinical trial. It has got to that stage.

**Chairman:** So the answer would be that once the method reaches clinical application the globulin would never be given in threatened abortion, but if there were evidence that abortion was a sensitizing agent, then you might recommend that it be given then to guard against future trouble.

**Dr Clarke:** Yes, it would be purely preventive. Dr Carter, is it really true that achondroplastics are particularly liable to die in the

neonatal period? If so, why—is it due to difficult presentations?

**Dr Carter:** I am inclined to think that is a question for a paediatrician or an obstetrician rather than a geneticist. I think quite a lot of these infants do die, particularly from hydrocephalus, but those who survive infancy seem to have an excellent expectation of life.

**Chairman:** We have had very few, but I do not think that difficult presentations are involved, because we usually deliver them by caesarean section, which, of course, also has its hazards. This is a field in which one has so little experience that it is difficult to generalize.

**Dr Clarke:** The estimation of mutation rate is based on the assumption that a whole lot of these infants die.

**Dr Woollam:** Oh, no, I think the original view of Birch was that so many of them did not have children.

***Question:*** Dr Laurence, how did you select your controls for your survey?

**Dr Laurence:** We used the local health authority birth registers and we selected one control case to two index cases, the index cases being chosen statistically and matched for sex and time of birth.

***Question:*** We have heard much of how to avoid undesirable deviations from the normal genetically. Would the panel tell us if there is much evidence to support promotion of desirable deviations, e.g. high intelligence or increased resistance to disease?

**Dr Watson:** Medicine is so much taken up with looking after the unhealthy individuals and families that general practitioners have been a bit forgetful of the other half of their practice, but recently I have been paying attention to these families with a high resistance to infection. It was brought to my notice by a mother who had a family of five, one of whom, a nine-year-old, had a high temperature from a virus infection. Just as I was going out of the door, the mother said, " Have you any special instructions about the treatment of this fever? You will remember that this is the first child I have had in bed with a temperature ". I had to admit that I had never been into that house to see a feverish child before, and this was very much in my mind because in the same village I had a small boy who had produced five major pathogens from his bowel that winter. Here you had the two sides of general practice. There was the family that never bothered you unless you went out of your way to look at them—most of my contact with them had been for vaccinations or special studies of different sorts—and a family one ought to look at much more closely. I believe you have all got families with this high resistance. This mother I have been telling you about

has never had any infectious diseases except rubella in pregnancy.

I think the most fascinating part of the afternoon has been to realize (one would not immediately suspect it) that Dr Carter runs a sort of medical betting shop.

**Chairman:** I wonder whether people who have been working in this field found that inquiries into siblings and special tests of heterozygotes, and so on, had any bad psychological effects. Perhaps Dr Carter would say a word about that. From the physical point of view it is extremely desirable that people at special risk should be discovered and recognized, but I wonder whether some people are not better remaining in blissful ignorance of being a heterozygote.

**Dr Carter:** I think that is a very difficult question to answer. If a family doctor sends a patient to me for advice, I imagine he has taken that into consideration. We did a follow-up of people (I think the total is now 200) to whom we had given advice, and this was one of the things we looked for, whether they had been upset by the advice we had given. I think there were only two cases where the social worker, who was very well trained, thought that the advice we had given had seriously worried the family; a great number of people had been very thankful and grateful. Whether they had taken our advice or not, they had appreciated it, so we did feel fairly encouraged.

***Question:*** We are all inclined to comfort our patients who have miscarried by telling them that probably this was nature's way of getting rid of an ovum that was not going to be satisfactory. Are we scientifically justified in so doing?

**Dr Woollam:** There have been a number of studies of the aborted ovum, and it does seem that about one-third of the ova expelled at abortion are in some way deformed. The difficulty is that some other studies have shown that large numbers of ova expelled at self-induced or criminal abortions are also deformed, and it is very difficult to know what the precise meaning of abortion is anyway. Two events occur when a miscarriage takes place. Firstly, there is the event in the foetus, and secondly there is the event in the placenta. We know that the placenta can survive without the foetus. We know that the foetus cannot survive without the placenta, and therefore I think that generally speaking we must look to the placenta as the prime source of the events determining miscarriage. I cannot believe that the foetus decides it is not really worth while going on in the state it is in, and therefore sends some message back in order to cause the placenta to separate. The process must start in the placenta, but the relation between placental and foetal events is unknown. Most people who have worked with teratogenic substances have come to the conclusion that there is

some difference between the events that lead to foetal death, and in the case of most experimental animals not abortion but absorption of the foetus. The foetus in the experimental animal generally absorbs rather than aborts and most people feel that there is some difference between the events leading to death of the foetus and its absorption and the events leading to malformation. They think that the two do not quite follow the same sort of pattern. Of course, placental metabolism cannot be very different basically from that of the foetus, and therefore certain events which are fatal to the foetus will also be fatal to the placenta, so one would expect a chance association between malformations and the loss of the foetus through abortion.

Finally, it is worth mentioning that when we see animal foetuses produced in all stages of abnormality, it is very remarkable to find so often a litter of young which are hopelessly malformed but alive and struggling, while the next animal, after apparently the same treatment, produces perfectly formed, dead, unmoving young. This is some slight indication that the two problems are not absolutely related, though probably the problem of separation of the placenta and malformation is related in the way that I have tried to point out. The same sort of events probably cause both, but the events are not identical.

**Dr Carter:** People are now looking at chromosomes in cases of early abortion. Only small series have been reported so far, but it does seem that in an appreciable number there are chromosome abnormalities. Speaking from memory, in a small American series of 13 three-month abortions there was one trisome 21 who would have been a mongol, one trisome 18 and one trisome 15. This may well be unrepresentative, but it will be very interesting to get more figures.

***Question:*** May I ask Dr Woollam something relevant to his last answer? In some cases we have been able to show a direct relationship between foetal resorption, foetal death *in utero*, and foetal malformation by devising an experiment whereby we kill treated animals at various stages of pregnancy from the moment of the noxious stimulus to term, and note a decreasing incidence of malformation and a parallel increase in incidence of resorption. We have done this for only one drug and I would like to stress that with this particular drug, trypan blue, there is a definite relationship. The question I was going to ask you was whether you had any explanation for the fact that certain types of malformation, such as conjoined twins and cyclops, are never produced experimentally. Could a case be made out for revising malformation statistics to exclude these things when one is dealing with possible environmental influences, because it would appear that environmental influences cannot

cause things which happen before gastrulation?

**Dr Woollam:** My colleague, Dr Milne, has on occasion produced cyclops by giving vast doses of vitamin A, so I cannot quite agree that it is impossible to produce these things, though I agree with the general principle. My colleagues and I have been thinking of this problem of the chromosomes in the deformed animal, and the difficulty is that in the experimental animal we know practically nothing about the chromosomes. It will be very difficult and will take a lot of work to build up the normal chromosome picture first, but I think this is a very promising line of approach. Another promising line of approach is the study of chromosomes in the placenta, and I believe that this work is also starting in the States. I do agree that trypan blue shows a closer relationship between malformations and abortion than do other teratogens, though I regard it as a somewhat untypical teratogen which may work in a rather more mechanical way.

***Question:*** Does disease in the male contribute in any way to congenital abnormality, for example, mumps shortly before conception?

**Dr Clarke:** Not as far as I know. Is that right, Dr Carter?

**Dr Carter:** I agree—not as far as I know.

**Dr Watson:** Is there any evidence in experimental animals of teratogenic effects of drugs on spermatozoa?

**Dr Carter:** None that I know of. We have kept a breeding colony of mice now through five generations on a diet of two per cent thalidomide in their drinking water, so that abnormalities would arise whether the males or females were affected. What has happened is that we have simply bred out the susceptible strains. I think a case was reported where deformity after thalidomide was thought to have come from the male. The father had had thalidomide and the mother had not.

**Chairman:** This was reported by Dr Jacobs in Cardiff.

**Dr Carter:** Someone approached an artificial insemination centre to try this experiment out on the bull, and to see what happened to his offspring after giving thalidomide to the bull.

**Dr Slater:** The College are about to investigate this subject in a new perspective survey, where we are including any details of any drugs given to the father or any of his illnesses round about the time of conception. There is another thing which might be relevant in mongolism. I believe that Professor Penrose has recently shown that in one type of mongolism it is the paternal age which is important rather than the maternal age.

***Question:*** Dr Woollam listed noise as harmful to the foetus

*in utero*. What is the mechanism of this?

**Dr Woollam:** This was discovered by Japanese workers. The Japanese are also experimenting with physical stimuli by keeping the mother in a cage with sharp projecting nails and so on, so that she cannot settle down. That also produces malformations, but I think in the experimental animal virtually any stress is liable to cause the animal to produce malformations. It is the response of the animal to stress, and I should think it probably works through some internal mechanism. For example, in my department we have to work while buildings are being erected the whole time; luckily the effect it has on our animals is to cause them not to breed, but I dare say it might upset quite a lot of experiments on teratogens if a drug were being tested and the animals were subjected to a very noisy environment.

**Dr Owen:** In defence of Porthcawl, I should like to point out to Dr Laurence that since it is a seaside resort, many people move into Porthcawl from the valleys to live there; this means that the population is anything but static. I should be very glad to know the names of the 13 families with the C.N.S. malformations you mentioned so that I might attempt my own follow-up. The one case I reported in my return was that of an anencephalic born to parents of pure Irish stock, and I was very interested to hear your remarks about the high incidence in the Irish. Are there any figures on the incidence of abnormalities following the mass vaccination of 1962?

**Dr Laurence:** I think Professor Duncan could answer that better. As far as I know there are no figures as yet, but it is being investigated, and I suspect that no worth while figures will be obtained, or at least nothing to suggest that there has been an increase. There were a small number of abortions, one of which is in a pot in my department. We grew vaccinia virus from the foetus.

**Chairman:** Yes, that case was reported. When the outbreak of smallpox in South Wales occurred, we felt it was an opportunity to be seized and we at once took the advice of the statisticians to see to what extent we could determine once and for all the influence of vaccination on the various factors of abortion, stillbirth and abnormality. Dr Lewis Fanning, who was advising us at that time, showed us that even if we studied the whole community in South Wales as far as vaccinated pregnant women were concerned and controls, we would not get anything statistically valid. Nevertheless, we thought it was worth while doing, and we are just trying to get round to analysing the material, and there have been one or two independent observations. We had to wait nine months after the epidemic, and we have only recently been able to start analysing it. In the course of the next few months there will be some evidence, but as Dr Laurence says I do not think it will be very useful.