Vascular Lesions in Infants with Congenital Rubella

By John R. Esterly, M.D., and Ella H. Oppenheimer, M.D.

SUMMARY
Vascular lesions were reviewed in 13 autopsied infants with congenital defects of maternal rubella. The characteristic finding was intimal fibromuscular proliferation. The internal elastic lamella and media were almost always unchanged, even in the presence of a greatly thickened intima. These arterial changes appeared to be unlike other vascular lesions described in infancy.

Severe and extensive lesions were found in four infants, and lesser changes in another five. The lesions in the pulmonary artery were probably related to clinically diagnosed peripheral pulmonary artery stenosis. Ostial stenosis of a renal artery was found in an infant with documented systemic hypertension.

Additional Indexing Words:
Fibromuscular dysplasia
Congenital heart disease

Renal artery stenosis
Pulmonary artery stenosis

The association of congenital defects and maternal rubella was first described by Gregg in 1941. Subsequent studies have confirmed the association, and abnormalities of nearly every organ system have been described following the 1964 rubella epidemic in the United States. Patent ductus arteriosus has been considered the most common cardiac malformation; but Rowe emphasized the frequency and importance of pulmonary artery stenosis. In spite of the frequency of cardiovascular disease in the congenital defects of rubella, detailed examination of the vascular system has been limited to isolated case reports.

The present study reviews the vascular changes in a group of autopsied infants with congenital defects due to maternal rubella and attempts to compare the findings to other vascular lesions seen in infancy.

Cases Studied
Autopsies on 13 infants with congenital defects of maternal rubella were available for study. Eleven of the infants were members of the Johns Hopkins Rubella Study. Virological and serological studies were carried out in the Perinatal Research Laboratory, NINDB, under the direction of Dr. John L. Sever, by methods already described. The results of specific diagnostic tests are summarized in table 1. Two additional cases (cases 12 and 13), both stillborn infants of mothers giving a history of exposure to rubella, autopsied prior to 1964, are also included. Multiple cardiac and genitourinary malformations were present in case 13.

The gross descriptions and the available gross and microscopic material from these cases were reviewed. Sections from vascular lesions were stained by the Verhoeff-van Gieson and Masson procedures, and step-sections were cut from several blocks that showed equivocal alterations.

Sections of the placenta from 23 additional premature stillborn and surviving liveborn infants with confirmed congenital rubella were examined.

Observations
Diffuse proliferation of the arterial intima was the most characteristic lesion in these

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Table 1

Summary of Specific Laboratory Findings

<table>
<thead>
<tr>
<th>Case</th>
<th>H/O maternal rubella (wk gest)</th>
<th>Birth weight (g)</th>
<th>Maternal sero-conv.</th>
<th>Antibody child 4-12 mo</th>
<th>Rubella virus isolation</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>520</td>
<td>Neut., HI</td>
<td>NE</td>
<td>NE</td>
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<td>2</td>
<td>7</td>
<td>440</td>
<td>Neut., HI</td>
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<td>4</td>
<td>0</td>
<td></td>
<td>HI</td>
<td>Neut., surviving twin at 1 yr</td>
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<tr>
<td>5</td>
<td>2</td>
<td>1790</td>
<td>NE</td>
<td>NE</td>
<td>+</td>
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<tr>
<td>6</td>
<td>Preconcept.</td>
<td>2510</td>
<td>CF</td>
<td>NE</td>
<td>+</td>
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<tr>
<td>7</td>
<td>7-8</td>
<td>2090</td>
<td>NE</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>3195</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>2550</td>
<td>NE</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>2660</td>
<td>NE</td>
<td>Neut. +, HI 16</td>
<td>Neg at 6 mo</td>
</tr>
<tr>
<td>11</td>
<td>At concept.</td>
<td>2350</td>
<td>CF, Neut., HI</td>
<td>CF 8 mo, neut. + at 7 mo</td>
<td>Neg at 7 mo</td>
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Specific diagnosis studies

<table>
<thead>
<tr>
<th></th>
<th>Throat</th>
<th>Urine</th>
<th>Other</th>
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<tbody>
<tr>
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<td>NE</td>
<td>NE</td>
</tr>
<tr>
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<td>NE</td>
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<td>NE</td>
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<tr>
<td>11</td>
<td>NE</td>
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</table>

Abbreviations: CF = complement fixation; HI = hemagglutination inhibition; NE = not evaluated; neut. = neutralizing antibodies; + = positive.

cases. The alteration was barely perceptible in some vessels, and definite intimal thickening could be recognized only with staining of the internal elastica. At other sites the intima was more than twice as thick as the remaining arterial wall (fig. 1). Nevertheless, it was difficult to recognize the lesions in the gross specimens except in areas of focal alteration such as arterial ostia. The pertinent pathological findings in the 13 cases examined are summarized in table 2.

The thickened arterial intima was composed of parallel fibers, and like the media stained for collagen and smooth muscle. The internal elastic lamella and media were usually intact. Only minimal elastic tissue was seen in the thickened areas and, when present, was in the form of short irregular fibrils adjacent to the internal elastica. Except in the most severe lesions, the vessel lumen was not significantly narrowed. The majority of lesions were found in large caliber vessels, in both the pulmonary and systemic circulations. Lesions in small arteries, though less
### Table 2

**Arterial Lesions in Infants with Congenital Rubella**

<table>
<thead>
<tr>
<th>Case &amp; autopsy no.</th>
<th>Age</th>
<th>Pulmonary arteries</th>
<th>Aorta</th>
<th>Other arteries</th>
<th>Other findings</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Major</td>
<td>Segmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 33190</td>
<td>26-wk fetus</td>
<td>0</td>
<td>0</td>
<td>At 2 intercostal ostia +</td>
<td>0</td>
</tr>
<tr>
<td>2 33191</td>
<td>26-wk fetus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 33205</td>
<td>28-wk fetus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 33328</td>
<td>15 day</td>
<td>0</td>
<td>+ Recent saddle embolus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 33579</td>
<td>31 day</td>
<td>R +</td>
<td>R +</td>
<td>Abdominal</td>
<td>R iliac ++ (dilated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L +</td>
<td>L +</td>
<td>+</td>
<td>L iliac +</td>
</tr>
<tr>
<td>6 33711</td>
<td>7 wk</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Segmental renals ++</td>
</tr>
<tr>
<td>7 33665</td>
<td>3 mo</td>
<td>R +++</td>
<td>R + (dilated)</td>
<td>0</td>
<td>Segmental renals ++</td>
</tr>
<tr>
<td>8 $$P66-383</td>
<td>5 mo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>R coronary +</td>
</tr>
<tr>
<td>9 33848</td>
<td>6 mo</td>
<td>Main +++</td>
<td>R ++</td>
<td>Entire</td>
<td>R renal +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R +++</td>
<td>L ++</td>
<td>++</td>
<td>L renal +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L ++</td>
<td>Muscular branches +</td>
<td>++++</td>
<td>Segmental renals ++</td>
</tr>
<tr>
<td>10 34708</td>
<td>6 mo</td>
<td>0</td>
<td>Organizing emboli</td>
<td>0</td>
<td>Segmental renals +</td>
</tr>
<tr>
<td>Case</td>
<td>Age</td>
<td>Birth</td>
<td>Other Conditions</td>
<td>Lesions</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>13 mo</td>
<td>0</td>
<td>Third degree burns; <em>Pseudomonas</em> septicemia; H/O hypertension, 150/90 mm Hg; mental retardation; possible peripheral pulmonic stenosis.</td>
<td>VSD; rectal atresia; agenesis of kidneys</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>35 wk</td>
<td>SB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>SB</td>
<td>0</td>
<td></td>
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</table>

Abbreviations: PDA = patent ductus arteriosus; PFO = patent foramen ovale; SB = stillborn; VSD = ventricular septal defect; + to ++++ = degree of severity.
in the pulmonary vessels could not be identified in these cases at the time of autopsy.

The aorta or the major elastic arteries, or both, were involved in eight infants. The most extensive changes were present in case 9. The entire length of the aorta was thickened (fig. 1), and fibromuscular proliferation extended into the thoracic great vessels and beyond the bifurcation in the iliac arteries. Extensive intimal proliferation was also seen in several muscular arteries derived from the iliacs (fig. 6). Less severe lesions were present in the segmental renal artery of both kidneys. In case 5, the thoracic aorta was normal, but there was minimal intimal proliferation in the distal part of the abdominal aorta with severe changes in both common iliacs (fig. 2). Multiple focal lesions were also present in the renal, prostatic, and mesenteric arteries.

The aorta was also affected in case 1. The intima showed focal areas of proliferation, and the ostia of several intercostal arteries were stenotic (fig. 7). The stillborn twin (case 2) showed no lesions.

Stenosis of the right renal ostium was identified in the gross specimen in case 11. Sections of this area showed intimal fibromuscular proliferation (fig. 8). This lesion was of particular interest because hypertension (150/90 mm Hg) was documented during life.
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The intrarenal arteries showed small focal intimal plaques.

Focal lesions of segmental pelvic branches of renal arteries were present in three additional cases. They were multiple and extensive in case 7, moderately severe in case 6 (fig. 9), but only minimal in case 10. No lesions were seen in the interlobar or smaller intrarenal branches in these cases. Blood pressures were not elevated in these infants.

Coronary artery lesions were seen in three cases. In case 9, changes were present in branches of both right and left arteries, and on the right there was fragmentation of medial elastic fibers, and stenosis with myocardial fibrosis (fig. 3). The lesions in the right coronary of case 11 were associated with minimal myocardial fibrosis (fig. 10). The changes in both coronaries of case 8 were not associated with myocardial injury.

No vascular lesions were found in the two stillborn infants that were autopsied prior to 1964. The placentas of infants with congenital rubella showed no specific lesions, but an area of diffuse intimal proliferation identical to that seen in the autopsied cases was found in a single umbilical artery.

Comment

The findings in the present series of infants confirm and extend the previous descriptions of vascular lesions in the rubella syndrome. Shortly after Gregg’s report, Swan\textsuperscript{12} examined the patent ductus arteriosus in three infants with a history of maternal rubella. He found the internal elastica ill-defined or absent and an absence of intimal proliferation. The first case of peripheral pulmonary artery stenosis in the rubella syndrome with histological documentation was reported by Franch and Gay.\textsuperscript{7} Among the findings were sclerosis and intimal proliferation in the pulmonary artery.

Recently, additional cases have been reported. Campbell has described marked intimal proliferation in the pulmonary and numerous systemic arteries, and focal loss of the elastica in an infant with pulmonary artery stenosis.\textsuperscript{8} Another case with intimal proliferation in the renal arteries and histological evidence of systemic hypertension has been reported by Menser and associates.\textsuperscript{9} Lesions in the pulmonary artery, aorta, and often systemic arteries were also mentioned in a review of cerebral lesions in the rubella syndrome.\textsuperscript{13}

The characteristic vascular alteration in the present cases was striking intimal proliferation. The arterial structure was preserved, and changes in the media and internal elastica were infrequent even at sites of severe intimal thickening. Stenosis or dilatation of the artery was also uncommon, and no lesions were found in arterioles or veins. The severity of involvement varied. Severe and extensive lesions were present in four infants; lesser changes—but usually multiple—were noted in

Figure 4

Right pulmonary artery, case 7. Peripheral pulmonary stenosis had been documented in this infant, but in spite of the extensive intimal thickening, stenosis could not be appreciated in the gross specimen. Note the normal structure of the media, and the minimal fragmentation of elastic fibers in the inner portion of the intima. Verhoeff-van Gieson, reduced from × 65.
another five. No lesions were found in the remaining cases.

Although pulmonary artery stenosis was not identified in the gross specimens, and even severe lesions did not appear to occlude the vascular lumen significantly, it seems probable that the physiological alterations in these infants were related to these vascular lesions. Furthermore, hypertension was documented in the infant with renal artery stenosis (case 11), and it seems likely that undiagnosed intrauterine rubella infection may be the etiology of hypertension due to renal vascular "anomalies" in many infants and children.

Töndury and Smith\textsuperscript{14} have described occasional endothelial necrosis in the arteries, capillaries, and veins of rubella-infected embryonic and fetal specimens. We found a vascular lesion in one of the five premature stillborn infants, a single focal alteration in an umbilical artery, but no significant changes in the placental tissue. It has been suggested that the severity of the vascular lesions (peripheral pulmonary artery stenosis) increases with age\textsuperscript{35}; the present data appear to support this impression.

The proliferative lesions in the arteries of these infants appear to be unique, but their pathogenesis is unknown. It is not possible histologically to distinguish between the response of earlier endothelial injury, and the results of chronic intracellular infection. Nevertheless, the latter hypothesis is attractive because rubella virus has been cultured from some infants for long periods, and because cellular proliferation is such a characteristic

\textbf{Figure 5}

Case 9. (A) Left pulmonary artery. This is another example of extreme intimal proliferation that was not identified at the time of the autopsy. Hematoxylin and eosin, reduced from $\times 30$.

(B) Right lung, case 9. The segmental branches of the pulmonary artery show fibromuscular proliferation which doubles the width of the vessel wall without significantly narrowing the vessel lumen. Verhoeff-van Gieson, reduced from $\times 14$. 
Renal ostium, case 11. Hypertension was documented in this 13-month-old infant. The ridge of fibromuscular proliferation caused ostial stenosis at the renal artery. The opposite renal ostium was normal. Verhoeff-van Gieson, reduced from × 35.

host response of the fetus and infant to other viral infections. Furthermore, calcification is a prominent sequela of necrosis at this age, and the absence of mineralization13,16 or an inflammatory infiltrate suggests that necrosis

Iliac artery branch, case 9. The lumen of this artery is nearly occluded, but the media and internal elastica remain unaltered. Several other muscular branches of the iliac artery showed similar changes. Hematoxylin and eosin, reduced from × 120.

Aorta, case 1. An overhanging wedge of fibromuscular intimal thickening has produced stenosis of an intercostal artery ostium. A less severe, but similar lesion was found at the ostium of another intercostal branch, and the intimal proliferation extended along the vessel. Hematoxylin and eosin, reduced from × 65.
plays no significant role in the evolution of this lesion.

The absence of calcification and inflammation, and the preservation of arterial structure distinguish the fibromuscular intimal proliferation in the present cases from other vascular lesions seen in infancy. Intimal plaques may be noted in the vessels of otherwise normal infants, but they are unlikely to be confused with pathological lesions because they are small in size and found only in areas of stress.19, 20

Medial calcification in the pulmonary and systemic arteries in newborn infants has been described in several reports, but intimal changes, when present, appear to be secondary to the striking medial necrosis and calcification.21 Similar alterations have also been the consistent findings in numerous studies of experimental vitamin D toxicity.22-25 Idiopathic pulmonary artery calcification and stenosis have also been described but are relative-

ly infrequent (Oppenheimer26 and personal communication from S. Williams). A recent detailed study of coarctation in segmental pulmonary arteries demonstrated changes in the media and perivascular fibrosis in addition to intimal proliferation.27

A peculiar endarteritis has been noted in association with congenital cardiac malformations, particularly stenosis of the ventricular outflow valves.28, 29 Intimal proliferation was present, but the disorganization of the elastic tissue and media was so severe that structural identity of the artery was lost. Less severe arteriosclerotic lesions with splitting and reduplication of the internal elastica have also been encountered in the coronary arteries of infants with other cardiac anomalies30, 31 (also personal communication from Franciosi and Blanc, 1965).

Systemic hypertension is uncommon in the

Figures 9 and 10

Segmental renal artery branch, case 6. Focal intimal thickening is evident; a lesser change is seen in a second branch. Verhoeff-van Gieson, reduced from × 90.

Epicardial branch of the left coronary artery, case 8. Focal intimal proliferation was seen in this vessel as well as in branches of the right coronary artery. Interstitial myocarditis was also present. Hematoxylin and eosin, reduced from × 75.
pediatric age group, but affected infants have shown both intimal fibromuscular hyperplasia and atheromata, the latter in association with hypercholesterolemia. These lesions were less extensive than those in most of the present cases, and all had changes in the elastica.

Vascular lesions in congenital syphilis and acute or healed periarteritis nodosa show inflammation and fibrosis and are therefore readily distinguished from congenital rubella. Likewise, the general appearance and absence of metachromasia preclude the diagnosis of mucopolysaccharidosis.

We have studied one previous case in which the vascular lesions were identical to the present findings. This 18-month-old infant had multiple malformations and was mentally retarded and hypertensive. As in our case 11, the main lesion was in the descending aorta, but the stenosis involved both renal ostia. There was no history of maternal rubella, but subclinical infection can never be excluded. A similar case of maternal "flu" and arteriosclerosis in a 7-week-old infant suggest that the first description of vascular lesions in congenital rubella may have been reported in 1926.

Addendum

A description of vascular lesions has been included in a recent study of the pathology of congenital rubella. Extensive intimal sclerosis was found in three of the 18 cases studied.

Acknowledgment

The virological and serological data were supplied by Dr. Janet B. Hardy. Dr. Herbert L. Elliott was responsible for the detailed examination of several of the cases. We are indebted to Mr. Raymond Lund for the photomicrographs.

References


Group Ethics

If the services of the group organization are on the level of self-interest and economic and material advantage to its members, it is not and cannot be a learned profession in any proper sense. Each group, whatever its qualifications for membership, can in the long run maintain its independence and liberty of self-direction only at the price of showing constantly its freedom from selfish group interests. The wise response of any profession to social change, its loyalty to the general welfare, and the clarity with which it makes its professional codes comprehensible to the public that it claims to serve through and by such codes, constitute the best bulwark for its cherished historic liberties.—Guy Stanton Ford: On and Off the Campus. Minneapolis, University of Minnesota Press, 1938, p. 152.
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