before you read that school report I would like to ask you a question". "Very good, my boy. What do you want to know?" He said: "Well, Dad, I don't think it's going to be a very good report, but what I want to know is, if it isn't a good one, do you think this is largely because of my heredity or my environment?" This still remains a problem.

We have here a number of experts, many of whom have travelled long distances to tell us about their researches and their studies. When you read original papers in genetics they are often very difficult to follow because it is a subject that many of us do not understand, and which introduces a new nomenclature. This applies to some extent to all new scientific work and to all generations. I do not think I have the slightest prospect of ever understanding anything about electronics or space physics, but for the next generation this knowledge comes in with their mother's milk, except that very few of them, of course, have mother's milk! The new generation seems to pick up the threads, but in order that we of the older generation can follow these erudite studies, we need an opportunity like today's symposium in which the real purpose is to ask our speakers to simplify and explain to us the difficulties of a relatively new subject, and to present to us what one might call the filtrate of their expert knowledge. With these very brief remarks, ladies and gentlemen, it is my pleasant duty to declare this symposium officially open.

## THE EPIDEMIOLOGICAL VIEW OF CONGENITAL ANOMALIES

**(Based on information gathered by members of the College of General Practitioners)**

### I

### The Problem and Some Results

**B. C. S. Slater,** M.D. (*Harrow*)

Although Dr Watson and I are representing the College here this morning, we do so with deep gratitude to the 1,250 members who

supplied us with this information. Without their contribution there could have been no College studies on congenital deformities.

Congenital abnormalities are not a prominent feature in general practice when compared with other causes of morbidity. If we look at volume I of *Morbidity Statistics from General Practice*, we find that for every 1,000 patients in general practice there are six consultations per annum for congenital abnormalities, and for every 1,000 patients aged 0–15 years that figure rises to 15. If we compare this with diseases of the respiratory system, the latter cause 880 consultations per 1,000 patients in the total group, and 1,108 consultations per annum per 1,000 patients in the 0–15 year group. Looked at numerically, therefore, congenital abnormalities seem almost insignificant, yet as we all know morbidity cannot be considered only in relation to statistics. Every family doctor who has had a congenitally deformed baby born in his practice realizes the distress and the disruption of family life which ensue. Ten little fingers and ten little toes assume far greater proportions than can be shown in terms of morbidity figures, and for this reason alone the importance of the subject which we discuss today is apparent.

Professor McKeown of Birmingham University has shown that while numbers of stillbirths and infant deaths from all causes declined in Scotland during the 1940s and 1950s, those attributable to congenital abnormalities in the same period remained constant, and in a recent editorial in *Developmental Medicine and Child Neurology* it was stated that between 1951 and 1960 the proportion of infant deaths due to congenital deformities actually rose by 50 per cent. This in itself is reason to intensify research into the causation of these deformities. Deaths from other causes have decreased for various reasons, such as the new therapuetic measures to control and counteract infection, immunization procedures and improved standards of living with all that that implies; one can expect the infant death rate from congenital abnormalities to decrease also with improved diagnostic techniques and surgical procedures, as it has done, for example, in cardiac malformations with the rapid advances in heart surgery made possible by improved diagnostic methods such as cardiac catheterization. Nevertheless, the main advance in reduction of mortality rate due to abnormalities could lie in the field of prophylaxis. Genetic counselling, about which Dr Clarke and Dr Carter will be speaking later, dietary supplementation during pregnancy, the prevention of infection, the restriction of certain drugs in the treatment of infection in early pregnancy, and the control of radiation dosage to the expectant mother may all play a part, but before prophylaxis can become more fully effective, more information

concerning the cause of these abnormalities will have to be forthcoming.

The research committee of the college Council in 1958 (well before the thalidomide era) decided to commence a study of prenatal influences on foetal development. It was decided in the first instance that two aspects should be investigated, the seasonal distribution of the various abnormalities and the effect of febrile illness during pregnancy, the seasonal distribution being investigated retrospectively and febrile illness prospectively. These aspects were selected because they seemed particularly suitable for investigation by family doctors. For the survey of seasonal variation, general practitioners could supply quite readily the few details necessary concerning children in their practices. This study was not concerned with the true incidence of the various defects, but with the distribution by season, so that practitioners did not necessarily have to make a thorough search of their practice records in order to find every case, a task which would have precluded many from participating. The basis for this view was that it seemed a reasonable expectation that doctors would notify cases regardless of the time of year the child was born.

The response to our enquiry was most gratifying. Several practitioners as well as providing information wrote letters of encouragement. One who took the trouble to provide us with the details wrote a letter to inform us that he did not think the study was worth undertaking, for nothing could come from a study merely involving the dates of birth of the patients. This is what is so nice about some members of the College! It was apparent here that the purpose of this study had been misunderstood. Inequality of seasonal distribution of any defect must reflect a similar inequality in the causative factor for that defect, the factor being affected in some way by season. Examples of factors that have to be considered are infections known to be seasonal, drugs used in the treatment of these infections, and temperature and seasonal dietary variations. Hence, any finding of variation in the seasonal pattern of a defect gives an important clue to an environmental factor in the aetiology.

The study of febrile illness in pregnancy was started because it seemed evident that a prospective study would be of value in view of the knowledge concerning rubella and the suspicion regarding some other illnesses, particularly in the virus group. It is generally accepted that a teratogenic agent must act in the early months of pregnancy, and it seemed that the person most likely to know of any illness from which the expectant mother might suffer at this particular time would be her family doctor, who generally also knows

the outcome of the pregnancy. If the infection happened to occur at a time when the patient did not yet realize that she was pregnant, which may well be the most vulnerable time, the family doctor is again most likely to have a record. Although rubella and thalidomide were both recognized to be teratogenic by retrospective investigation, the difficulties of this type of investigation are very great. We can imagine how bias creeps in when a mother who has given birth to a defective child is trying to remember events which have taken place in the early stages of her pregnancy; the mother may magnify some unimportant event or on the other hand may forget some minor but nevertheless important illness.

For the study of seasonal variation, reports on approximately 10,000 infants were received. Our first difficulty in this study came when we tried to classify these reports, for there was no classification suitable for our purpose. Lack of a suitable classification arises from the lack of an agreed definition of congenital abnormality. We solved this problem by drawing up our own classification, based on the material with which we had been provided. As calculations of incidence were not involved, it was decided for the purpose of the study to err on the side of including rather than excluding conditions which some would consider doubtful under the definition of congenital deformities. The classification now includes 83 categories, listed under eight body system headings, and has a miscellaneous group in each heading. The hand analysis which was recently completed was done in order to check this classification and to provide some clues for the mechanical analyses which are now taking place in the records and statistical unit in Birmingham. This present analysis is one of individual defects, and takes no consideration of the association of defects in individual children. Analysis was made by quarters, and the main comparisons were between the two summer quarters and the two winter quarters defined quite arbitrarily, the two summer quarters being from the beginning of April to the end of September and the two winter quarters from October to the end of March. Most of these categories showed no seasonal variation in distribution at all, but in anecephaly, spina bifida, partial absence of limbs (in view of thalidomide this was of interest), congenital dislocation of the hip, oesophageal atresia, pulmonary stenosis, abnormality of the lower gut, and cataract there was a variation which seemed greater than could have been accounted for by chance.*

The study of febrile illness in pregnancy has not yet reached a stage from which any definite conclusions can be drawn. It is of necessity a long-term study, and we require a follow-up of approxi-

*The findings based on this analysis have been published in detail in the *British Journal of Preventive and Social Medicine.*

mately two years, owing to the fact that some deformities such as deafness, mental deficiency and some heart defects may not be recognizable at birth. Approximately 500 cases of febrile illness occurring during pregnancy have been reported, and of those about 150 were in the first trimester. In spite of the fact that the general practitioner is probably the only person who can recognize infections in the first month of pregnancy, we are still not having these reported in sufficient numbers for analysis. Illnesses with approximately 40 different diagnoses have been notified, so that there are very few under some diagnostic headings. Nevertheless, one gets the impression, and it can only be an impression from the study at this stage, that febrile illness usually has no appreciable adverse effect on the embryo. This negative conclusion may not necessarily apply to any specific type of infection, and we may have to modify our views by the time the study is concluded. One wonders if in fact we will make much progress in investigating the teratogenic activities of infection before our diagnostic criteria for the virus infections are improved. We need only think of the varied types of infection included under the general term ' influenza ' to add point to this.

The notifications of rubella give an idea of the difficulties of this type of investigation. There were 35 cases of rubella in the first 16 weeks of pregnancy, two in the first four weeks, eight in the second four weeks, 14 in the third four weeks and 11 in the fourth four weeks. Of the two in the first four weeks, one mother had a therapeutic abortion and the other baby appeared normal, except for a mild inversion deformity of the foot. Of the eight cases in the second four weeks, three mothers had therapeutic abortions and one a spontaneous abortion, one had a stillborn macerated foetus, and the other three babies were normal. Of the 14 cases in the third four weeks, three mothers had therapeutic and three spontaneous abortions while one baby had a large naevus on the back, another had hypospadias and the other six infants were normal. Of the 11 cases in the fourth four weeks, three mothers had therapeutic abortions and the remaining eight babies were normal. This was the position at birth, and all of the defects might not have revealed themselves at this stage; with this proviso one can say that of the 35 cases, ten mothers had therapeutic and four spontaneous abortions while one baby was stillborn, three had comparatively minor defects, and 17 were normal. In other words 17 of the 21 pregnancies that went to term produced normal babies. This is the difficulty which I was talking about in this type of investigation; we have 35 cases and none of these babies when examined at birth showed the characteristic rubella embryopathy. This helps to confirm the view that there should be some reappraisal of the attitude towards therapeutic

abortion in these cases. It has been shown in a British investigation in 1960 that of babies born alive to mothers who had rubella in the first trimester of pregnancy, 84.2 per cent were free of major congenital abnormalities, and in an American study these findings were confirmed, for 85 per cent of infants carried to term had no congenital abnormalities. Of the abnormalities which do present in the other 15 per cent some will be amenable to surgical treatment; while I certainly do not underestimate this problem, there is little doubt that the incidence of abnormalities after rubella in pregnancy has been overstressed in the past.

While these College studies were in progress the thalidomide disaster took place. This was a disaster which, however unwitting and however unfortunate, was the largest experiment ever in human teratology. If the opportunity had been grasped more firmly much more might have been learned from it concerning the aetiology of defects. While a certain amount is known about the mothers who took thalidomide and produced abnormal babies, very little is known about those who took thalidomide and produced normal babies, so that the quantitative teratogenic effect of thalidomide remains unknown. A study of these two groups might have yielded some important clues, and one cannot help feeling that this was a study which the College might have undertaken after the first announcement of the danger. At that time there were certain to have been mothers who had taken thalidomide in early pregnancy and had not yet been confined, so that a prospective survey could still have been mounted at this stage. I do not know of anyone who obtained this information, and I am sure that we missed a great opportunity.

There is no doubt that this occurrence and the publicity given to it put the profession on its guard concerning drugs in pregnancy. Several schemes have been initiated in an attempt to prevent or to limit a similar catastrophe in the future. Malformation registries have been set up in some places. In fact, some had been set up prior to thalidomide. The best known examples of these are probably in Birmingham and Liverpool. If records of the various defects notified for a given population are kept it is hoped that any sudden increase in incidence of any defect will point the way to urgent investigation of the cause. The College, through its Epidemic Observation Unit, started an early warning system by instituting a toxicity register to which family doctors could notify toxicity or side-effects of a drug at a stage when this is only suspicion. Before this, there was no place to which general practitioners could notify their suspicions, except to the drug houses themselves. The Cohen committee's report, which was recently accepted by the

Government, recommends the setting up of an early warning system and mentions this pilot study conducted by the College. Yet one wonders whether the dangers of thalidomide would have been noticed even now if the defects caused by it had not been so distinct and so obvious.

Experimental teratology has, of course, an important part to play in the detection of drug toxicity, but there are still difficulties in relating animal experiments to human experience. Cortisone and some salicylates are teratogenic to animals in certain conditions, but the medical world would be a much poorer place without these drugs. The prospective survey of the outcome of pregnancy about to be launched by the College will include details of illnesses and drugs given in an attempt to elucidate this problem. Until experimental methods can give more precise answers, the tendency will be for doctors to give drugs to women in early pregnancy only if they are life-saving, though the difficulty here is that the embryo is at its most vulnerable stage before the mother may know that she is pregnant.

It is now over 20 years since the association between maternal rubella and congenital abnormalities was reported. In the interval several studies have been conducted with a view to discovering other maternal infections which might act in a similar way; so far with the exception of toxoplasmosis and possibly influenza (I think the evidence incriminating influenza is very thin, though some people would disagree) no other infections have been incriminated. These investigations have however been worth while, for it is important to be able to say with confidence that a certain infection does not cause abnormalities. Nevertheless, while our minds were preoccupied with infections, along came a teratogenic drug and our lines of thought had to be completely reorientated. It is equally important that drugs at present in use should be investigated, if only to exclude the harmless ones, but one hopes that the lesson has been learned and that we will not now limit ourselves to the investigation of drugs and infection.

Many questions come readily to mind, to some of which family doctors could help to provide answers. Why do only 15 per cent of mothers who suffer from rubella in the first trimester produce babies with congenital defects? Is there something in the mother's constitution which makes her more susceptible to this teratogenic insult? Could there be some dietary insufficiency at the appropriate time as may be suggested by the fact that some congenital abnormalities are more common in the lower social classes? There is experimental evidence that the teratogenic action of vitamin A can be

modified by the administration of insulin or thyroxin, and Dr Woollam may be saying more about this. Perhaps we should be casting our net wider by including some aspects of the mother's metabolism in our investigations. We hope that from further studies based on our main retrospective series we shall obtain more clues, which we can include in our future prospective studies. Information concerning the 10,000 infants is now ready for mechanical analysis, and part of this has been done. We shall be carrying out more detailed studies of seasonal distribution, using a monthly analysis for each year instead of the quarterly analysis for the whole seven-year period. We shall be attempting some studies on geographical variations and secular trend. Whether this will be possible from our information is perhaps open to question, but it will be an interesting epidemiological exercise. The most fruitful study may prove to be one of association of defects in individual infants, in an attempt to provide more information on malformation syndromes, something sadly lacking at present. Rubella, for instance, gives rise mainly to cardiac defects, particularly patent ductus arteriosus, to cataract and to deafness. Patent ductus arteriosus is rarely associated with rubella unless it is accompanied by either cataract or deafness, so that a retrospective study of patent ductus arteriosus alone would not have been likely to reveal the association with rubella, while a study of the association of patent ductus arteriosus with either cataract or deafness might well have done so. We find the same thing in thalidomide babies, where there is also this tendency towards a pattern of deformity, the limb defects being accompanied by ear defects or anomalies of the intestinal or urinary tract. If we can obtain more information from this investigation of malformation syndromes, retrospective research will be greatly facilitated. Investigation of prenatal pathology bristles with difficulties, but these difficulties are gradually being overcome and it is expected that as more clues are unravelled the prospect of diminishing the incidence of these defects by prophylactic methods will become more hopeful.

REFERENCES

Logan, W. P. D., and Cushion, A. A. (1958). *Morbidity Statistics from General Practice*. Volume 1. G.R.O. Studies on Medical and Population Subjects, No. 14. London. H.M. Stationery Office.

MacKeith, R. C., and Bax, M. C. O. (1963). *Developmental Medicine and Child Neurology*. Volume 5, No. 4.

Manson, H. M., Logan, W. P. D., and Loy, R. M. (1960). Rubella and other Virus Infections during Pregnancy. Ministry of Health reports on Public Health and Medical Subjects, No. 101. London. H.M. Stationery Office.

Slater, B. C. S., Watson, G. I., and McDonald, J. C. (1964). *Brit. J. prev. soc. Med.*, **18**, 1.