Ingram, V. M. (1958). *Biochim. Biophys. Acta.* (*Amst.*), **28**, 539.
Jervis, G. A. (1939). *J. ment. Sci.*, **85**, 719.
Jervis, G. A. (1953). *Proc. Soc. exp. Biol.* (*N.Z.*), **82**, 514.
LaDu, B. N., Zannon, V. G., Laster, L. and Seegmiller, J. E. (1958). *J. biol. Chem.*, **230**, 251.
Pauling, L., Itano, H. A., Singer, S. J. and Wells, I. C. (1949). *Science*, **110**, 543.

DISCUSSION

Question: Why are genes with harmful effects not gradually removed from the population despite their association with reduced fertility?

Dr Clarke: The geneticist's answer is that the heterozygote is at an advantage. For instance, a person who is heterozygous for the sickle-cell trait is at an advantage over the normal because he does not get malaria, and is obviously at an advantage over the homozygous person with double 'S' because he does not die of sickle-cell anaemia. That is one of the explanations. It is also probably true that being heterozygous for an abnormal gene may make a person more fertile; if that is so, equilibrium will result and unpleasant genes will not be removed from the circulation.

Dr Watson: When I started being interested in viruses I was intrigued with their characteristic capacity to alter cell function and I came to look on them as parasitic genes. I wonder whether we are not constantly forgetting this side of biology, and I wonder whether trisomy from rubella viruses is not one reason why some people get rubella defects and others do not. Could Dr Clarke say whether that is complete nonsense or not? These viruses have many points of contact with gene biochemistry and biophysics; perhaps we are really looking at two sides of a coin, and the infective seasonal variation has to be explained eventually through a genetic mechanism.

Question: Has any investigation been carried out into the pregnancies of women suffering from congenital syphilis, in view of the high miscarriage, stillbirth and congenital anomaly rates in this group, particularly in untreated cases?

Chairman: I do not recall a pregnancy in a case of congenital syphilis with any abnormality at all; this also raises the question of

third-generation syphilis, which the late Dr Nabarro was always very interested in.

Question: Dr Slater mentioned maternal bias in thinking back to some possible cause of malformation. How serious a problem was this, and how was it dealt with?

Dr Slater: I do not think there is any difficulty, here in our present studies, because the studies on febrile illness and drugs in pregnancy are all prospective. In the past, few results have come from retrospective studies of conditions in early pregnancy, and emphasis has been laid on the need for prospective studies because of this difficulty. That is why we started these prospective studies.

Question: Are there any views as to the cause of the greater incidence of deformities around the month of June? Is there a peak period for virus or other infections?

Dr Watson: We have so far detected two patterns of seasonal variations. In one pattern, the birth months in the four quarters show a gradual rise in frequency and then a sudden and abrupt drop, as if a factor has ceased to work; in the other there is a gradual diminution in the number of births occurring in each quarter, as if a factor had suddenly started to work. It is not true by and large that our results show all the peaks in June. We have a summer excess in some defects and an equally high peak in the first quarter in some others. The particular case we looked at was the unexpected finding of a seasonal variation in limb deformities with a peak in June. Noboby knows why.

Question: Seasonal incidence of congenital dislocation of the hip has been mentioned this morning, and a hereditary influence has been postulated for this condition in the past. Could we hear the geneticist's and epidemiologist's point of view?

Dr Carter: Of course, it is never a question of either genes or environment; it is always a question of both. There are genetic factors in congenital dislocation of the hip, and there are also environmental factors. I think the way the seasonal effect works is this. Testing for congenital dislocation of the hip at birth gives about four times too many positive results; in other words, many children whose hips can be dislocated at birth are not going to become true cases of congenital dislocation of the hip. If a newborn baby is wrapped up tightly, as the American Indians and Lapps do, you will probably increase the incidence of congenital dislocation of the hip, because the baby is put in the dislocating position, with the hips extended and abducted; on the other hand, if in the tropics the baby is allowed to lie with hips flexed and abducted, fewer dislocations will result. Hence the environment works through temperative variation and it applies more in areas where mothers

do swaddle the babies, thus preventing the natural correction of a good many cases.

Question: I would like to comment on the specificity of viruses in producing congenital malformations. I was struck by the analogy with some work done in Cardiff on production of congenital malformations by means of azo-dyes. This has shown that with one blue dye not used clinically a whole gamut of congenital malformations, such as exencephaly and spina bifida, can be produced, but by very slightly varying the chemical structure of the dye and using Evans blue, by just knocking off a methyl group, this effect is abolished. If the dose is increased to a toxic level, the embryo or the mother is killed but no malformations are produced. I wonder whether these results might be some stimulus to not necessarily regarding every virus as a possible cause of congenital malformations.

Dr Watson: I think that is an important part of our clinical work. Yesterday morning I delivered a mother who had had a rhinovirus infection at the eighth week and who had also had another unidentified virus infection a week or so before that. She miscarried during her previous pregnancy and she went into her second labour very scared. If we could have told her beforehand that rhinoviruses did not matter, she would have been a happy woman. She had a perfectly normal baby, but I also was wondering what I was going to see yesterday morning, and I think that it is just as important to be able to tell a mother that such and such a drug is harmless as it is to warn her.

We must not forget that alongside us we have our veterinary colleagues with a very much freer chance of killing and curing, and they are doing some very interesting work. They have recently developed a unit, like our epidemic observation unit, among practising veterinary surgeons to collect just this sort of information from our cats, dogs, horses and cattle.

Question: The consolation of a mother who has miscarried a much-desired baby is quite an important part of our work as general practitioners, but are we right in assuming that the best means of comfort is to say that nature is getting rid of something imperfectly formed? Are we scientifically right in continuing to console on those lines?

Chairman: I think I shall ask permission to leave this question, because Dr Carter is going to talk about genetic counselling. This, of course, is a fundamental question for all of us in clinical practice.

May I just bring you back to the clinical side, and remind you of the extreme importance of making the diagnosis of a congenital defect, especially in a newborn baby? This does mean careful and

expert examination of every newborn baby. It is a skilled and difficult job, and I think we should go a little further than just picking up the baby and saying to the mother, " This is a bony child ", and " good morning ". These babies require very careful examination, because not all congenital defects are obvious. There is the obvious group of hare-lips, syndactylies and things of that kind, and there is the group that needs looking for, including cleft palate and congenital heart disease. Then there is the group of congenital defects that appear when body function is put to the test. The best examples of those, of course, are alimentary obstructions. Until the baby feeds, you will not discover a duodenal obstruction. There is the much more difficult kind of abormality, which does not reveal itself for some time and thus creates a problem because of its effect on statistical analysis. I am thinking, for instance, of the child who presents at the age of three or four with recurrent urinary infection, and on examination is found to have a congenital defect of the renal tract. A fortunately less common variety is the abnormal structure which may become malignant. We do not finish with congenital abnormalities at birth, but unless we look for them carefully, we are not going to be able to advise parents correctly. We are not going to be able to help the College of General Practitioners in surveys unless we make a complete examination so that we can report these abnormalities, and we are not going to help the geneticist either. Until we have collected the cases and acquired an understanding of the aetiology we cannot start working on prevention. I would like to finish by thanking our speakers this morning very sincerely for their excellent contributions, which I know we have all enjoyed extremely.

AFTERNOON SESSION

CHAIRMAN'S ADDRESS

Professor Duncan (*Professor of Obstetrics and Gynaecology in the Welsh National School of Medicine*): I agree with Professor Watkins that this subject is a most appropriate choice for the Faculty of the College of General Practitioners. It is, after all, the practitioner who see the pregnant patient for the first time, and who sees the patient even before she has conceived. His work is obviously going to play an increasingly important part in the search for the aetiology of congenital malformations. The general practitioner prescribes