Congenital Cardiovascular Anomalies Induced by Pteroylglutamic Acid Deficiency during Gestation in the Rat

By CATHARINE D. C. BAIRD, MARGERIE M. NELSON, IAN W. MONIE, AND HERBERT M. EVANS

Congenital cardiovascular anomalies were observed in the offspring when rats were placed on a dietary regimen deficient in pteroylglutamic ("folic") acid during gestation. These cardiovascular malformations occurred only when the mothers were given this diet for specific periods, as short as two or three days, in early pregnancy, at a time when the heart and aortic arches were in the initial stages of development.

CONGENITAL cardiovascular anomalies have been produced in rats or mice by several experimental methods: for example, irradiation of implantation sites (Wilson and colleagues1,2), injections of trypan blue or azo blue (Wilson3), maternal anoxia (Ingalls and associates4) and maternal vitamin A deficiency (Wilson and Warkany5). Previous studies by Nelson, Asling and Evans6 have shown that when normal female rats are given a diet deficient in pteroylglutamic acid from the tenth or eleventh day of pregnancy onwards, 95 to 100 per cent of the resulting offspring exhibit multiple congenital anomalies.

The present communication reports the nature and incidence of cardiovascular anomalies observed in fetal rats from mothers given a diet deficient in pteroylglutamic acid (PGA) for varying periods during gestation. It includes fetuses from every pteroylglutamic acid-deficient group in which markedly abnormal fetuses have been observed.

METHODS

The experimental diets and procedures were the same as those used previously by Nelson and associates. Normal female rats of the Long-Evans strain, 3 to 4 months of age, were bred with normal males and given the diet deficient in pteroylglutamic acid for 2 to 11 days during gestation. When a transitory deficiency period of two or three days was used, the animals were placed on the diet deficient in pteroylglutamic acid for exactly 48 or 72 hours, starting on the seventh, ninth, tenth or eleventh days; they were then transferred to the diet supplemented with pteroylglutamic acid for the remainder of the gestation period. All dietary changes were uniformly made at 10:00 a.m. When the longer deficiency period of 10 or 11 days was used, the diet deficient in pteroylglutamic acid was given from the tenth or eleventh day of gestation to the time of autopsy. On day 21, the day before parturition, the fetuses were obtained by cesarean section, a procedure necessary as the markedly abnormal young did not survive after birth and were eaten by the mother. The groups deficient in pteroylglutamic acid studied and the incidence of fetuses with macroscopic abnormalities of all types were as follows: pteroylglutamic acid-deficient diet days 7 to 9, 51 per cent; days 9 to 11, 99 per cent; days 10 to 12, 78 per cent; days 10 to 13, 100 per cent; days 10 to 21, 100 per cent; days 11 to 14, 70 per cent; and days 11 to 21, 95 per cent.

The diet deficient in pteroylglutamic acid1 was

1 The diet deficient in pteroylglutamic acid consisted of 24 per cent alcohol-extracted casein, 62.5 per cent sucrose, 8 per cent hydrogenated cottonseed oil (Crisco or Primex), 4 per cent salts no. 4 (Hegsted and colleagues13), 1 per cent succinylsulfathiazole, and 0.5 per cent x-methyl-pteroylglutamic acid. Crystalline vitamins per kilogram of diet were: 300 µg. d-biotin, 5 mg. 2-methyl-1,4-naphthoquinone, 5 mg. thiamine hydrochloride, 5 mg. pyridoxine hydrochloride, 10 mg. riboflavin, 10 mg. para-aminobenzoic acid, 20 mg. niacin, 50 mg. d-calcium pantothenate, 400 mg. inositol, and 1.0 Gm. choline chloride. All rats received weekly a fat-soluble vitamin mix-

Received for publication July 16, 1954.
a purified diet lacking pteroylglutamic acid. It contained succinylsulfathiazole (SST) to depress intestinal synthesis of the vitamin, and a "crude" pteroylglutamic acid-antagonist (x-methyl-PGA) to interfere with the functioning of the stored vitamin. The diet supplemented with pteroylglutamic acid contained all the above constituents but was supplemented with 50.5 mg. synthetic pteroylglutamic acid per kilogram diet. The stock diet, used for normal animals and for experimental animals during the early part of pregnancy before the diet deficient in pteroylglutamic acid was given, consisted of natural foodstuffs.

A total of 513 fetuses was examined for cardiovascular anomalies: 423 fetuses were from mothers on the pteroylglutamic acid-deficient diet for varying intervals during gestation as mentioned above, and 90 fetuses were from mothers maintained on the stock diet or the diet supplemented with pteroylglutamic acid throughout gestation. The first 200 fetuses studied were injected at autopsy with India ink through the umbilical vessels by a method similar to that described by Sanford. After injection, the fetuses were fixed in Bouin's solution for later dissection of the heart and aortic arch structures under the binocular microscope (magnification × 7). After studying these fetuses, injection with India ink was no longer necessary for recognition of the cardiovascular anomalies, and the remaining fetuses were examined, un.injected, after fixation.

Results

Table 1 presents the incidence of congenital cardiovascular anomalies observed macroscopically in 21-day fetuses from mothers given the diet deficient in pteroylglutamic acid for specified periods during gestation. One or more cardiovascular anomalies occurred in 130 of the 423 fetuses studied. These anomalies were observed in all groups in which the diet deficient in pteroylglutamic acid was started on day 10 or earlier, but they were not found in any offspring of animals given the diet later, from days 11 to 14 or days 11 to 21. In the offspring from mothers given the diet from days 7 to 9, 28 per cent exhibited cardiovascular anomalies, principally cardiac defects. Fetuses from mothers given the diet from days 9 to 11 showed a higher incidence of anomalies, 57 per cent, the majority of these being vascular defects. In fetuses from mothers given the diet from days 10 to 12, 10 to 13, and 10 to 21, the incidence of cardiovascular anomalies was 31 per cent, 29 per cent and 22 per cent, respectively.

Macroscopic anomalies of other systems, namely the nervous, ocular, skeletal, integumentary, or urogenital systems, were found in 87 per cent of the 423 fetuses studied. Of the 130 fetuses with cardiovascular anomalies, 120 had other abnormalities and only 10 appeared to be free of macroscopic anomalies other than those of the cardiovascular system. Of these 10 fetuses, seven were from mothers receiving the pteroylglutamic acid-deficient diet during days 7 to 9, one from a mother given the diet

**Table 1.** Incidence of Congenital Cardiovascular Anomalies in 21-Day Fetuses from Mothers Given Diet Deficient in Pteroylglutamic Acid for Specified Periods during Gestation

<table>
<thead>
<tr>
<th>Period of Gestation</th>
<th>Fetuses Studied</th>
<th>Cardiac Anomalies</th>
<th>Vascular Anomalies</th>
<th>Both Cardiac and Vascular Anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-9</td>
<td>15</td>
<td>67 (29*)</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>9-11</td>
<td>21</td>
<td>111 (108)</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>10-12</td>
<td>21</td>
<td>75 (70)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>10-13</td>
<td>12</td>
<td>62 (62)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>10-21</td>
<td>13</td>
<td>32 (32)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>11-14</td>
<td>8</td>
<td>43 (33)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11-21</td>
<td>6</td>
<td>33 (33)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>96</td>
<td>423 (367)</td>
<td>33</td>
<td>38</td>
</tr>
</tbody>
</table>

* Number of fetuses with grossly visible anomalies of other systems (namely, the nervous, ocular, skeletal, integumentary, or urogenital systems) is given in parentheses.
Table 2.—Incidence of Types of Cardiovascular Anomalies in 21-Day Fetuses from Mothers Given Diet Deficient in Pteroylglutamic Acid for Specified Periods during Gestation

| Pteroylglutamic Acid-Deficient Dietary Period (days of gestation) | Total with Cardiovascular Anomalies | Interventricular Septal Defect | Truncus Arteriosus | Double Aortic Arch | Right Aortic Arch | Absence of Ductus Arteriosus | Hypoplasia of Ductus Arteriosus | Distal Origin of Right Subclavian Artery | Distal Origin of Left Subclavian Artery | Left Subclavian Artery from Ductus Arteriosus | Aortic Arch from Ductus Arteriosus | Arterial Remnants | Abnormal Course of Descending Aorta |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7-9 | 19 | 63 | 23 | 18 | 7 |
| 9-11 | 17 | 36 | 20 | 17 | 2 |
| 10-12 | 2 | 7 | 6 | 6 | 0 |
| 10-13 | 0 | 4 | 2 | 0 | 0 |
| 10-21 | 2 | 10 | 9 | 5 | 4 |

from days 9 to 11, and two were from mothers receiving the diet from days 10 to 12 of gestation.

No cardiovascular malformations were observed in any of the 90 offspring of animals given either the stock diet or the diet supplemented with pteroylglutamic acid throughout pregnancy.

**Description of Anomalies**

Both cardiac and vascular anomalies were observed in fetuses from every group receiving the diet deficient in pteroylglutamic acid on day 10 or earlier, namely from days 7 to 9, 9 to 11, 10 to 12, 10 to 13, and 10 to 21. The incidence of the different types of cardiovascular anomalies in the varying periods of dietary deficiency is given in table 2. As a basis for interpretation of the vascular malformations to be described, diagrams of the hypothetic embryonic arch pattern and the adult derivatives therefrom are shown in figures 1A and 1B, respectively.

**Interventricular Septal Defect.** The only macroscopic cardiac defect was the failure of closure of the interventricular foramen, which was observed in 92 fetuses (fig. 21). This anomaly occurred as the only defect of the cardiovascular system in 33 fetuses and in combination with vascular anomalies in 59 fetuses (table 1).

**Persistent Truncus Arteriosus.** A single vessel serving as the only channel from the heart to the descending aorta was observed in 21 fetuses (figs. 2 and 23). This anomaly represents failure of development of the aortopulmonary septum which normally divides the truncus arteriosus into aortic and pulmonary channels. In all fetuses showing this anomaly, there was also persistence of the interventricular foramen, and the pulmonary arteries arose directly from the truncus as it left the heart. In seven fetuses with this anomaly there were other associated vascular anomalies as illustrated in figures 3, 4, 5 and 6. Persistent truncus arteriosus was observed in fetuses from mothers given the pteroylglutamic acid-deficient diet during days 7 to 9, 10 to 11, 10 to 12, and 10 to 13.

**Double Aortic Arch.** In six fetuses a functional channel between the heart and the descending aorta persisted on the right as well as on the left side; this resulted in a vascular ring encircling the trachea and esophagus. This anomaly was associated in all cases with a persistent interventricular foramen. In two fetuses the right as well as the left fourth arch connected the heart and descending aorta (figs. 3, 8, and 24). These fetuses were from mothers given the pteroylglutamic acid-deficient diet during days 10 to 12 of gestation. In four fetuses the vascular ring around the trachea and esophagus was formed by a right aortic arch (right fourth arch) and the ductus arteriosus (left sixth arch) (figs. 7 and 25). These fetuses were from mothers given the diet deficient in pteroylglutamic acid during days 9 to 11.

**Right Aortic Arch.** In 30 fetuses the aortic arch descended on the right of the trachea and esophagus (fig. 9). In 19 of these, this persistence of the right rather than the left fourth
arch as the functional channel between the heart and descending aorta was associated with an interventricular septal defect. Sixteen of the 30 fetuses showed a "mirror image" pattern with regard to the origin of the innominate artery and the right common carotid and subclavian arteries (fig. 9). Various additional vascular anomalies in association with the right aortic arch were observed in 19 fetuses (figs. 4, 5, 10, 11, 12, 13, 14 and 26). Instances of a right aortic arch were found in fetuses from mothers of all the groups deficient in pteroylglutamic acid showing cardiovascular anomalies (table 2).

Absence or Hypoplasia of the Ductus Arteriosus. In 18 fetuses the ductus arteriosus was absent (fig. 15). This anomaly, representing failure of development or persistence of that part of the sixth arch which normally results in this vessel, was associated with an interventricular septal defect in all but two fetuses. In 15 cases it was associated with a right aortic arch as shown in figures 10, 11, and 12. Absence of the ductus arteriosus was observed in fetuses from mothers given the diet deficient in pteroylglutamic acid during days 9 to 11, 10 to 12, 10 to 13 and 10 to 21 but was not

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**Key to Illustrations:** The following abbreviations are used in all diagrams and photographs:

- Aot, Aortic Trunk
- AR, Arterial Remnant
- DA, Ductus Arteriosus
- DAO, Descending Aorta
- E, Eosophagus
- I, Innominate Artery
- LAo, Left Aortic Arch
- LCC, Left Common Carotid Artery
- LDAO, Left Dorsal Aorta
- LP, Left Pulmonary Artery
- L7S, Left Seventh Segmental Artery
- LS, Left Subclavian Artery
- ML, Midline
- PIF, Persistent Interventricular Foramen
- PT, Pulmonary Trunk
- RAo, Right Aortic Arch
- RCC, Right Common Carotid Artery
- RDAO, Right Dorsal Aorta
- RP, Right Pulmonary Artery
- R7S, Right Seventh Segmental Artery
- RS, Right Subclavian Artery
- TA, Truncus Arteriosus
- VAO, Ventral Aorta
- 1-6, Embryonic Arterial Arches
Figs. 2-10. Diagrams of abnormal aortic arch patterns. Those portions normally persisting are shown in black, with the exception of the pulmonary trunk and arteries which are represented in white. The ductus arteriosus is indicated by white and black lines. Abnormal persisting vascular channels are stippled.

Fig. 2. Persistent truncus arteriosus.
Fig. 3. Persistent truncus arteriosus with double aortic arch.
Fig. 4. Persistent truncus arteriosus with right aortic arch.
Fig. 5. Persistent truncus arteriosus with right aortic arch and distally arising left subclavian artery.
Fig. 6. Persistent truncus arteriosus with distally arising right subclavian artery.
Fig. 7 "Double aortic arch" formed by a right aortic arch and the ductus arteriosus.

found in the group receiving the diet earlier, from days 7 to 9.

The caliber of the ductus arteriosus in 21-day fetuses was normally equal to that of the arch of aorta (fig. 22), but in three fetuses from the groups deficient in pteroylglutamic acid it was approximately half the caliber observed in the control animals. This anomaly probably represents hypoplasia of the distal portion of the sixth arch, since regression of the ductus arteriosus does not usually occur until post-natal life. These fetuses were from mothers given the diet deficient in pteroylglutamic acid during days 7 to 9, 9 to 11 and 10 to 12.

Absence of Arch of the Aorta. In three fetuses, the heart was connected with the descending aorta by the pulmonary trunk and ductus arteriosus only, the left fourth arch having failed to develop or persist (figs. 16 and 18). One fetus showed an interventricular septal defect also. Only fetuses from mothers on the
diet deficient in pteroylglutamic acid during days 9 to 11 exhibited this abnormality wherein the left sixth arch remained as the only channel between the heart and the descending aorta.

**Aberrant Origin of Subclavian Arteries.** In 40 fetuses the right subclavian artery arose from the descending aorta and passed dorsal to the esophagus towards the right forelimb (figs. 17 and 27). This distally arising (or retroesophageal) right subclavian artery represents loss of the right fourth arch with persistence of that portion of the right dorsal aorta which lies caudal to the origin of the seventh segmental artery; in 14 fetuses there was an associated interventricular septal defect. In 35 fetuses this was the only vascular abnormality observed, the remaining five showing additional anomalies as illustrated in figures 6, 18 and 19. This distal origin of the right subclavian artery was observed in fetuses from all groups showing cardiovascular anomalies except the group given the diet deficient in pteroylglutamic acid on days 10 to 12.

In 12 fetuses, the left subclavian artery had
an unusual origin; 10 of these fetuses also exhibited a persistent interventricular foramen. In five fetuses in which there was an associated right aortic arch, the left subclavian artery arose from the descending aorta and passed dorsal to the esophagus towards the left forelimb, being examples of a distally arising left subclavian artery (fig. 11). In these fetuses, only the caudal portion of the left dorsal aorta was present, being retained to supply blood to the seventh segmental artery; the usual pathway through the left fourth arch was absent. This anomaly occurred in fetuses from mothers given the diet deficient in pteroylglutamic acid from days 9 to 11, 10 to 12, and 10 to 13 of gestation.

In seven fetuses, the left subclavian artery arose from the ductus arteriosus, the left fourth arch having failed to develop or persist (figs. 7, 13, 14, 16 and 18). This anomaly occurred only in fetuses from rats receiving the diet deficient in pteroylglutamic acid during days 9 to 11.

Arterial Remnants. Five fetuses showed vessels having no comparable representation in control fetuses of the same age; these were ap-
Fig. 20 and 21. Dissected hearts of 21-day rat fetuses from mothers maintained on pteroylglutamic acid-supplemented and pteroylglutamic acid-deficient diets. In each heart the wall of the left ventricle has been removed to show the interventricular septum. (X 15)

Fig. 20. Diet supplemented with pteroylglutamic acid. Intact interventricular septum.

Fig. 21. Diet deficient in pteroylglutamic acid (days 7 to 9). Persistent interventricular foramen with truncus arteriosus.

Apparently vestiges of the embryonic arch pattern, its branches and related segmental vessels (figs. 12, 14, 18 and 19). These arterial remnants occurred in fetuses from mothers on the diet deficient in pteroylglutamic acid from days 9 to 11, 10 to 13, and 10 to 21.

Abnormal Course of Descending Aorta. In two fetuses a left descending aorta was observed to cross the vertebral column dorsal to the esophagus and descend on the right side of the midline (fig. 19). The reason for this anomaly is uncertain but might have resulted from the influence of a potential right-sided aorta. These two fetuses were from mothers given the diet deficient in pteroylglutamic acid from days 9 to 11 of gestation.

DISCUSSION

The data presented show that congenital cardiovascular anomalies have been produced in 28 to 57 per cent of the offspring from pregnant rats given a diet deficient in pteroylglutamic acid for only two or three days starting on the seventh, ninth or tenth days of gestation. Both cardiac and vascular anomalies were observed in all groups although the group receiving the diet deficient in pteroylglutamic acid during days 7 to 9 showed a higher incidence of cardiac (interventricular septal) defects than of vascular anomalies, while the vascular anomalies were more prevalent when the diet was started on day 9 or 10 of gestation. When the diet deficient in pteroylglutamic acid was begun on day 11, only one day later, no macroscopic defects of the cardiovascular system were observed.

Previous studies on fetal cardiovascular development in the rat have shown that cardiogenic mesoderm can first be recognized by day $8^{1/2}$ of gestation (Burlingame and Long) whereas the first aortic arch cannot be seen until day 10 (Wilson and Warkany). Development of both the heart and aortic arch structures continues actively until day 15 or 16, following essentially the same pattern as in other animals. It is apparent, therefore, that

† All references to days of gestation are adjusted to correspond to the timing used in this study of pteroylglutamic acid-deficiency in which the day of finding sperm is considered to be day 0.
Figs. 22-27. Dissections of 21-day rat fetuses from mothers on pteroylglutamic acid-supplemented and pteroylglutamic acid-deficient diets to show vascular patterns. The duration of the deficient diet is given in parentheses. (× 6)

Fig. 22. Control fetus. The heart has been displaced to the right. Compare with figure 1B.
Fig. 23. Persistent truncus arteriosus. The heart has been displaced to the right. Compare with figure 2. (Days 9 to 11.)
Fig. 24. Double aortic arch with persistent truncus arteriosus. The heart has been removed. Compare with figure 8. (Days 10 to 12.)
Fig. 25. "Double aortic arch" formed by a right aortic arch and the ductus arteriosus. The ductus arteriosus has been severed to allow the heart to be displaced to the right. Compare with figure 7. (Days 9 to 11.)
Fig. 26. Right aortic arch. The ductus arteriosus is absent and the innominate artery is on the left side. Compare with figure 10. (Days 9 to 11.)
Fig. 27. Distally arising right subclavian artery. The ductus arteriosus has been severed to allow the heart to be displaced cranially. Compare with figure 17. (Days 9 to 11.)
under the experimental conditions the pteroylglutamic acid-deficiency regimen interferes only with the earliest stages of cardiovascular development, since the fetal cardiovascular system is not affected when the diet is started later than the tenth day of gestation.

The importance of timing in the production of congenital cardiovascular defects has been indicated by a number of previous studies. Wilson, Roth and Warkany found that in chronic vitamin A deficiency the cardiac anomalies could not be prevented by giving a vitamin A supplement as early as day 9, whereas the aortic arch anomalies could be prevented by vitamin supplementation given as late as day 10. The latter findings are in contrast to the appearance of aortic arch anomalies in fetuses from mothers given the pteroylglutamic acid-deficient diet from days 7 to 9 only and the diet supplemented with pteroylglutamic acid from day 9 onwards. In another study Wilson and co-workers observed more severe damage to the fetal cardiovascular system from direct irradiation of placental sites on day 9 than on day 10 of gestation. Similarly, Wilson has recently reported the production of cardiovascular anomalies by injection of azo blue or trypan blue into pregnant rats on days 7, 8 and 9 of gestation.

The types of cardiovascular abnormalities (interventricular septal defects, persistent truncus arteriosus, double or right aortic arch, absence of the ductus arteriosus, aberrant origin of subclavian arteries, and additional variations of the vascular pattern) observed in this study with diets deficient in pteroylglutamic acid are similar to those observed by Wilson and co-workers in their studies with chronic maternal vitamin A deficiency. These authors found cardiovascular anomalies in 28 of 64 rat fetuses examined by serial sections. Ingalls, Curley and Prindle have reported the occurrence of interventricular septal defects in 7 of 210 offspring from mice subjected to anoxia during pregnancy. Other types of cardiovascular anomalies that have been produced experimentally in mammals are dilatation of the pericardium, sometimes accompanied by increased heart size, in embryos from mice injected with trypan blue seven days after breeding (Waddington and Carter) and ectocardia observed in one fetus from rats maintained on a pteroylglutamic acid-deficient diet containing succinylsulfathiazole.

The experimental study of cardiovascular anomalies in mammals can thus be approached in a number of different ways. The occurrence of such malformations in the offspring of rats maintained on a diet deficient in pteroylglutamic acid during the early part of pregnancy, particularly during days 9 to 11, adds another method for such studies. Histologic studies are now being made of earlier stages of cardiovascular development and should aid in clarifying the pathogenesis of the anomalies described in the present report.

**SUMMARY**

Congenital cardiovascular anomalies have been produced in the offspring of rats given a diet deficient in pteroylglutamic acid for periods as short as two or three days, during the early part of gestation. The incidence of macroscopic anomalies observed in 21-day fetuses was as follows: 28 per cent for the pteroylglutamic acid-deficiency regimen during days 7 to 9; 57 per cent during days 9 to 11; 31 per cent during days 10 to 12; 29 per cent during days 10 to 13; and 22 per cent during days 10 to 21. No anomalies were found in fetuses from mothers on the stock or the pteroylglutamic acid-supplemented diets throughout pregnancy.

The types of cardiovascular anomalies observed included interventricular septal defects, persistent truncus arteriosus, double or right aortic arch, absence of the ductus arteriosus, aberrant origins of the subclavian arteries, and additional variations of the arterial pattern derived from the embryonic arch system.

§ Two cases of ectocardia (ectopia cordis) have been observed in the offspring given the diet deficient in pteroylglutamic acid during days 9 to 11 and injected with suboptimal levels of the synthetic vitamin pteroylglutamic acid during this period (unpublished data).
ACKNOWLEDGMENTS

The authors wish to express their appreciation to Dr. C. Willet Asling and Dr. H. V. Wright for assistance with this study.

We are indebted to Dr. T. H. Jukes, Lederle Laboratories, Pearl River, N. Y., for generous supplies of synthetic pteroylglutamic acid and the "crude" pteroylglutamic acid-antagonist (x-methyl-PGA); to Dr. W. A. Feirer of Sharp and Dohme, Inc., Glenolden, Pa., for succinylsulfathiazole; to Dr. E. L. Severinghaus of Hoffman-La Roche, Inc., Nutley, N. J., for crystalline d-biotin, d-calcium pantothenate, and dl-alpha tocopherol; and to Dr. Randolph Major of Merck and Company, Inc., Rahway, N. J., for crystalline B vitamins and 2-methyl-1,4-naphthoquinone.

REFERENCES

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Circ Res. 1954;2:544-554
doi: 10.1161/01.RES.2.6.544

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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http://circres.ahajournals.org/content/2/6/544