H

Possible Contributions by General Practitioners to Future Research

G. I. Watson, M.D., M.R.C.S., D.T.M. & H. (*Peaslake*)

As in so many fields of medical research, the contribution family doctors can make to the study of congenital anomalies is not dramatic compared with that of the specialist, yet we are the people who, with midwives, first see many of these deformed children. We have to help the parents to care for those who survive, and to explain, or even explain away, miscarriages and stillbirths, whether associated with defect or not. We are called upon to give advice to young and not so young couples about their chances of having further healthy or deformed children. We are usually but not always the ones to whom mothers come for treatment of sickness in early pregnancy. These in themselves are all important practical contributions, and we should be thankful to the Board of the Welsh Faculty for giving us this opportunity to learn more about a rapidly expanding subject.

A register of congenital abnormalities

Dr Slater has given you an excellent account of how the College came to be involved in several studies aimed at finding clues which may prove useful for others to follow. Finding clues rather than finding answers may eventually be the most useful contribution that family doctors can make to this subject. This will call for an adequate interchange of ideas such as we are having today if the best use is to be made of the material which we collect. We hope that the new College register of over 10,000 reports about congenitally defective children will be one means by which specialists can gain assistance from their colleagues in general practice. Our notifications of defective children, live or stillborn, go back to 1954, and new reports as they are sent in are added to the register. Anyone interested in finding examples of a particular defect or group of anomalies may write to the College asking to be put in touch with doctors who have notified cases. Through the family doctor the research worker will thus get the information he needs, or be able to examine affected children and their relatives. We look on this as one more step towards a national registration scheme for important congenital anomalies.

The first use we made of our register was when news about thalidomide came out. We looked to see whether there had been any difference in pattern of limb defects before and after 1958. We found that before thalidomide was introduced single limb defects had been commonest; for comparison, we took hare lip and cleft palate as a type of defect which we did not think had been influenced by

thalidomide. Single limb defect is, as Dr Slater has told you, a type which shows seasonal variation in its prevalence. After 1958, defects involving more than one limb, particularly defects involving both fore and hind limbs together, increased in frequency. When we told the Ministry about our finding of this seasonal variation in partial and single limb defects, they looked again at their figures for thalidomide babies (something nobody had done either here or in Germany) and found no variation in seasonal prevalence. The birth-month distribution is a straight line, whereas for the group of mothers whom the Ministry know about who either certainly or probably did *not* take thalidomide, the distribution of their birth-months shows this same variation with a peak in June that we found in our preliminary study of the College material. This is something which has to be looked at further.

The next enquiry was from a doctor in Wales interested in syndactyly. He wanted names and addresses of affected children to try to trace connections with families which he already knew about. The cases we were able to tell him about were clustered in certain parts of the country, but this may only reflect the distribution of reporting doctors or of large centres of population. We shall learn more about the significance of these irregular regional distributions when the mechanical analysis of our data has gone further.

In the College survey the distribution of the first 391 notifications of hydrocephalics showed some peculiar irregularities, both by region and seasonally, which will need further study. One would not have expected to find a curve of the birth-month distribution looking so irregular yet showing such similarity in the distribution of irregular bumps in different regions. We do not pretend to know what it means. It may mean nothing, but this is the sort of clue that we think our register may throw up.

Rubella

Rubella awakened a general interest in antenatal infection as a possible cause of congenital anomalies. It was therefore natural that gamma globulin should be given to mothers exposed to the disease in an attempt to prevent foetal damage. Until recently, however, no base-line existed by which to judge the benefit derived from such prophylaxis. In 1957, the Epidemic Observation Unit of the College began a study of the secondary attack rate of rubella in 500 families exposed to a primary case at home. The attack rate varied by age, but it was unexpected to find a considerable excess in females, particularly in child-bearing women, who are ten times more liable to a clinical attack than males of the same age. This difference seems larger than can be explained by the fact that

men are in less contact with their children or away from home each day for longer than women, and was evident although not always significantly greater in females at all age groups over five years. It looks as if there may be a sex difference in susceptibility, not necessarily to infection but to a clinically apparent attack of German measles.

The main purpose of our survey, which was published recently (*Brit. med. J.* (1963), **2**, 419), was to measure the secondary attack rate in untreated women of child-bearing age. The rates of 3.7 per cent for this group and 5.5 per cent for those with no past history of rubella compared with a rate of less than one per cent among mothers treated with gamma globulin after exposure in early pregnancy, as shown by the Public Health Laboratory Service, whose study was also based on reports by family doctors. Of added interest in this Public Health Laboratory Service report is the suggestion that gamma globulin can perhaps be given too soon after exposure. The failure rate, if one may call it that, was 1.65 per cent among mothers given gamma globulin within five days of exposure, but only 0.75 per cent among those treated after the fifth day of contact. Gamma globulin is eliminated from the body fairly rapidly, and it may be that after a very early injection the concentration of gamma globulin was inadequate to control a later viraemia.

Now that rubella virus has been isolated, family doctors will be able by collecting blood and other specimens, as some College doctors in London have already done, to assist those like Dr J. A. Dudgeon at Great Ormond Street who are trying to determine, for example, whether there are several types of this virus, perhaps not all equally damaging to the foetus. The existence of more than one type of rubella virus could account for those instances, of which I know three, where a mother who has previously had German measles suffers a second attack during pregnancy, resulting in a typically damaged baby. One of these mothers had her first attack in 1940, when the current strain of virus was admittedly teratogenic, but that was not the one that gave her a damaged baby. Several years later she was exposed to rubella at home, contracted it probably a day before conception, and had a rash two days after she missed her period; she had a totally damaged baby. Again, can a woman who has had rubella in the past be re-infected subclinically during pregnancy by a second strain of rubella virus? Is a woman in pregnancy more than usually susceptible to rubella? I have one patient who has had none of the childish diseases in spite of home contact except rubella in pregnancy; it seems as though her susceptibility to rubella was increased by pregnancy. Might this

be one explanation of those cases in which babies have had the rubella pattern of defect, yet the mothers deny having had German measles in pregnancy? Dr McCracken's interesting case of neonatal rubella (*Brit. med. J.* (1963), **2**, 420) lends support to this idea of subclinical rubella infection.

Other viruses

When the teratogenic effect of rubella was discovered, it was natural that other infections should also be studied, first the easily-diagnosed diseases like mumps and measles, chickenpox and vaccinia, then influenza, colds (whatever we mean by that), and many other ill-defined febrile illnesses. Dr Slater has told you of some enquiries the College is at present making along these lines, but we wonder whether our search is yet wide enough or deep enough into this subject. What further clues can we offer from general practice? Think of the known seasonal variations in the incidence of certain congenital anomalies. Could there be a link here with known seasonal variations in the prevalence of some neurotropic virus, for example one of the enteroviruses? Most of these are infections of childhood, and like measles and chickenpox they cause epidemics. For example, I saw an epidemic of eventually 44 cases of adenovirus type 3 infection in 1959–60, though we have never had a case since. Coxsackie virus B4 caused a big outbreak last autumn, though in the period of our survey up till then we had seen only two previous sporadic cases. Such viruses come, they attack and they disappear. There is no baseline constant, just as we are not constantly surrounded by chickenpox and measles. They have seasons of prevalence, and this is something we should look at more critically in the ' new ' viruses; but because of the lack of characteristic signs and symptoms, they are not easily recognized and are even more troublesome to differentiate. Many of the bowel viruses are known to be neurotropic and some, for example the Coxsackie type A or B viruses, are more abundant in summer and autumn and have a predilection for muscle and nerve tissue; others die out in summer, including the true cold viruses or rhinoviruses, some strains of which are undoubtedly neurotropic.

There is a great variety of these newly identified viruses, not all enteroviruses. Table I sets out the eight that we commonly think of and immunize against, but we do very little to prevent our patients getting infected by 28 other viruses which we have isolated in the practice during the last four years. It is hard to believe that out of the whole list rubella is the only one which can get through to the foetus. Subclinical infections are common, particularly among adults in contact with infected children. I myself have so far

acquired a symptomless immunity to five of these viruses shortly after they appeared in the practice. What happens to her baby when a pregnant mother undergoes a symptomless infection by a virus which is going round her family? Her pregnancy cannot initially be protected by any antibody against a virus to which she is acquiring a subclinical immunity. Are any of these newer viruses responsible for these congenital anomalies which show marked seasonal or regional variation? In any prospective study, should we record other virus infections in the family, even if the pregnant mother herself does not become ill?

TABLE I

VIRUS INFECTIONS ENCOUNTERED IN THE TILLINGBOURNE VALLEY, 1959-63

Eight diseases recognizable on sight	*28 only diagnosed by virus isolation*
Measles	Influenza A and B
Rubella	Rhinovirus—H and M strains
Roseola infantum	Parainfluenza group—three types
Mumps	Respiratory syncytical virus
Chicken-pox	Adenovirus group—several types
Cowpox	Coxsackie A and B—several types
Shingles	Polio—types 1—3
Infectious hepatitis	Echo virus group—several types

We know that stillbirths may also be increased by a teratogenic agent. Is there a need for a nation-wide serological study of mothers who give birth to malformed babies or have stillbirths and of cord blood from all babies seen at birth to be deformed? Would a centralized study of abortion material be feasible to try to find out how many of these are abnormal or infected by viruses? Can rubella virus be isolated from material removed at therapeutic abortion? I have taken part in one such attempt, unfortunately without success, but I am sure that if we go on looking for long enough we shall find rubella virus in the foetal material. If any such surveys are set up, family doctors will certainly be called on to play a part in collecting some of the specimens for the laboratories, and the College itself can contribute to the organization of such help.

Drugs

Years before Gregg's work incriminating rubella or thalidomide was heard of, the reputation of quinine as a cause of abortion was so strong that mothers in the tropics at the beginning of this century would not take it for malaria. While he was still in general practice, my father showed that it was the malaria itself and not quinine

which caused this high abortion rate in malarious districts of Malaya. These women miscarried more often whether their malaria was treated with quinine or not. We all know how difficult it is to disentangle the influence of a drug even on non-pregnant people, let alone on the foetus. I have been told by several doctors connected with the pharmaceutical industry that scarcely anything is known about the concentration in foetal tissue of drugs taken by a pregnant animal, and perhaps we may hear more today about the difficulty of such work. Moreover, examining the teratogenic influence of drugs used to relieve the symptoms of nausea and vomiting in pregnancy is further complicated by the fact that the outcome of that pregnancy itself seems to be influenced, apparently for the better, by the cause of nausea and vomiting. Recent College studies have confirmed an earlier report from Israel in 1957 that abortion is nearly four times less frequent in women with troublesome nausea and vomiting than among those who think they are getting away lightly. The old wives' tale of " the worse for the mother, the better for the baby " that I was brought up on seems to be true. Malformations and stillbirths were about equally distributed in the two groups. We would do well to remind our young pregnant patients about this when they seek a prescription for their sickness, but I expect that, in your practice as in mine, you are no longer being asked for pills of any sort by women in pregnancy.

Dr Slater has reminded us that the College lost an opportunity to study prospectively the outcome of pregnancy in women who had taken thalidomide, to find out how many babies were not affected. We must not make the same mistake again and miss this present chance to study the outcome of pregnancy in women who have taken no drugs at all. The College is mounting a prospective enquiry which aims at collecting reports about a very large number of pregnancies, studied in a variety of ways, not only as regards drugs and infections. One of the things we want to know is the malformation rate in women who take no drugs and have no infection. We want the base-line, as we have found it for the rubella secondary attack rate. I have tried to suggest that family doctors have still a great deal of work to do on their own as well as in collaboration with others in this field of congenital anomalies. They should be able to provide clues for others to follow, if the quality of their contribution matches that of their specialist colleagues, about which we are going to hear more today.