Papers and Originals

Population and Clinic Studies of Congenital Heart Disease in Liverpool*

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Since Gross and Hubbard (1939) first reported tying a patent ductus arteriosus the increasing range and complexity of the treatment and diagnosis of congenital heart disease have led to rapid expansion of the services for patients with malformations of the heart. Though initially these facilities were required for many adults in addition to children, the needs of children and babies have become increasingly dominant. The services required to meet these needs have, so far, been developed only to a limited extent, and at the first Paediatric Conference in the Royal College of Physicians (London) to be devoted entirely to cardiology it was thought appropriate to consider the extent of the diagnostic and therapeutic problems with which we are faced today in terms of the total numbers of infants and children involved and of the relative frequency of the various heart lesions with which they present; and to review briefly the value of epidemiological studies of congenital heart disease.

General Incidence of Congenital Heart Disease

Attempts have been made in this country and abroad to find out the incidence of congenital heart disease at birth. In Birmingham, among 199,418 total births in 1940-9, MacMahon, McKeown, and Record (1953) found 633 children who were recorded as having a congenital heart lesion after adjusting for the diagnoses that had been missed at birth and made in the next few years—that is, an incidence of 3.2 per 1,000 total births. The figure for those followed longest—namely, for the babies born during the earlier years 1940 to 1944—was 3.6 per 1,000 total births, or 3.7 per 1,000 live births. In only 372 of the 633 cases, however, had a definite diagnosis been made, and one does not know in how many of the remaining 261 children it will eventually be decided that, for example, the murmur which at first suggested a malformation is in fact functional, so reducing the incidence of malformations. One must also doubt the adequacy of their methods of finding those babies with a malformation because of their figure in schoolchildren, of only one affected child in every 1,000, which is about half that of other published series, to which reference will be made later.

Since this publication of an incidence at birth of 3.2 per 1,000 in Birmingham higher figures have been suggested from other parts of the world (Table I). In America Harris and Steinberg (1954) found 6.8 per 1,000 live births in Rochester, Minnesota; McIntosh *et al.* (1954) at least 6.5 and possibly 7.6 per 1,000 live births in New York City; and, more recently, Mustacchi *et al.* (1963) 5.9 per 1,000 among children born in San Francisco and followed up until school age; while in Sweden, Carlgren (1959) found 369 children with malformations of the heart among 58,105 live births in Gothenburg, or 6.4 per 1,000. His study was particularly valuable in that he

had access to almost all babies born in the city and was able to examine most of those who survived over a follow-up period of 7-16 years. Moreover, his diagnosis was reasonably firm in 87% of cases. He has subsequently continued his follow-up, and, owing to still later discoveries of children with congenital heart lesions among the age groups he is observing, his estimate in 1965 was about 7 affected babies per 1,000 live births (Carlgren, 1965).

TABLE I.—Incidence of Congenital Heart Disease in Live Births			
MacMahon <i>et al.</i> (Birmingham)	..	..	3.2 per 1,000
Harris and Steinberg (Rochester, Minnesota)	..	..	6.8 " "
McIntosh <i>et al.</i> (New York City)	..	..	6.5 " "
Mustacchi <i>et al.</i> (San Francisco)	..	..	5.9 " "
Carlgren (Gothenburg)	..	..	6.4 " "

The later publications therefore all suggest that at least 6 out of every 1,000 babies born alive have a congenital heart lesion.

Liverpool Malformations Registry

In Liverpool the setting-up in 1959 of a registry of all babies born with a malformation of any sort has provided an opportunity to study the incidence of malformations of the heart in babies born within the registry area, which in 1960 included only the City of Liverpool and the adjoining borough of Bootle, but since 1963 has covered still more of the region—a total population of about 1½ million.

In Liverpool, with an average population of 742,918, during the five-year period January 1960 to December 1964 there were 80,641 live births, and the last review of the registry in November 1965 suggested that among them there were 376 babies with a reasonably certain cardiac malformation—an incidence of 4.7 per 1,000. This figure is being modified constantly by previously undiagnosed cases coming to light, and still more of these are to be expected, especially for 1964, for which the follow-up period is still very short. It has, of course, been necessary to make certain arbitrary decisions on what is and what is not valid evidence of a congenital heart lesion, and in estimating the number with each type of lesion inadequate evidence has had to be accepted in some cases.

These difficulties can be best illustrated by a description of the experience gained in Liverpool of the collection of data and their interpretation over the past five years.

With regard to the organization of the registry (Smithells, 1962), it was started by Dr. R. W. Smithells, then Lecturer in the Department of Child Health in the University, in co-operation with the City of Liverpool Health Department. It is housed in the Department of Child Health, which is in Alder Hey Children's Hospital, the largest children's hospital in Liverpool. Notification was entirely voluntary, but it is, of course, now compulsory throughout the country to notify all babies born with a congenital malformation.

As there is no satisfactory definition of a congenital abnormality, people were initially asked to notify "any abnormality,

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however slight, detectable in the first week of life and in still-born infants." It soon became clear that not all cases were being notified—for example, borderline abnormalities such as tongue-tie and post-anal dimples—and these are therefore no longer registered.

Notification from maternity hospitals is by paediatric registrars, and sometimes also, in the case of stillbirths, by obstetricians, by means of a simple card which is sent in a prepaid envelope to Dr. Smithells and does little more than identify the infant and the abnormality. Babies born at home with a congenital malformation are notified by the district midwives to the Maternity and Child Welfare Department of the Local Health Authority, where all relevant details of the case are entered on a special domiciliary notification form, which is then sent to the registry.

Clearly, certain groups of malformed babies tend to slip through the net of this primary notification. First, stillborn babies: many of these are picked up when they appear on the lists of the monthly perinatal conferences of the large maternity units. Secondly, neonatal surgical emergencies, as they may be transferred for surgical treatment so quickly from the maternity units that notification may be overlooked: these are found by a regular review of the neonatal surgical unit records. Thirdly, of course, congenital heart lesions.

Many babies with a congenital heart lesion will obviously not be notified during the neonatal period: some of them will die undiagnosed and some will be found to have a murmur or develop symptoms later. Fortunately for the purpose of the registry, there is only one heart clinic for children in Liverpool, at the Royal Liverpool Children's Hospital, and it is believed that nearly all those whose lesions are found later by their general practitioners or paediatricians are referred to that clinic. It is known that all such cases when recognized among school-children are so referred. In due course, then, all these are added to the register. Of those who die undiagnosed in hospital, most are revealed in the necropsy registers or at the perinatal conferences of the maternity hospitals. Those on the register for any one year are therefore added to from time to time and the total becomes progressively more accurate. Similarly, its accuracy is improved by the removal from it of babies whose systolic murmurs were thought initially to be of organic origin but have subsequently been regarded as functional.

The success of such a registry as this depends, of course, not only upon the constant activity of one enthusiastic individual who runs it but also on the availability of a secretary or research assistant, who spends most of her time making sure that primary notifications are in fact coming from the various sources, stimulating those whose duty it is to send them, and conducting a regular examination of necropsy records and of the registers of

new patients in special clinics which deal with malformations of the various systems. It is the lack of such detailed checking that will inevitably result in the figures in the National Registry being lower than those of, for example, the Liverpool and Birmingham registries.

Incidence in Liverpool

As a result of these various measures 510 babies out of 80,641 live births during the five years 1960–4 were notified to the Liverpool registry as having a possible congenital heart lesion—that is, 6.3 per 1,000 (Table II, col. 2). By the end of November 1965 many of these babies had been seen in the heart clinic at the Children's Hospital, where a murmur was considered to be definitely functional in 79 patients and of uncertain origin in 55. If the infants and children in both these categories, totalling 134, are excluded, 376 remain, or 4.7 per 1,000 (Table II, col. 3).

If only those with a definitely functional murmur are excluded the remaining cases, 455, give an incidence of only 5.7 per 1,000, and the questions arise, "Why are these figures one or two per 1,000 lower than those of Carlgren and the Americans?" Are an appreciable number being missed at birth? Is there a failure to recognize them later? Or are fewer with a malformation of the heart being born in Liverpool than, for example, in Gothenburg?

A great many are certainly being missed at birth. This is inevitable, not only because they have neither signs nor symptoms of a cardiac malformation during the neonatal period, but also because in Liverpool many babies are born at home: moreover, it is known that a high proportion of the total notifications for any given year are received subsequently as a result of the various follow-up measures.

These follow-up measures may also be so inadequate that a significant number of cases are not being recognized later; or it may simply be that the follow-up period is, as yet, too short to include all the affected children.

A review of some of the figures in the registry points to certain inadequacies. If the up-to-date figures for each of the five years covered by the registry are compared—namely, for 1960 75, for 1961 108, for 1962 102, for 1963 130, for 1964 95, (a total of 510)—their differences from year to year are striking. The high figure of 130 for 1963 was partly due to a small "epidemic" of congenital heart lesions in that year. The low figure for 1960 is less easily explained with certainty, but there are good reasons for believing that an appreciable number of cases were missed in that first year of the registry: first, that the 23 deaths which have occurred in that group represent only

TABLE II.—Congenital Heart Disease in Liverpool

In 80,641 Live Births in Liverpool, 1960-4											
Malformations	At Birth			Deaths before November 1965	Survivors, November 1965	In 130,936 Schoolchildren 5-15 yrs of Age, Liverpool Education Authority Schools, July 1963	Differences between Estimated and Observed Percentages in Survivors				
	In Registry		Excluding Systolic Murmurs, Functional or of Doubtful Origin								
Total Number:	510	(6.3/1,000)	376 (4.7/1,000)	153	(1.9/1,000)	223 (2.8/1,000)	291 (2.2/1,000)	Decreases	Increases		
	No.	%	%	No.	%	%	No.	%	%	%	
Ventricular septal defect ..	128	25.1	34.0	21	13.7	16.4	107	48.0	82	28.1	19.9
Patent ductus arteriosus ..	29	5.7	7.7	10	6.5	34.5	19	8.5	41	14.1	5.6
Atrial septal defect, a-v canal, total anom. pul. ven. drainage	44	8.6	11.7	20	13.1	45.5	24	10.8	44	15.1	4.3
Fallot's tetrad ..	22	4.3	5.9	15	9.8	68.2	7	3.1	11	3.8	1.3
Coarctation of aorta ..	20	3.9	5.3	11	7.2	55.0	9	4.0	7	2.5	1.5
Pulmonary valvar stenosis ..	30	5.9	8.0	2	1.3	6.6	28	12.6	51	17.5	4.9
Aortic stenosis ..	16	3.1	4.2	3	2.0	18.8	13	5.8	34	11.7	5.9
Pulmonary atresia ..	10	2.0	2.7	8	5.2	80.0	2	0.9	1		
Transposition of great vessels ..	21	4.1	5.6	18	11.8	85.7/83.8	3	1.3/3.2	2	1.4	1.8
Common truncus arteriosus ..	6	1.2	1.6	5	3.3	83.3	1	0.5	0		
Tricuspid atresia ..	5	1.0	1.3	4	2.6	80.0	1	0.5	1		
Miscellaneous ..	45	8.8	12.0	36	23.5	80.0	9	4.0	17	5.8	1.8
Systolic murmurs, functional ..	79	15.5									
Doubtful ..	55	10.8									
Totals ..	510	100%	376 100%	153 100%	40.7%		223 100%		291 100%		23.2% 23.2%

31% of 75, whereas Carlgren's death rate by the age of 6 years was 38%, and the overall mortality rate among cases on the Liverpool registry is already 40%; and secondly, that of the 75 there were 43 survivors in whom a murmur was not regarded as functional. This represents an incidence of 2.7 per 1,000, which is higher than the 2.2 per 1,000 in Liverpool schoolchildren, and suggests that some babies born in that year may have been missed and subsequently died. Had these been registered they would have increased the mortality rate and reduced the survival rate to conform with the overall figures. It also seems probable that as time passes there will be more registrations of cases born in 1964.

The incidence of congenital heart disease in Liverpool babies is therefore almost certainly higher than the 4.7 per 1,000 entered in the Liverpool register up to November 1965. Time alone will show how much higher it will be. It is very unfortunate that it is so difficult to be sure of finding most of the cases born in any district, for, without them, fruitful comparison of incidence in various parts of the world may be impossible. Comparison of incidence from time to time will be equally valueless. There seems so far to be no good evidence of an actual increase in recent years in the number of babies born with a congenital heart lesion or indeed with any other malformation. Although the percentage of deaths due to malformations as a whole has increased, we do not know at present if there has been an absolute increase in the number (Lamy, 1960).

What has it been possible to learn from the registry of the fate of these Liverpool babies born with a malformation of the heart? How many survive to school age? Considering only those with definite lesions, of the 376 who were born in Liverpool during 1960–4, 153, or 40.7%, died before the end of November 1965 (Table II, col. 4). This agrees with most other published figures of the mortality rate during the first year or so of life. Only 223 children were alive out of the 376 babies—that is, 2.8 per 1,000.

Which were the most fatal lesions? They were transposition of the great vessels (see Table II, col. 4), common truncus arteriosus, pulmonary atresia and tricuspid atresia, but in addition a considerable number of deaths occurred in babies with Fallot's tetrad, the atrial septal defect group, coarctation of the aorta, and perhaps, most surprisingly, patency of the ductus arteriosus.

The effect of these deaths upon the percentages of each lesion among the survivors is shown in Table II (col. 5). The high percentage of children with a defect in the ventricular septum is remarkable—that is, 48% of the total—as MacMahon *et al.* (1953) found only 23% with this malformation among their children in whom a definite diagnosis had been made, and Carlgren (1959) 31% in his cases. In children with cardiac malformations attending heart clinics Keith *et al.* (1958) found 25% with a ventricular septal defect, and Nadas (1963) found 20% (Table VI).

Among patients attending heart clinics in hospitals there may well be a smaller proportion with a ventricular septal defect than among those found in a population survey, owing to the assumption by the family doctors that their patients' lesions are small and do not require investigation and treatment. In the series of MacMahon *et al.* it is possible that the percentage of children with a ventricular septal defect is so much lower than the Liverpool figure because the defect was present in a significant number of their 261 undiagnosed cases. However, this consideration does not apply to Carlgren's series, and it was clearly of great interest to see if the percentage incidence of the various malformations in the Liverpool children would change as time went on and, if so, what those changes would be.

It seemed highly likely that such changes would occur, as the percentage distribution of the various cardiac malformations among Liverpool schoolchildren aged 5–15 years differs considerably from the registry figures of November 1965. Among the 130,936 children in Liverpool schools in July 1963, 291

were found to have a congenital heart lesion and the percentages with each type of lesion are listed in col. 6 of Table II.

The differences between these percentages and those of the survivors at the end of November 1965 are striking. Assuming that there has been no significant difference in the incidence at birth between the period 1948–58, when the schoolchildren were born, and the period 1960–4 of the registry, any differences between the percentages of each lesion in the two groups should be due solely to those children who will die during the remainder of the five-year follow-up. Are such deaths to be expected? The figure of 2.8 per 1,000, compared with 2.2 per 1,000 among the schoolchildren, suggests that many deaths are unlikely; but it is possible that some of the 55 babies with murmurs of doubtful significance may have a cardiac malformation, and that therefore the figure of 2.8 per 1,000 in the survivors should be higher. Together, these two factors might modify the picture a little before all the registry babies have reached school age, but a more important cause of the discrepancy between the two columns is incorrect diagnosis in one group or another. The possibility of an occasional spontaneous cure of, for example, a patent ductus arteriosus or a ventricular septal defect in one or other group has also to be remembered.

So far as diagnosis is concerned, both the total number of cases and the diagnosis are probably accurate in the schoolchildren. For the past 13 years I have been conducting a heart clinic for the Liverpool Education Authority, to which the school medical officers refer all children with a definite or possible cardiac malformation and indeed all children with a murmur about which they are not absolutely certain. A few years ago, in order to make quite sure that they were referring to me all suspect cases among a year's intake of 10,000 children, I examined, in addition to those children the medical officers did refer to me, most of 200 other children with murmurs they had noted as functional on their school card and had not intended to refer; and among those children I found only two with a definite congenital lesion and one with a murmur of doubtful significance. So that, so far as the overall number of schoolchildren with a cardiac malformation is concerned, the figure of 2.2 per 1,000 is probably accurate.¹

With regard to the diagnosis in the schoolchildren, this has been established in many of them by operation, cardiac catheterization, or angiocardiography in the heart clinic at the Children's Hospital, and in most of the others is reasonably certain on clinical grounds. There is therefore no doubt that the diagnosis also is far more accurate in the schoolchildren

TABLE III.—Congenital Heart Disease, Liverpool

	80,641 Live Births, 1960–64, Survivors, Nov. 1965 (%)	130,936 Schoolchildren, Age 5–15 yrs., July 1963 (%)
Ventricular septal defect ..	48	28.1
Pulmonary stenosis ..	12.6	17.5
Aortic stenosis ..	5.8	11.7
Atrial septal defect ..	10.8	15.1
Patent ductus arteriosus ..	8.5	14.1
Fallot's tetrad ..	3.1	3.8
Coarctation of aorta ..	4.0	2.5
Others ..	7.2	7.2

than in the babies and toddlers, who make up a high proportion of the registry group. Consequently, it seems that any discrepancy between these percentages of the registry group and the schoolchildren is at any rate mainly due to errors in diagnosis in the former. Confirmation of this is found in a review carried out since February 1965 of those babies initially diagnosed as having a ventricular septal defect which resulted in the diagnosis being altered to functional systolic murmur in

¹ That this conclusion may not be justified is suggested by the publication, since this paper was completed, of a report by Morton and Huhn (1966) of congenital heart lesions in 4.6 per 1,000 schoolchildren in Denver, following an exceptionally thorough investigation of 17,366 children.

15 cases, to pulmonary stenosis in at least 10, to atrial septal defect in one, to common A-V canal in two and to double out-flow-tract right ventricle in one. Such changes of diagnosis fit in well with the trends to be expected from the percentages of each lesion in the two groups in Table III, with the registry group on the left and the school group on the right: the ventricular septal defects decrease, and the pulmonary stenoses, the aortic stenoses, the atrial septal defects, and the patent ductuses increase.

The change from ventricular septal defect to pulmonary stenosis is in keeping with the experience of those who see many babies with congenital heart disease. At the first examination the systolic murmur is maximal at the left lower sternal edge, and the pulmonary vascularity on x-ray is within normal limits; and a ventricular septal defect is as likely as any other lesion. At 9 months the murmur is loudest in the third left interspace; and at 18 months its maximal loudness in the pulmonary area suggests pulmonary stenosis. Similarly, delay in the development of typical diagnostic signs in young children with aortic stenosis, a defect in atrial septum, or a patent ductus is not infrequent.

Another possible cause of the discrepancy between the numbers of ventricular septal defects in the schoolchildren and in the registry group is spontaneous closure of some of the defects. That some do close spontaneously has now been established, and, though the percentage is uncertain, 25% has been suggested (Evans *et al.*, 1960; Hoffman and Rudolph, 1963).

It seems likely that more such changes in diagnosis in the registry group will occur before all the children in it reach school age, and also that some of those at present excluded on account of systolic murmurs of doubtful significance will be included in one of the other diagnostic groups.

With regard to the percentages of the various lesions at birth in the Liverpool babies, comparison with Carlgren's series (Table IV) shows the greatest differences to be in babies with ventricular septal defects, patent ductus arteriosus, and coarctation of the aorta, of which half seems so far to have been missed in Liverpool. The diagnosis of both patency of the ductus arteriosus and coarctation of the aorta is often not made until after the first year of life, and may well be established in some of the Liverpool children before they reach school age. In some cases this may involve a change of diagnosis from, for example, ventricular septal defect, of which Liverpool has more than Carlgren; but in others, especially those with coarctations, new children may be added to the total number, so raising the overall incidence a little nearer to Carlgren's.

TABLE IV.—Percentage Incidence of Congenital Heart Lesions at Birth

	Carlgrén. 322 Cases with Firm Diagnosis	Hay and Smithells. 376 Cases
Ventricular septal defect	31	34.0
Patent ductus arteriosus	11	7.7
Atrial septal defect, a-v canal, total anom. pul. venous drainage	9	11.7
Fallot's tetrad	5	5.9
Coarctation of aorta	11	5.3
Pulmonary valvar stenosis	5.5	8.0
Aortic stenosis	6	4.2
Transposition of great vessels	7	5.6
Common truncus arteriosus	1.5	1.6
Tricuspid atresia	1.5	1.3
All others	11.5	14.7
	100	100

In considering the very high mortality rate in the Liverpool cases of 40% within the first five years of life, comparison with the rates in other published series is also of interest. In Carlgrén's cases it was 38%, and in those of McMahon *et al.* 61%. The latter authors' Birmingham series is in many respects not comparable with the Liverpool series, and Carlgrén's longer follow-up, while probably including not more than a few deaths, has resulted in the addition of recently

diagnosed milder cases, with consequent reduction in the overall mortality.

In the Liverpool series the overall mortality rate cannot be less than 40%, and may be more before the group reach school age, with the mortality for each lesion varying from 6.6% in babies with pulmonary stenosis to 85.7% in those with transposition of the great vessels. It is important to know how many of these deaths were due to the malformation of the heart and how many to other factors.

The information obtained from the hospital case-sheets and reports of the 153 deaths is shown in Table V. Deaths probably due entirely or mainly to the cardiac lesion itself account for at least 59.4% of the total, and 83% of all deaths occurred before 7 months of age. For example, of the 21 deaths in babies with ventricular septal defects, 5 were due entirely or mainly to cardiac failure, in some cases precipitated by a respiratory infection, and 18 occurred before 7 months of age; and, of the 10 deaths in babies with persistent patency of the ductus arteriosus, 6 were due to that condition and 9 occurred before the infants were 7 months old. In some cases it was difficult to assess the part played by the cardiac malformation and by other conditions, such as malformations of other organs, in causing death—and this was especially so in the miscellaneous group—but it seems probable that over half of the total deaths were due mainly or entirely to the heart lesion, and that over three-quarters occurred before the babies were 7 months old. So that of the 376 babies born with a congenital heart lesion 82, or 21.8%, died as a result of their cardiac malformation before they were 7 months old. In some of them the malformation was correctable by modern surgical techniques; in others there were gross abnormalities for which there is as yet no satisfactory procedure.

TABLE V.—153 Deaths Among 376 Live Births with Congenital Heart Disease

Malformation	No.	Deaths due to Cardiac Lesion	Deaths due to Other Causes or Unknown	Deaths before 7 Months of Age	Deaths due to Cardiac Lesion before 7 Months of Age
Ventricular septal defect ..	21	5	16	18	5
Patent ductus arteriosus ..	10	6	4	9	5
Atrial septal defect ..	20	14	6	18	12
Fallot's tetrad ..	15	8	7	7	3
Coarctation of aorta ..	11	9	2	11	9
Pulmonary stenosis ..	2	1	1	2	1
Aortic stenosis ..	3	3	—	3	3
Pulmonary atresia ..	8	5	3	7	4
Transposition of great vessels ..	18	14	4	18	14
Common truncus arteriosus ..	5	5	—	5	5
Tricuspid atresia ..	4	4	—	4	4
Miscellaneous ..	36	17+	19	25+	17
Totals ..	153	91 (59.4%)	62	127 (83%)	82 (21.8%)

Services

We therefore are faced with a challenge to our diagnostic and therapeutic services which demands serious attention. Our modern diagnostic techniques have recently been applied more successfully in infants, but there is still need for methods which are accurate and rapid and can be employed more safely in the newly born baby than at present. The ultimate aim of surgical treatment of all these malformations must clearly be complete correction, and in those where this seems to be a practical proposition but has not yet been achieved, intensive research is indicated for which adequate financial support is essential.

For some of the lesions such corrective procedures have been employed successfully but only to a limited extent in this country, and for their more widespread and successful application there is a need for more cardiac surgeons to devote all their time to cardiac surgery in the infant and small child; and for more anaesthetists to become expert in anaesthesia of

babies. We also need to know more of the disturbances of pulmonary function and of acid-base changes which occur in infants following cardiac surgery and of the serious and more general electrolyte disturbances which may develop so rapidly in any ill infant.

Of equal importance is efficient nursing and overall management of the baby before, during, and after surgery. They are, of course, necessary also for babies requiring surgical treatment of malformations of other organs, such as the nervous system or alimentary tract. As they depend to a great extent upon adequate experience and knowledge of the general care of ill babies, they can probably be most effectively and economically provided in a large children's hospital, where they are a basic requirement for many of the patients and where the staff of the special surgical units can be drawn from the pool of experienced nurses working in the rest of the hospital.

In planning the size of the diagnostic and therapeutic services required in any area one has, of course, to consider the total population to be served and to assume that a heart clinic will be required not only for most of the children with heart disease or suspected heart disease in its immediate vicinity but also for many cases from farther afield. Among those coming from a distance there will tend to be fewer symptomless children and a higher proportion of lesions for which surgical treatment is currently practicable. There may also be fewer babies with very severe or inoperable lesions, as some of them will die before they are transferred.

The percentages of the various lesions among infants and children attending such heart clinics will therefore tend to differ a little from those found either in the registry or among schoolchildren. In Table VI the percentages published by Keith *et al.* (1958) and Nadas (1963) and those found in the patients seen in the heart clinic at the Royal Liverpool Children's Hospital since 1947 are compared with those of the Liverpool schoolchildren. The mean of these percentages differs from those of the schoolchildren in including, as one would expect, more cases of transposition of the great vessels, more of Fallot's tetrad, and fewer of pulmonary and aortic stenosis owing probably to a number of milder symptomless cases among the schoolchildren.

Similarly, in clinics which treat adults as well as children, the percentage and distribution of the various lesions will be slightly different. In any published series they will also be

weighted by those lesions for which surgical treatment was practicable and in demand during the periods reported. This is illustrated in Table VII, in which, by comparison with the mean of the children's clinics, series reported by Campbell (1957) and by Wood (1956) both show fewer ventricular septal defects and more atrial septal defects, while among Campbell's patients there was also a greater proportion of Fallot's tetrad.

Studies of the incidence of congenital heart disease may therefore be of use in planning diagnostic and therapeutic services.

Aetiology

The value of these studies in relation to the aetiology of malformations of the heart may, of course, ultimately be much greater, and it was in order to investigate the epidemiology of congenital malformations as a whole that Dr. Smithells started the registry in Liverpool. Such a registry may supply information of importance from observations on varying incidence from place to place, from time to time, from one social class to another, on varying maternal states such as age and illness, and perhaps on the sex of the child.

These studies are, naturally, more easily conducted in relation to malformations that are obvious at birth than to malformations of the heart; nevertheless it is an approach to the epidemiology of congenital heart disease that should not be neglected. With regard to the geographical distribution of a malformation, anencephaly is an obvious example of lesions that are easily recognized, and Dr. Smithells and his colleagues (1964) have already published their findings in relation to its incidence in Liverpool, and have shown that this is 3.2 per 1,000, which is half-way between the 0.12 per 1,000 in Lyons and the 6.7 per 1,000 in Belfast quoted by Penrose (1957). This is in accordance with Penrose's observation that the incidence increases as one travels through Europe from East to West. The geographical proximity of Liverpool and Belfast might indicate an environmental factor as responsible for Liverpool's relatively high incidence. On the other hand, the considerable proportion of Irish in Liverpool suggests the possibility of common genetic factors.

That the incidence of other malformations varies in different parts of the world has, of course, long been known. Anencephaly, spina bifida, hydrocephalus, talipes, and mongolism are commoner in Birmingham than in Japan, while cardiac malformations, cleft-lip and cleft-palate, and dislocation of the hip are more numerous in Japan than in Birmingham (McKeown and Record, 1960): for these differences, too, either environmental or genetic factors could presumably be responsible. In addition, there is the interesting phenomenon of the tendency of some malformations, such as oesophageal atresia, to "cluster" in time (Knox, 1959) and of others to cluster in space—for example, in one street in a town (Pleydell, 1960).

A study of the incidence of congenital heart disease might reveal equally interesting differences between one place and another. Data will be accumulating year by year in the Liverpool registry which, with the Birmingham figures, may profitably be compared with those being collected in registries in other countries, partly because the epidemiology of congenital malformations of the heart is now one of the joint projects being undertaken by members of the Association of European Paediatric Cardiologists.

Differences in incidence from time to time, with apparent epidemics of one malformation or another, are suggestive of factors which alter the uterine environment in such a way as to distort the normal growth pattern of one or more organs in the foetus, and in Liverpool the most obvious example of the value of the registry has been in relation to the easily diagnosed malformations ectromelia and microtia, and to the possibility that thalidomide taken by the mother during her pregnancy might have been the responsible factor.

TABLE VI.—Congenital Heart Lesions. Percentage of Each Lesion

	Heart Clinics in Children's Hospitals				School-children
	Keith <i>et al.</i> (1958), 1,866 Cases	Nadas (1963), 2,786 Cases	Hay <i>et al.</i> , 4,022 Cases	Mean	Hay <i>et al.</i>
Ventricular septal defect ..	25	20	27.6	24.2	28
Atrial septal defect group ..	11	14	12.2	12.4	15
Patent ductus arteriosus ..	17	12.5	14.9	14.8	14
Coarctation of aorta ..	6	5	3.9	4.9	2.5
Aortic stenosis ..	4	6	6.8	5.6	11.5
Pulmonary stenosis ..	7	12	12.7	10.5	17.5
Fallot's tetrad ..	11	14	7.7	10.9	4
Transposition of great vessels ..	8	4	4.4	5.4	0.5
Common truncus arteriosus ..	1	0	1	0.5	—
Tricuspid atresia ..	3	1	1.3	1.7	0.3
Others ..	7	11.5	7.5	8.6	6

TABLE VII.—Percentage of Congenital Heart Lesions in Heart Clinics

	Mean of Children's Clinics	Campbell (1957), 1,130 Cases	Wood (1956), 200 Cases
Ventricular septal defect ..	24	15	12.3
Atrial septal defect ..	12	16	20.5
Patent ductus arteriosus ..	15	15.5	15
Coarctation of aorta ..	5	8	9
Aortic stenosis ..	5.5	5	3
Pulmonary stenosis ..	10.5	15	16
Fallot's tetrad ..	11	15.5	12.7
Transposition of great vessels ..	5.5	2	1
Tricuspid atresia ..	2	1	1.5
Others ..	8.5	7	9

As a somewhat similar registry had been in operation in Birmingham for many years and many of these unfortunate babies were also being born there, the information from both registries was pooled by Leck of Birmingham and Smithells of Liverpool (Smithells and Leck, 1963). Seventy-one children with limb and ear defects of the type often caused by thalidomide were born to residents of Birmingham, Liverpool, and Bootle in 1960–2. It was found that the frequency of affected births rose to a peak in late 1961, nine months after the time when thalidomide output was highest, and that the incidence fell during 1962, being lower nine or more months after the withdrawal of thalidomide than in any other period since early 1960. There seemed to be no doubt that thalidomide was largely, if not entirely, responsible for the epidemic of these malformations.

In that investigation, information concerning the taking of thalidomide was of necessity largely retrospective, but when meclozine fell under suspicion the registry was used in a prospective study which provided no evidence that this drug is teratogenic (Smithells and Chinn, 1964).

Written evidence that a drug has been prescribed for a mother is obtained by reference to official prescription forms which are kept at a central office of the Ministry of Health in Liverpool, and it is presumably true to say that, with a computer and a staff large enough to go through innumerable prescription forms, it should be possible in time to check up very rapidly on the teratogenicity of any suspect drug which is being prescribed sufficiently freely in the Liverpool area.

It is clearly desirable that any agent with a teratogenic effect should be recognized without delay, and to this end all malformations notified are displayed in the Liverpool registry on a peg-board. The "epidemic" of ectromelia was noted by this means, but unfortunately its significance was not appreciated until Lenz (1961), of Hamburg, and McBride (1961), of Melbourne, published their work linking the malformation with thalidomide.

An "epidemic" of babies born with cardiac malformations was observed in the Liverpool district during 1962–3. There had been an epidemic of rubella approximately 9 months previously, but on cross-examination not one of the mothers of the affected babies admitted to such an infection. The babies are nevertheless now being examined for rubella antibodies.

The Ministry of Health has accepted the necessity of keeping a closer eye upon the occurrence of malformations, and has now made notification of these compulsory throughout the country. It is not expected, however, that notification on a national basis will be anywhere near complete, and it is not thought that this nation-wide scheme will render registries such as those of Birmingham and Liverpool redundant.

Another interesting investigation which is being carried out by means of the Liverpool registry is in relation to folic-acid deficiency during pregnancy predisposing to foetal malformations in general and of the nervous system in particular. Hibbard and Smithells (1965), of the Department of Obstetrics and Gynaecology in the University of Liverpool, have already shown in their preliminary findings that in the mothers of malformed babies the incidence of such defective folate metabolism is approximately five times the incidence in mothers of normal babies, a correlation which clearly merits further investigation.

The teratogenic effect of virus infections in the pregnant woman has, of course, now been investigated in many parts of the world. The early studies of Gregg (1941) and of Swan and his colleagues (1943) in Australia, which suggested a high incidence of malformations with infections in the first trimester, were inevitably retrospective, but a prospective study which was later organized by the Ministry of Health and General Register Office of the United Kingdom suggested a much lower incidence (Ministry of Health Report No. 101, 1960). However, in Switzerland, Klein (1960) found that 57% of embryos

obtained by therapeutic abortion following rubella in the first trimester had abnormalities in the eyes. The Ministry of Health study also revealed that the abortion rate and stillbirth rate in affected women were twice the normal—a timely reminder of these possible effects of malformations of important organs. Lamy and Frézal (1960) have pointed out that, whereas malformations probably occur in between 5 and 10% of all infants born after the 28th week of gestation, they have been found, according to Neel (1958), in 25% of all embryos; and Edith Potter (1960) reported that of 10,000 embryos she had examined over 75% were so affected.

In the Ministry of Health's large prospective study there was no clear evidence of any other virus infection harming the foetus, but mumps has been incriminated more frequently than any virus except rubella (Rhodes, 1960), and opinions vary with regard to influenza (Walker and McKee, 1959; Wilson *et al.*, 1959; Coffey and Jessop, 1963). It has now become possible to culture the rubella virus, and a recent epidemic of a severe form of rubella on the east coast of the United States has enabled the staffs of several of the medical schools to show that from most babies with malformations the virus can be cultured, and that generalized viraemia occurs in many of them (Korones *et al.*, 1965; Lindquist *et al.*, 1965; Plotkin *et al.*, 1965). At Johns Hopkins attention has been drawn to the fact that so far as the cardiovascular lesions are concerned the sixth aortic arch seems to be the most vulnerable part, whether the time of the maternal infection coincides with or precedes its period of most rapid development (Neill, 1965). Recently Landtman (1965) published his findings on the association between the seasons, the prevalence of infections, and the incidence of congenital heart disease in Finland.

In Liverpool, definite association between a virus infection and cardiac malformations has not been demonstrated, but retrospective investigation of the "epidemic" in 1962–3 is proceeding. Prospective studies of such associations will of course be carried out in future whenever possible.

Accurate recording of the familial incidence of cardiac malformations may also be of great value in demonstrating the part which genetic factors may play in their production, outstanding examples of this approach being Campbell and Polani's studies of 377 families containing children with all types of congenital heart disease (Polani and Campbell, 1955) and of the families of 151 patients with coarctation of the aorta (Campbell and Polani, 1961). A more recent study by Nora and Meyer (1966) of 517 families of children with all types of cardiac malformation yielded a higher incidence than previously recorded of siblings and parents with heart lesions (3.4% and 1.8% respectively) which the authors attribute to their attempt to examine every member of the family who accompanied a patient to their clinic.

These family studies and knowledge of the sex incidence may also point to the type of inheritance involved. Many authors have reported the sex distribution of the various lesions among children and young adults, but of greater value is the sex incidence at birth. From the figures published by MacMahon and his colleagues (1953) from Birmingham, and by Carlgren (1959) from Gothenburg, patency of the ductus arteriosus is commoner in girls, and all the other lesions with the exception of atrial septal defects tend to be a little commoner in boys.

The association of other malformations with those of the heart may also be helpful in pointing either to an abnormal intrauterine environmental state or to a genetic factor, when chromosomal abnormalities may be demonstrated. In Birmingham, MacMahon and his colleagues found associated abnormalities in 21% of 488 cases. In Liverpool it seems to be about 29%.

With all these and other possible aetiological factors in mind, Smithells (1965) has recently reviewed the Liverpool series of babies with cardiac malformations from 1960–3. He has found that they show no significant difference from his controls

in respect of seasonal distribution, sex, maternal ABO blood groups, maternal parity, fallow period, outcome of previous pregnancy, or toxæmia of pregnancy.

On the other hand they do show a highly significant increase in the incidence of hydramnios and of prenatal bleeding, and there is a statistically significant increase in maternal Rhesus negativity: this is most pronounced in babies with a complicated ventricular septal defect, coarctation of the aorta, or patent ductus arteriosus, but the individual groups are of course small. There is also a statistically significant increase in babies born of mothers aged 30 or more. This is probably accounted for by the number of mongols with a congenital heart lesion, such as common atrioventricular canal, which are three times as common in the mothers over 30 as they are in those under 30, whereas in the controls the ratio of the over 30s to the under 30s is the reverse—one to three. These findings from the Liverpool registry are of interest, and Dr. Smithell's observations will continue.

Similar registries in those centres capable of running them well might produce equally interesting information which could be of great value in the furtherance of our ultimate aim of prevention of malformations and would at least be a form of research which is harmless to our patients.

Summary

Previous attempts to estimate the incidence of congenital heart disease are reviewed. The Liverpool Malformations Registry is described and the difficulties inherent in this type of investigation are emphasized.

At the time of writing, notifications to the Liverpool registry have suggested a lower incidence than that recorded from some other centres, but the figure is likely to increase over the years as more cases come to light. Of the babies born in Liverpool during 1964 with a definite cardiac malformation, 40.7% died before the end of November 1965, 21.8% before they were 7 months old. The incidence of the various malformations diagnosed in the survivors differs from that found among Liverpool schoolchildren owing mainly to subsequent revision of the initial diagnosis. The high mortality rate during the first six months of life, despite the achievements of cardiac surgery, presents a challenge to our diagnostic and therapeutic services which demands serious attention. How this challenge may best be met is discussed. The value of the registry in throwing light upon the aetiology of malformations of the heart and of other organs is described.

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