PLACE OF MATERNAL RUBELLA IN THE AETIOLOGY OF CONGENITAL HEART DISEASE*

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In 1941 Gregg, of Australia, made the clinical observation that maternal rubella in early pregnancy was followed by congenital cataract and malformation of the heart. This discovery was important not only in itself but by stimulating a wide interest in the aetiology of congenital heart disease—a problem that had seemed to be without a clue to its solution. Swan and Tostevin, of Adelaide, with their colleagues added the production of deaf-mutism, and by a widespread inquiry in South Australia confirmed Gregg's observations and provided fuller information about their cases of congenital heart disease (Swan *et al.*, 1943). Evans (1944) added the production of anomalies of the incisors, defects of the dental enamel, and delayed eruption; at 4 years, however, the children have acquired a full complement of teeth. These defects and less commonly others—for example, microcephaly and mental defect—may occur alone or together.

Retrospectively, Lancaster (1951) pointed out that, at any time after Knibbs (1917) had recorded the erratic incidence of deaf-mutism among Australian children in his statistical reports, it would have been possible to incriminate some epidemic disease that affected prenatal life as one significant cause of deaf-mutism. Lancaster (1954) extended his inquiries to other countries that have included statistics about blindness and deaf-mutism since this was recommended at an international conference in 1872. The most pertinent findings were in Australia, New Zealand, and Iceland, and he thought that the relative isolation of many communities in these countries might account for the larger and therefore more noticeable epidemics at longer intervals. In Iceland, for example, he found that 10 deaf children were born in 1941, compared with an annual average of 1.2 in 1935–47, following 2,347 notified cases of rubella in 1940 and 1941 compared with 60 cases annually. And in Birmingham 9 deaf mutes were born in September and 12 in October, 1940, compared with a monthly average of under 2.5 for the previous ten years.

At first cataract seemed to be the most frequent malformation and deaf-mutism the least so, for Murphy (1947) found 161 examples of cataract, 117 of heart malformations, and 88 of deaf-mutism among 295 cases. But, of these three conditions, cataract is the least likely to be overlooked at an early age and deafness may not be recognized until the child is 4 years of age. Now that there has been time to get more accurate information, this order of frequency has been reversed,

and Julia Bell (1959) found 263 examples of deafness, 210 of heart malformation, and 149 of cataract among 421 cases.

The mechanism by which these malformations are produced is of great interest. The virus of rubella circulates in the maternal blood during the incubation period and for a short time after, and passes through the chorionic epithelium to the blood-stream of the foetus. Tondury (1953) examined 10 human embryos from mothers who had been attacked by rubella between the fifth and seventh weeks of pregnancy, and found that the virus had a strikingly selective action on the heart and on three epidermal structures of the foetus. In these last three the respective cells are severely damaged, becoming swollen and vacuolated and sometimes destroyed, producing a central cataract (most often bilateral), deafness from damage to the internal ear and the cochlea (less often bilateral), and defects of the dental enamel. Although Tondury found malformations of the heart in 5 of the 10 embryos, he found less evidence of how these were produced.

In this paper I shall try to answer four questions. (1) What is the risk to the child after maternal rubella during pregnancy? (2) When the heart is affected, what malformations are most common? (3) Looking at congenital heart disease as a whole, what proportion is due to maternal rubella? (4) How important are any other infections—viral or bacterial?

1. Increased Risk of Having Children with Malformations

The risk of having a malformed child for the mother with rubella during the early weeks of her pregnancy is of great practical importance. It has given rise to wide differences of opinion that are not yet resolved, though it became clear at an early stage that the risk was greatest in the first 12 weeks. It is generally agreed that the risk is mainly confined to this period, that there is some much smaller risk during the 13th to 16th weeks, and that after this there is no more risk than normally. It is the magnitude of the risk that is still uncertain. Some early estimates of 70 to 90% have been suspected because the authors were more likely to know about the infection when the child was malformed than when it was normal. Prospective rather than retrospective studies are essential for a true picture.

One of the best of these prospective inquiries is that by Hill *et al.* (1958) with the methods that Hill and Galloway (1949) had suggested earlier and used on a smaller scale. They found that the risk of a malformed

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child if the mother had rubella during the first four weeks of her pregnancy was 50%, during the second four weeks 25%, during the third four weeks 17%, during the fourth four weeks 11%, and after this negligible.

Lamy and Seror (1956), in another excellent prospective inquiry, found a higher risk of 50% (70% if abortions were included) during the first 12 weeks. They did not give separate figures for each of the first four months, but it appears from their table that the risk was 100% during the first month (when for some unexplained reason there were less than half the expected number of mothers affected); 55% (82% with abortions) during the second month; and 37% (47% with abortions) during the third and fourth months, combined because the percentage during the fourth month in a rather small number of cases was higher than during the third month.

Lundström (1952), in an inquiry covering 1,067 women in the maternity hospitals in Sweden, found that the number of children with malformations was 10% in the first four weeks, 14% in the second four weeks, and 10% in the third four weeks, but it seems likely that this included only those malformations that were readily diagnosed at an early stage.

Ministry of Health Report

Since this address was delivered, a valuable report from the Ministry of Health has been published (Manson *et al.*, 1960). It deals mainly with the degree of risk for the mother who has rubella, or other virus infections (see below), during the relevant pregnancy, but does not attempt any diagnosis of the types of congenital heart disease concerned. It deals with nearly all the pregnancies in England and Scotland during 1950-2 and gives a more optimistic picture than the first two inquiries discussed.

The percentages of abortions and stillbirths and of deaths during the first two years of life were twice as high among those where there had been rubella during the first 12 weeks of the pregnancy as among the controls (Table I); after two years there were only 84% instead of 93% of living children. If, however, rubella occurred after the first 12 weeks of pregnancy there was no difference in these figures. Among the stillbirths after the "rubella" pregnancies there were

TABLE I.—*Abortions, Stillbirths, Neonatal Deaths, and Malformations after Maternal Rubella and in Controls*

	Abor- tions	Still- births	Deaths before 2 years	Children Alive at 2 years	With Major Malfor- mations
Maternal rubella in first 12 weeks	5.0%	4.5%	6.9%	83.6%	15.8%
Controls	2.4%	2.4%	2.4%	92.8%	2.3%

From Manson *et al.* (1960).

slightly more major malformations. Among the children dying during their first two years, major malformations were found in 46% compared with 34% of the controls; malformations are now an important cause of neonatal deaths in nearly all groups.

Among the 547 children who were born alive after maternal rubella, 37 (7%) had "major" congenital malformations compared with 2.3% among the controls: the number with malformations was increased to 15.8% in those where the maternal rubella occurred during the first 12 weeks. The numbers for

each of the four weeks of the first trimester did not vary greatly—15.6% for the first four, 19.7% for the second four, and 13.0% for the third four weeks. In the fourth four weeks (13th to 16th) the number of malformations was much less (4.2%) but was still increased compared with 2.3% among the controls, and at later stages of the pregnancy maternal rubella was without any significant effect.

Congenital heart disease (7%) was 14 times as common as among the controls, cataract (5.5%) was 78 times as common, and deafness (2.7%) was nearly 40 times as common; in fact, the last was even commoner than this, for more cases were discovered when the children were re-examined at the age of 4 years. These malformations, either alone or in combination, were as usual the most common, but there were three cases each of mental defect, oesophageal atresia, and pyloric stenosis—that is, four times, six times, and three times as common as among the controls.

The percentages quoted are, in my view, minimal figures—for two reasons. Apart from the 37 "major" defects there were 18 with "suspicious" defects, mainly heart murmurs or backwardness in development or speech. Secondly, deafness often went undetected at the age of 2 years, when the main examinations were made, and was revealed when they were re-examined at 4 years of age; so that its incidence was increased from under 3 to 14%, and even to 35% in a smaller group of 57 children examined fully by Jackson and Fisch (1958). For these reasons the percentages for the incidence of major malformations should be increased by about half, from 15.8 to 24%, and these additions have been made, in parentheses, in the fifth column of Table II: it is still a minimal figure, though it will include all those with the major degrees of deafness.

Comparison of These Series

The results obtained in these three series are summarized in Table II. I have added the cases

TABLE II.—*Incidence of Malformations According to Period of Maternal Rubella*

Weeks of Pregnancy	No. of Reported Cases (Bell, 1959)	Percentage of Births with Malformations in Prospective Studies			
		Lamy and Seror (1956)	Hill <i>et al.</i> (1958)	Manson <i>et al.</i> (1960)	General Estimate (M.C.)
1st to 4th	103	100	50	16 (+8)*	30-70
5th " 8th	175	55	25	20 (+10)	25-55
9th " 12th	100	37 {	17	13 (+7)	20-40
13th " 16th	25		11	4 (+2)	10-25
Later	14		0	0	0
1st to 12th Controls	— —	50 2.7	31	16 (+8) 2.3	25-50

* See text for explanation of the added figures in parentheses.

reported by Julia Bell (1959); though these give no information about the absolute degree of risk, they help with the relative risks during the different periods. Bell found 103 in the first four weeks, 175 in the second four weeks, 100 in the third four weeks, only 25 in the fourth four weeks, and 14 subsequently, but many or all of these 14 may have been only coincidences.

When the methods used and the care taken in these three series are considered it is surprising to find so much difference between the results, for there does not seem to be any technical reason for this. The series of Lamy and Seror and of Hill *et al.* are smaller than that of Manson *et al.* (50, 68, and 277 cases of maternal rubella during the first four months

respectively) but have the advantage of a more uniform assessment of the malformations. Possibly they have included more minor malformations, but, apart from the incidence being higher in these first two, it diminishes greatly during the first three four-week periods—to about half during the second four weeks and to about a third during the third four weeks—while in the series of Manson *et al.* it does not change much until the fourth month (see Table II).

The most obvious difference is that Lamy and Seror collected their cases during a local epidemic round Paris in 1953–4, and a relatively large number of adults must have been affected, for in the women written to during their pregnancy the incidence of rubella was between 0.5 and 1 per 1,000. This suggests that in some particular epidemics more women may be affected and more children with malformations may be born, as I suspect was the case in the epidemic of 1940 (see below).

Can malformations arise when the mother is exposed to rubella without an overt attack? Coffey and Jessop (1959), in a Dublin epidemic, found an incidence of malformations of 3% among the exposed mothers—some increase, but much less than the 30%, among the affected mothers. Lamy and Seror, however, found no increase of malformations among the exposed mothers, but there were more abortions. Probably a mother who is herself immune to any overt manifestations of rubella may acquire the infection enough to risk damaging the foetus. Certainly malformations may follow very mild infections, and do so as often or nearly as often as after severe infections.

The different malformations may be greater risks at different periods (Bourquin, 1948; Bamatter, 1949; and others). Cataract is thought to be most common with infection during the fifth and sixth weeks but may be as early as the third week; malformations of the heart especially from the fifth to ninth weeks; and deafness especially during the eighth to twelfth weeks. Jackson and Fisch (1958) found as many as 55% affected with deafness between the ninth and twelfth weeks, inclusive, when the children were carefully examined and followed up to the age of 4 years, but this was much higher than the figure for the larger number found by Manson *et al.* (1960) for the same period.

It seems, therefore, that the risk of a malformation lies somewhere within a rather wide range—between 30 and 70% during the first four weeks, 25 and 55% during the second four weeks, 20 and 40% during the third four weeks, and 10 and 25% during the fourth four weeks (see Table II and Fig.). These figures may be increased by another four-tenths if abortions are

The very small normal risk of bearing a malformed child (about 2.5%) is shown by the dotted line. The much greater risk of a malformed child after maternal rubella during the first 16 weeks of pregnancy is within the shaded area but is not known exactly.

included. Possibly the lower figures are generally more accurate and the higher figures are found in particular epidemics. The problem of a therapeutic abortion, therefore, remains a difficult one for the doctor during the first three months of pregnancy and must be settled according to individual circumstances. After the third month the question does not arise.

The 1940 Epidemic

The first cases of this "rubella syndrome" described in Australia all followed maternal rubella in the epidemic of 1940. In my own four cases of Fallot's tetralogy following maternal rubella, seen in 1947–9, I was interested to find that two of them were born towards the end of 1940 as the result of the same epidemic (PO37 born on October 18 and PO45 on October 13). In London this epidemic was of high virulence and unusually prone to attack adults—a fact of which I have personal memory because of the difficulty in finding accommodation for the nurses and soldiers with rubella who were admitted to the war hospital where I was working. Even more striking, Stuckey (1956) found that 16 of his 27 patients had been born in 1940. He was able to calculate that the incidence of persistent ductus in children born to mothers who had suffered from rubella during pregnancy in New South Wales during 1940 was 88 times as high as normal, and the incidence of several other heart malformations about 11 times as high.

In my opinion, the rubella epidemic of 1940 in Australia and in England, and probably elsewhere, was unusually potent in producing these cardiac and other malformations. Since then the danger of maternal rubella producing these malformations seems to have been less generally, but perhaps not in some epidemics, though its effects could have been lessened by therapeutic abortions.

2. Types of Congenital Heart Disease

This paper is concerned mainly with the cardiac malformations. Bell (1959) found these to occur alone in 50 cases, with cataract in 78, with deafness in 52, and with deafness and cataract in 30. Cataract alone was uncommon (7%) and deafness alone very common (40%), deafness and cataract combined without a defect of the heart being the least common of all groups (3%). This can be explained because cataract is most likely to follow early infection and deafness late infection, and malformations of the heart in between. Heart malformations alone or in combination occupy an intermediate position as regards frequency—alone (12%), with cataract (19%), with deafness (12%), and with deafness and cataract (7%): they are therefore present in half the cases. Those with combined defects are probably reported more often, and I think heart malformations occur alone more often than these figures would suggest.

Relatively few of the series have been reported by cardiologists, and often the diagnosis is of congenital heart disease without any details, so that we have less information about the types that occur most frequently. From the beginning (Gregg, 1941; Swan *et al.*, 1943) persistent ductus arteriosus was prominent among them and cyanotic heart disease was much less common. Gibson and Lewis (1952) could find little information about the types of heart malformation, but had 17 examples among their patients—11 with persistent

ductus alone, 3 with this and some other malformation, and only 3 with any other cardiac malformation alone. Stuckey (1956) also, both in his own cases and in the reported cases that he collected, found that persistent ductus was much the most frequent, and this is also the case in the series of Julia Bell (1959, and personal communication).

The malformations found in these two series and a few other cases that I have collected are shown in Table III. There were 136 cases with 153 cardiac malformations, as 17 had two. Persistent ductus was much the most common malformation, being the only one present in more than half the cases (74 out of the 136 and another 15 where it was combined with a second cardiac defect—that is, 58% of the 153 malformations). Ventricular septal defect (17+10 cases) was the only other condition that occurred in as many as one-tenth of the cases (nearly 18%). Fallot's tetralogy (11 cases, 7%), atrial septal defect (10 cases, 6.6%), and pulmonary valvular stenosis (9 cases, 6%) were the next most frequent malformations.

TABLE III.—Types of Congenital Heart Disease after Maternal Rubella

	Alone	With P.D.A.	With V.S.D.	With P.V.S.	With Other	Total	Percentage
P.D.A.	74	—	9	4	2	89	58.1
V.S.D.	17	9	—	1	0	27	17.6
A.S.D.	9	0	0	0	1	10	6.6
P.V.S.	4	4	1	—	0	9	5.9
Fallot	10	0	0	0	1	11	7.2
Other*	5	2	0	0	0	7	4.6
Total	119	15	10	5	4	153	100.0

* Coarctation 4 (2 with P.D.A.); aortic stenosis 1; transposition 1; tricuspid atresia 1.

17 cases are included twice, as they had two malformations.

It is particularly striking that the combination of persistent ductus and ventricular septal defect should have occurred in 9 cases (6%)—nearly as often as any malformation except these two separately—for in general it is not a very common association. This relative distribution of the different forms of congenital heart disease is totally unlike anything that is found elsewhere, and helps to justify the use of such a term as the "rubella syndrome."

3. Proportion of Cases of Congenital Heart Disease Due to Maternal Rubella

No one has claimed that maternal rubella is responsible for a very large proportion of cases of congenital heart disease. Three of the highest estimates I have seen are the following: Conte *et al.* (1945) found an incidence of 4%; Mouquin *et al.* (1956) thought it might be as high as 6% but that there were genetic causes for the great majority of cases; and Keith *et al.* (1958) found 8 examples in 100 cases of persistent ductus. It may appear that Stuckey (1956) found an incidence of 10%, for there were 44 examples among 426 cases of congenital heart disease; but 21 of these had been referred specially because of the history of maternal rubella and 17 of the 44 had innocent systolic murmurs only: the percentage therefore cannot have been more than 5.4, and more likely was only 3.3 if the innocent murmurs were distributed at random.

Most estimates are much lower than these. Gibson and Lewis (1952) thought that maternal rubella was the cause in 1.2% of 1,366 patients. Lamy *et al.* (1957) also found an incidence of 1.2% of 1,200 cases of congenital heart disease, and it was highest among cases of

persistent ductus (3.7%). My own experience is that maternal rubella is responsible for less than 2% of the cases.

Among 250 children with Fallot's tetralogy there were 4 (1.6%) with a history of maternal rubella. Though the percentage for Fallot's tetralogy was low, it might be much higher for persistent ductus, considering the pre-eminence of this in most series. Though Keith's 8 examples in 100 cases have been mentioned, our experience does not support this. Among 261 patients with a persistent ductus, where we made detailed inquiries about the families and the other malformations, there were only 5 examples (1.9%) (Polani and Campbell, 1960).

The relatively low incidence in 500 cases made us less thorough in trying to get a history of maternal rubella subsequently; and in the questionnaires sent out to get fuller details about the families of our patients no specific question about this was asked. We have only three positive histories of maternal rubella in 151 patients with coarctation, 36 with tricuspid atresia, and 126 with simple pulmonary stenosis, and none in 156 patients with atrial septal defect and 71 with ventricular septal defect.

The estimates of various workers vary between 1.2 and 6 or even 8%, but we think it most unlikely that it is more than 3 or 4% at the most. At the recent International Congress on Congenital Malformations in London (July, 1960) the view was expressed that less than 10% of *all* congenital malformations were caused by maternal rubella and *all* viral infections.

4. Importance of Other Viral Infections

The discovery of the role of maternal rubella in causing congenital malformations was important not only in itself but because it suggested that some other infections might be equally important. If so, these infections are elusive, for they have been searched for by many workers, without any of them being able to produce convincing evidence or indeed much more than isolated cases. Grönvall and Selander (1948) thought one of their cases was due to maternal mumps; Landtman (1948) thought one was due to maternal influenza; and I have seen three where a viral disease seemed the probable cause (one due to maternal measles, one to maternal herpes zoster, and one to maternal vaccination during pregnancy). No one, however, has produced a striking series of cases, though it did not take long for Gregg's observations about maternal rubella to be confirmed in most parts of the world. It is possible that these isolated cases are no more than chance findings.

The work of Tondury (1953) is more decisive in proving the possibility. Examining the lenses of four foetuses whose mothers had been attacked by viral diseases in the early months of their pregnancies—one by epidemic parotitis, one by epidemic hepatitis, and two by poliomyelitis—he found changes similar to but not identical with those he had found after maternal rubella. Later, examining more foetuses after maternal poliomyelitis, he found necrosis and vacuolation in the cells of the brain and of the spinal cord. The disease had, of course, caused an abortion in these cases, but lesser changes could probably cause malformations in foetuses that were able to survive.

Among the carefully planned prospective studies on this aspect Hill *et al.* (1958) found no evidence that

maternal measles, mumps, or chicken-pox had any deleterious effect on the children, except that after chicken-pox an unusual number had a light birth-weight: they did not exclude the possibility that the number of abortions might have been increased by these infections.

The inquiry of Manson *et al.* about the effects of maternal rubella covered also 103 pregnancies where the mother had measles, 298 where she had chicken-pox, 501 where she had mumps, and 166 where she had virus influenza during the epidemic of 1950-1. Measles, even during the first 12 weeks of the pregnancy, had little effect on the number of abortions or stillbirths, but the number of infants dying during the first two years was more than six times as great as in the controls when the measles was in the first trimester. The proportion of dead infants with malformations was higher also—50% instead of 34%—but this was not enough to account for all the excess mortality. The result was that for maternal measles during the first trimester the proportion of children still living at the age of 2 years was only 78% instead of 93%.

Of the children born alive 7% had major malformations compared with 2.3% in the controls, and this effect was not limited to the first trimester. The malformations were very variable—of the brain twice, of the heart twice, and once each of congenital dislocation of the hips, pyloric stenosis, and neoplasm. The mother's measles was in the 35th week of the pregnancy in the case of the child with C.D.H., corneal opacities, and severe talipes. Admittedly the numbers are small and might be due to chance, but the increased death rate in infancy after measles during the first trimester and the increased number of malformations after measles at any stage of pregnancy cannot be dismissed without further inquiries.

There was no evidence that *chicken-pox*, *mumps*, or *influenza* during any stage of pregnancy had any effect on the number of abortions or stillbirths or on the infant mortality or number of malformations.

The proportion of infants born after maternal rubella in the first trimester with a *low birth-weight* of $5\frac{1}{2}$ lb. (2.5 kg.) or less (17.7%) was four times as large as among the controls (4.3%), and this excluded the children who were premature—that is, delivered before the 36th week. Half the children who died after maternal rubella or measles weighed $5\frac{1}{2}$ lb. (2.5 kg.) or less, but only 4 out of 20 who died after maternal mumps or chicken-pox.

There were only 33 pregnancies complicated by maternal *poliomyelitis*—too few for statistical treatment. However, in the six pregnancies where the mother had *poliomyelitis* between the 9th and 12th weeks there were one abortion, two stillbirths, and one child who died at 7 days from hydrocephaly and spina bifida; there were only two children who lived longer than this.

Apart from these two important papers I have not found much statistical evidence about viral infections other than rubella. According to Rhodes (1960), there is good evidence that vaccinia has no effect in producing malformations in the foetus. Influenza as a cause of such malformations is supported by some Dublin statistics but denied by most American ones; and an investigation from Finland found that mumps might sometimes be important as a cause of congenital malformations.

Other Infections and Disturbances During Pregnancy

Lamy *et al.* (1957) found a history of some infection during early pregnancy in 5.5% of the mothers of children with congenital heart disease compared with 2.4% among their controls. Among the mothers of 250 of my children with morbus caeruleus (mostly Fallot's tetralogy) there were 24 who gave a history of some illness or disturbance during the first three months of the relevant pregnancy—4 of rubella, 14 of other illnesses, and 6 of threatened abortion (Campbell, 1949); the other illnesses included pneumonia and one example each of shingles (the only certain viral disease) and whooping-cough. Among 126 of my patients with pulmonary valvular stenosis there was a history of severe maternal measles in one (third month), of a severe electric shock in one (second month), of heavy bombing and anxiety in two (first and second months), of corpus luteum injections during the second and third months because of two previous miscarriages in one, and of very severe vomiting and of exceptional anxiety, both these throughout most of the pregnancy. It is difficult to assess the significance—if any—of these histories, but it would seem worth carrying out an inquiry on a large scale where the decision about the inclusion of reported accidents and infections was taken during the pregnancy, before it was known if the child was normal or malformed.

Malformations in General

To turn to this wider field, Pleydell (1960) thought that in Northamptonshire there was a connexion between maternal infections early in pregnancy and the births of children with anencephaly and other congenital malformations, including heart disease. His evidence was perhaps not conclusive, but it was sufficient to make further inquiries well worth while. There is some evidence from Scotland and from Dublin that Asian influenza in the first trimester may increase the incidence of anencephaly by 25%. Threefold variations in the incidence of some malformations from month to month in some statistics have suggested the importance of infections.

Diseases of animals caused by viruses are common, but so far few attempts have been made to discover if any of them are responsible for malformations. Vaccines against hog-cholera virus and the blue-tongue virus have, however, caused malformations among the offspring (Rhodes, 1960), so that care may need to be taken about using poliomyelitis vaccine during a pregnancy.

That other viral infections as well as rubella can cause some congenital malformations seems to be established. It is most unlikely that they cause any substantial amount of congenital heart disease. Further prospective investigations covering measles and even minor infections do, however, seem worth while making.

Summary and Conclusions

The risk of abortion and of malformations in the child after maternal rubella during the first 12 weeks of pregnancy is considerable, though it must still be expressed as lying between wide limits. It is between 30 and 70% during the first four weeks, between 25 and 55% during the second four weeks, between 20 and 40% during the third four weeks, and between 10 and 25% during the fourth four weeks; later than this there is no increased risk. Perhaps the lower figures are

nearer the true risk generally and the higher ones apply to particular epidemics.

Deafness is the greatest risk, then congenital heart disease, and then cataract: mental defect and microcephaly and several other malformations are lesser risks. All these may occur alone or quite often in combinations. Of the heart malformations persistent ductus is much the most common (58%); then comes ventricular septal defect (18%). In about 6% of these the two defects are combined, and in ordinary practice this is not a very common finding. Atrial septal defect, pulmonary valvular stenosis, and Fallot's tetralogy each occur in about 6% of cases. This distribution is quite unlike anything found under other conditions.

Numerically, maternal rubella during pregnancy is not one of the major causes of congenital heart disease, though it is one of the best-proved causes. It is responsible for something between 2 and 4% of all cases. At the Congress on Congenital Malformations in London in July, 1960, the proportion of *all these* caused by maternal rubella and *all other viral infections* was thought to be less than 10%.

Other viral infections, including mumps, measles, epidemic hepatitis, and poliomyelitis, can produce similar malformations. It seems unlikely that they often do so, though measles and even any minor infections during pregnancy need further investigation.

I am most grateful to Dr. Julia Bell for letting me have the details of the type of congenital heart disease in the reported cases she had collected.

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ENDOCARDIAL CUSHION DEFECTS

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The surgical implications involved in misdiagnosing an endocardial cushion defect as a simple patency of an ostium secundum may be very serious. This is because the former cannot always be corrected satisfactorily without the application of an extracorporeal circulation, whereas an ostium secundum can usually be closed in a shorter time with moderate hypothermia or by the use of an atrial well. It is therefore of great importance to be able to differentiate these two types of lesion with reasonable certainty pre-operatively, so that the surgeon may be enabled to select the appropriate technical methods to achieve repair with an open heart.

It is easy to make this differentiation in most cases on clinical and other grounds. However, there is a type of large ostium secundum, in which the lower margin of the defect may reach to within a few millimetres of the endocardial cushion area, which so closely resembles an endocardial cushion defect in all characteristics that we believe it to be virtually indistinguishable from the latter before cardiectomy. We have also encountered an endocardial cushion defect in which all the evidence pointed to a large ventricular septal defect with pulmonary hypertension. We think it will be useful to describe our experience with 10 proved cases of endocardial cushion defect and to compare them with the two cases of large ostium secundum which we incorrectly diagnosed as endocardial cushion defects before operation.

Our cases have all been seen in infancy or early childhood and have been fully investigated, with the exception of one infant who died at 2 months before cardiac catheterization was performed. The diagnosis in all has been verified by visual inspection at operation or necropsy.

Nature of the Endocardial Cushion Defect

The embryological failure which gives rise to the varying degrees of endocardial cushion defect is well known, and excellent descriptions are given by Kramer (1942), Wakai and Edwards (1956), and Campbell and Missen (1957). It is clear that failure of normal fusion of the dorsal and ventral endocardial cushions of the primitive atrio-ventricular canal can lead to a spectrum of lesions extending from persistence of the ostium primum with deformity of the atrio-ventricular valve cusps to the complete anomaly in which, the cushions having failed to approximate, there is a persistency of the atrio-ventricular canal with a functionally unilocular heart. Numerous variations of the complex have been described, and a review of these is given by Kiely *et al.* (1958) together with a tabulation of 14 possible combinations of the defects comprising the syndrome.

Ostium primum patency without atrio-ventricular valve deformity appears to be exceedingly rare, if it ever occurs. Wakai and Edwards (1958), in a recent review of 100 cases of endocardial cushion defect, could