CONGENITAL AND NEONATAL THROMBOCYTOPENIC PURPURA

BY

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Haemorrhagic disease due to a deficiency of blood platelets is stated to be a very rare condition in the newborn. Considerable interest has been shown in the condition recently, however, and examples are being reported with increasing frequency. Barclay (1945), Schefrin and Shechtman (1945), Waters (1946), and Landolt (1948) all review small series of cases; McAlenney and Kristan (1949) collected and reviewed a total of 34 cases, adding a further six examples of their own. A survey of the world’s literature shows that in fact some 52 cases of thrombocytopenic purpura in the neonatal period have now been reported.* We have recently encountered three further examples of this condition. The features of these three cases differed so markedly as to suggest that the haemorrhagic tendency was due to different causes. It seemed desirable therefore to review and classify the previously reported cases of thrombocytopenia in the newborn. Such a classification has not previously been made, apart from a suggestion by Landolt (1948) that there were three forms of congenital thrombocytopenia; one associated with maternal purpura, one in which there was no maternal disorder, and a third type in which there was congenital hypoplasia of the bone marrow. It must be pointed out that purpura is not a disease entity, but a sign of a bleeding tendency, which may be due to platelet deficiency, capillary disorder, or a defect in blood coagulation. A haemorrhagic state associated with thrombocytopenia is the condition primarily under discussion in this paper.

Case Reports

Case 1. Baby D. (a boy), was born spontaneously at full term on September 27, 1949 (weight 7 lb. 10 oz.). At birth the baby was in good general condition, but petechiae were seen scattered on the trunk. The spleen was not palpable and the liver not enlarged. Examination revealed nothing else of note. No further crops of petechiae occurred.

On September 28 the original petechiae seemed larger, but were not increased in number. Blood findings were Hb. 155%, and platelets 130,000 per c.mm. The baby cried readily on the breast and continued to feed well till the fourteenth day when artificial feeding began. Vitamin K was given on two occasions, but no blood transfusion. On September 29 jaundice developed and lasted for four days. On September 30 the platelet count was 85,000 per c.mm. Progress was satisfactory apart from the development of thrush, which was treated with gentian violet. Further blood examinations gave the following results.

October 3, bleeding time 7½ minutes; clotting time 2 minutes.

October 12, platelets 30,000 per c.mm.; bleeding time 2 minutes; Hb. 122%, and W.B.C. 8,200 per c.mm.

October 16, Hb. 109%; platelets 85,000 per c.mm.; bleeding time 2 minutes.

October 18, Hb. 110%; W.B.C. 9,400 per c.mm.;

platelets 125,000 per c.mm.

December 8, Hb. 110%; W.B.C. 11,200 per c.mm.; and platelets 310,000 per c.mm.

The child left hospital on October 16, 1949, and when last seen at the sixth week was thriving well.

The mother was primiparous, aged 20 years, and labour lasted 50 hours. She was suffering from idiopathic thrombocytopenic purpura, and had been observed in hospital throughout the later part of her pregnancy. Her blood findings on September 28, 1949, were Hb. 69%, R.B.C. 3·46 million, W.B.C. 16,000, platelets 70,000 per c.mm. She had frequent purpuric episodes during pregnancy. Her case is fully described by Robson and Davidson (1950).

Case 2. Baby F., aged 3 weeks, was admitted to the Royal Hospital for Sick Children, Edinburgh, on April 27, 1948, because he failed to thrive, and because of an increasing blue discoloration of the skin of the abdomen and right arm of 24 hours’ duration.

The mother had remained well during pregnancy, and was delivered spontaneously at term in five hours. The baby, whose birth weight was 11½ lb., cried normally and showed no evidence of shock, asphyxia, or birth injury.

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* The cases mentioned by de Lingen (1828), de Saussure, Townsend, and Charlestone (1935), Potter (1945), Rushmore (1925), and Siegler (1934), were discarded because in these evidence was insufficient even for a provisional diagnosis to be made. Eleven cases have been included in which no infant platelet count was reported but in which other evidence was sufficient for their classification in this series.
No abnormal degree of jaundice was noted. She fixed readily, and was breast-fed until admission, but had lost 5 lb. in weight. She had not vomited, but she was constipated. Twenty-four hours before admission a small, blue-red area was noticed on the anterior abdominal wall and a similar area appeared on the right arm. The former increased rapidly in size. There were no other bleeding manifestations.

The child was thin and grossly dehydrated, and weighed 6½ lb. The skin generally was pink, dry, warm, thick, and leathery in consistence. Over the right upper arm and abdominal wall there were areas of what appeared to be intracutaneous haemorrhage (Fig. 1). The edge of the lesion was raised and bright red in colour, the centre being deep blue-black. The surface was rough and leathery to touch, of normal temperature, and adherent to subcutaneous tissues. The area on the abdomen stretched from the rib margin to the iliac crest and from the umbilicus round to the mid-line posteriorly. That on the antero-medial aspect of the arm was circular and about 2 in. in diameter. Small petechiae were scattered over the rest of the body. There was some discharge from the umbilicus.

The baby was semiconscious, and limb muscles were hypotonic. There were very few spontaneous movements. No enlargement of liver or spleen could be detected. Other systems showed no abnormality. The blood findings were Hb. 120%o; R.B.C. 5·1 million per c.mm.; W.B.C. 4,800 per c.mm.; a blood film showed anisocytosis of red cells, but no normoblasts; platelets 10,000 per c.mm.; the bleeding time was markedly prolonged; blood urea nitrogen, 140 mg. %o; serum chlorides, 590 mg. %o; prothrombin concentration, 100%. The dehydration was relieved by intravenous glucose saline, plasma, and Hartmann’s solution. Penicillin, vitamin K, and ascorbic acid were given intramuscularly. After hydration, blood examination showed Hb. 65%o and R.B.C. 3·9 million per c.mm., so a transfusion of 100 ml. of fresh blood was given. Further examinations then showed Hb. 100%o; R.B.C. 5·2 million per c.mm.; platelets 10,000 per c.mm.; blood urea nitrogen 133 mg. %o; and serum chlorides 600 mg. %o. The ecchymotic areas had spread slightly in all directions, and a fresh area was noticed on the left cheek.

The following day the baby had a blood-stained nasal discharge, and the stools, which were infrequent, contained occult blood. Mild head retraction then developed. Sacral oedema was noted, and bullae were found on the back and left side. One of these ruptured spontaneously, and discharged watery, dark-brown fluid. On April 30 a further blood transfusion was given because of the continued thrombocytopenia. After this there was more head retraction, and neck rigidity with generalized hypertonicity developed. The clinical picture was that of cerebral haemorrhage, and death ensued.

**Necropsy Report.** A large area of skin, of a uniform dark cyanotic colour extended over the left side of the chest and abdomen down to the level of the umbilicus. Posteriorly it affected the whole of the skin of the trunk and spread on to the upper part of the left thigh. Several ruptured bullae were on the skin of the back, but these showed no sign of sepsis. Numerous petechial haemorrhages were seen on the left leg, and a few on the right leg. Microscopically, sections of the skin showed haemorrhage into the cutis and to a less extent into the subcutaneous tissue. There was no evidence of haemangioma, and there was no inflammatory reaction.

The brain showed a lesion in the left frontal lobe, where a large softened area was found, consisting of degenerate brain tissue stained with fresh blood. The lungs showed marked basal congestion, and historically there were many areas of haemorrhage with some intra-alveolar clot formation, but no inflammatory reaction. The heart was markedly dilated, particularly the right ventricle. The liver was enlarged and showed severe fatty degeneration affecting the central zones of the lobules. The left kidney was large and had a double ureter with two pelvis. The suprarenals were normal. The spleen was of normal size and consistence. The bone marrow showed marked aplasia. No inclusion bodies, such as are described by Wyatt, Saxon, Lee, and Pinkerton (1950), could be found in the sections of the various organs.

The mother, father, and five siblings were all well. There was no family history of bleeding disease. The mother had not been taking any drugs. An examination of her blood showed a negative Wassermann reaction: Rh positive, Group B bleeding time 2 minutes; clotting time 6 minutes; platelets 290,000 per c.mm. The father’s blood was Rh positive, Group O and the Wassermann reaction negative.

**Case 3.** Baby C. (a boy) was born spontaneously following a third medical induction at 42 weeks’ gestation on November 11, 1950 (weight 7 lb. 3 oz.). At birth the baby was in good condition and no petechiae were noticed. Three hours after birth a purpuric rash developed on the forehead, ears, posterior aspect of both

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**Fig. 1.—Drawing of Case 2 showing areas of intracutaneous haemorrhage.**

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upper arms, groins, and the back of the knees (Fig. 2). There was some bruising of the ears, a few petechiae were seen on the tongue, and slight haematemesis occurred. The spleen was not palpable. At eight hours the platelet count was 30,000 per c.mm., and at 11 hours the bleeding time was 9 minutes, the clotting time 7 minutes, and the prothrombin time 19 seconds (control 19 seconds). No further petechiae developed, but there was slight haemorrhage from the cord on the fourth day and slight melena on the ninth day. The baby was breast-fed from the second day and made very good progress without any specific treatment.

Further blood examinations gave the following results.

November 8, platelets 70,000 per c.mm.; capillary resistance within normal limits. Tibial puncture: only narrow blood obtained. No megakaryocytes were found in smears.

November 20, platelets 56,000 per c.mm.

November 22, platelets below 5,000 per c.mm.; bleeding time 5 minutes.

November 24, platelets 10,000 per c.mm. Tibial marrow puncture gave same result as previously; capillary resistance had fallen but was within the lower limit of normality.

November 27, platelets 15,000 per c.mm.

The child was discharged home on November 27, 1950, and was thriving well.

The mother, aged 30, was multiparous. Her four previous children, all girls, aged 8, 6, 4, 1½, were all alive and well, and all births were normal. Three weeks after the birth of the fourth child, she developed, for the first time, petechial rashes and spontaneous bruising. There was no family history of bleeding disease. Full investigation at this time led to a firm diagnosis of idiopathic thrombocytopenic purpura. During the following 18 months, the mother was seen regularly as an out-patient. Her general health remained good, and bleeding manifestations were slight, consisting only of occasional crops of petechiae and bruising. Menstrual loss was not excessive. She remained thrombocytopenic throughout, the platelet count ranging from 20,000 to 50,000 per c.mm., but the bleeding time was within normal limits. The present fifth pregnancy was confirmed at the beginning of April, 1950. Continued surveillance throughout the remainder of pregnancy revealed no significant change in her clinical or haematological state. She went into labour at the 42nd week after medical induction. Delivery was spontaneous, and the blood loss was normal. The platelet count at delivery was 25,000 per c.mm.; bleeding time 3 minutes; capillary resistance was low. The lochia was normal and the puerperium was uneventful.

Excess breast milk from this mother was fed to another infant whose haemopoietic system appeared normal but who was suffering from an inoperable spina bifida. The blood findings were as follows:

November 24, 1950, R.B.C. 6·09 million; platelets 530,000 per c.mm.

November 25, a.m., platelets 380,000 per c.mm. (milk started) p.m., platelets 330,000 per c.mm.

November 26, a.m., platelets 250,000 per c.mm.; p.m., platelets 430,000 per c.mm.

November 27, a.m., platelets 317,000 per c.mm.; p.m., platelets 359,000 per c.mm.

November 28, a.m., platelets 235,000 per c.mm.; p.m., platelets 569,000 per c.mm.

There was thus no significant fall in the platelet count while the milk was being given.

Discussion

The three cases reported above illustrate different syndromes arising from thrombocytopenia. In cases 1 and 3 the mother was known to be suffering from idiopathic thrombocytopenic purpura, the manifestations in the infants were present at or soon after birth, were mild and transient, and the condition resolved spontaneously. In case 2 there was no family history of bleeding disease, the mother's blood findings were normal, the manifestations of the disease in the child did not appear until the third week of life, and the condition proved rapidly fatal.

Thrombocytopenia in the adult is known to result from many different causes which may be classified thus. (A) Idiopathic (essential) thrombocytopenic purpura; (B) secondary (symptomatic) thrombocytopenic purpura caused by (i) bone marrow defect,
e.g. aplasia, leukaemia, carcinoma; (ii) toxic agents, e.g. heavy metals, quinine, sulphonamides; (iii) infection and toxaemia, e.g. septicæmia, eclampsia; (iv) splenic disorder, e.g. ‘hyper-splenism’ of congestive, syphilitic, tuberculous splenomegaly.

The clinical features of the disease in the adult vary with the cause. It would therefore seem of importance to discover whether thrombocytopenia in the newborn also has diverse origins, and variation in clinical manifestations. A study of the three cases just described indicated that this was indeed the case, and further suggested a logical classification of cases of thrombocytopenia in the newborn into two main groups: those associated with thrombocytopenic purpura in the mother, and those in whom the disease appeared as a primary condition, the mothers being apparently normal. With this idea in mind, the cases recorded in the literature have been critically reviewed, and classified into these two broad groups. The information provided was incomplete in many cases, and it became necessary in each group to list first those cases about which sufficient information was available to permit of accurate classification, and second, those cases in which the data provided was inadequate, permitting only of a provisional diagnosis.

**Group 1: Purpuric Infants of Mothers with Purpura**

Thrombocytopenia in the pregnant woman may be either idiopathic or secondary. The recorded examples of purpuric infants born of mothers who were themselves suffering from purpura have therefore been divided into two groups, according to the type of disease in the mother.

**A. Idiopathic Thrombocytopenic Purpura in the Mother.** The criteria required for this diagnosis are (1) thrombocytopenia 100,000 per c.mm. or less, (2) no evidence of any cause for the thrombocytopenia, (3) normal clotting time, (4) prolonged bleeding time, (5) increased capillary fragility.

### Table 1

**Purpura in Infants of Mothers with Idiopathic Thrombocytopenic Purpura**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author</th>
<th>Maturity</th>
<th>Sex</th>
<th>Age at Onset</th>
<th>Distribution of Lesions</th>
<th>Duration (days)</th>
<th>Treatment</th>
<th>Feeding</th>
<th>Platelets (thousand per c.mm.)</th>
<th>Outcome</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Walsner, 1924</td>
<td>Prem.</td>
<td>F</td>
<td>1 day</td>
<td>Skin</td>
<td>2</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Liebling, 1926</td>
<td>F.T.</td>
<td>F</td>
<td>Birth</td>
<td>Skin, bowel</td>
<td>5</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Sanfey et al., 1936</td>
<td>F.T.</td>
<td>F</td>
<td>Birth</td>
<td>Skin, bowel</td>
<td>6</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Davidson, 1937</td>
<td>F.T.</td>
<td>F</td>
<td>Birth</td>
<td>Skin, bowel</td>
<td>6</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Urbankis and Hutner, 1942</td>
<td>F.T.</td>
<td>M</td>
<td>Birth</td>
<td>Skin, C.N.S.</td>
<td>2</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
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<tr>
<td>6</td>
<td>Whitney and Barritt, 1942</td>
<td>F.T.</td>
<td>M</td>
<td>Birth</td>
<td>Skin, C.N.S.</td>
<td>2</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Prem.</td>
<td>M.</td>
<td>Birth</td>
<td>5 hours</td>
<td>Skin</td>
<td>2</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<tr>
<td>8</td>
<td>Finn, 1944</td>
<td>F.T.</td>
<td>M</td>
<td>1 hour</td>
<td>Skin</td>
<td>2</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<tr>
<td>9</td>
<td>Morrison and Samwick, 1945</td>
<td>F.T.</td>
<td>M</td>
<td>8 hours</td>
<td>Skin, bowel</td>
<td>2</td>
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<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<td>10</td>
<td>Patterson, 1946</td>
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<td>M</td>
<td>2 days</td>
<td>Bowl</td>
<td>3</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<tr>
<td>11</td>
<td>Talmadge and Berman, 1947</td>
<td>F.T.</td>
<td>F</td>
<td>6 hours</td>
<td>Skin, bowel</td>
<td>10</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<tr>
<td>12</td>
<td>Prem.</td>
<td>F.</td>
<td>6 hours</td>
<td>2 days</td>
<td>Skin, bowel</td>
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<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<tr>
<td>13</td>
<td>McAleoney and Kristan, 1949</td>
<td>F.T.</td>
<td>F</td>
<td>4 hours</td>
<td>Skin, bowel</td>
<td>1</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
<td>+</td>
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<tr>
<td>14</td>
<td>F.T.</td>
<td>F.</td>
<td>4 hours</td>
<td>2 days</td>
<td>Skin, bowel</td>
<td>7</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
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<tr>
<td>15</td>
<td>McAleoney and Kristan, 1949</td>
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<td>F</td>
<td>3 hours</td>
<td>Skin, bowel</td>
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<td>B</td>
<td>40</td>
<td>90 R</td>
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<tr>
<td>16</td>
<td>Robson, 1949</td>
<td>P.M.</td>
<td>M</td>
<td>3 hours</td>
<td>Skin</td>
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<tr>
<td>17</td>
<td>Bayer, 1931</td>
<td>F.</td>
<td>Birth</td>
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<td>Skin</td>
<td>3</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
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<tr>
<td>18</td>
<td>Dohrn, 1874</td>
<td>F.T.</td>
<td>F</td>
<td>Birth</td>
<td>Skin, bowel</td>
<td>8</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
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<tr>
<td>19</td>
<td>F.T.</td>
<td>M.</td>
<td>36 hours</td>
<td>2 days</td>
<td>Skin, bowel</td>
<td>4</td>
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<td>90 R</td>
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<td>20</td>
<td>Rodecut, 1928</td>
<td>F.T.</td>
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<td>90 R</td>
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<tr>
<td>21</td>
<td>Conti, 1933</td>
<td>Prem.</td>
<td>M.</td>
<td>Birth</td>
<td>C.N.S.</td>
<td>3</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
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<td>+</td>
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<td>22</td>
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<td>23</td>
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<td>Soon</td>
<td>Skin, bowel</td>
<td>120</td>
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<td>0</td>
<td>0 D</td>
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<td>+</td>
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<tr>
<td>24</td>
<td>Prem.</td>
<td>F.</td>
<td>4 months</td>
<td>3 hours</td>
<td>Skin</td>
<td>42</td>
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<tr>
<td>25</td>
<td>Prem.</td>
<td>F.</td>
<td>6 weeks</td>
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<td>Skin</td>
<td>3</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
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</table>

**Cases of doubtful diagnosis**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author</th>
<th>Maturity</th>
<th>Sex</th>
<th>Age at Onset</th>
<th>Distribution of Lesions</th>
<th>Duration (days)</th>
<th>Treatment</th>
<th>Feeding</th>
<th>Platelets (thousand per c.mm.)</th>
<th>Outcome</th>
<th>Mother</th>
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<td>26</td>
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<td>M</td>
<td>38 hours</td>
<td>Skin, bowel</td>
<td>4</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
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<tr>
<td>27</td>
<td>F.</td>
<td>M.</td>
<td>36 hours</td>
<td>300 B</td>
<td>Skin</td>
<td>3</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
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<tr>
<td>28</td>
<td>F.</td>
<td>M.</td>
<td>36 hours</td>
<td>300 B</td>
<td>Skin</td>
<td>3</td>
<td>B</td>
<td>40</td>
<td>90 R</td>
<td></td>
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</tbody>
</table>

**F.T.** = full term; **Prem.** = premature; **B** = breast; **B1** = blood transfusion; **R** = recovered; **D** = died; **S.D.** = spontaneous delivery; **F** = forceps; **Ind.** = induced labour; **P** = in puerperium; **P.M.** = Post-mature.
(6) normal or increased numbers of megakaryocytes in the bone marrow.

It has been found necessary to accept several cases in which all the above criteria were not satisfied, since certain investigations, such as sternal puncture, have only recently come into routine practice. The history, clinical, and haematological findings were carefully studied in each case before arriving at a conclusion. Twenty-eight examples of idiopathic thrombocytopenic purpura in pregnant women who were delivered of purpuric children have been collected; the details of these cases are shown in Table 1 and the salient features summarized in Table 4. Of these 28 cases, 19 were accepted as definite examples of idiopathic thrombocytopenic purpura, while the remaining nine cases were insufficiently documented to allow of a firm conclusion.

From Table 4 it is evident that the female infant was more commonly affected than the male in a proportion of 10:7 in those cases in which the diagnosis in the mother was certain, while if the whole group is included, a similar proportion is maintained. No female child died in this group, if the fatal case in which the sex is unknown is excepted. Three of the male infants in this group died. All four deaths occurred in infants of the 13 mothers who are stated to have had active manifestations of idiopathic thrombocytopenic purpura during pregnancy, while no deaths occurred in the children born of the four mothers known to have the disease, but who were not purpuric during pregnancy. Haemorrhagic manifestations appeared within the first 24 hours of life in 17 infants (89%), and in 11 of these the purpura was noted at birth.

The ratio of females to males in this series is about 3:2, which may be compared with a ratio 4:3 in adults and older children (Wintrobe, Hanrahan, and Thomas, 1937). It must be noted that while more females were affected, all the infants who died or were stillborn were male. The severity of the disease in the child seems related to that in the mother. It has been shown by Robson and Davidson (1950) that the heaviest infant mortality in this type of thrombocytopenia is found in the children of women suffering so severely from the disease that splenectomy had failed to control it. In the present study, the lowest mortality occurred among infants born of mothers who, while thrombocytopenic, showed no outward manifestations of the disease during pregnancy. On the other hand, there are several instances on record of normal infants born of mothers suffering from the disease. The similarity as regards sex incidence, mortality, and onset between the accepted and the doubtful cases (Tables 1 and 4) suggests that the majority of the latter were in fact classified correctly in the group of infants born of mothers with idiopathic thrombocytopenic purpura.

B. Secondary Purpura in the Mother. Fourteen cases have been assigned to this group, in which a definite aetiological factor was present to cause purpura in the mother, and could have been responsible for the purpura in the child. The features of these cases are shown in Table 2, and salient points have been summarized in Table 4. Of these 14 cases, only four could be unreservedly accepted as examples of a mother with secondary thrombocytopenic purpura giving birth to a thrombocytopenic child. The remaining 10 cases were classified as doubtful, since in three of them (McAlenney and Kristan, 1949; Bayer, 1931) the child was thrombocytopenic, but the mothers' platelet counts were not stated; in another two cases (Landolt, 1948; Diehl, 1899) no platelet counts were recorded for the infants although the mothers were thrombocytopenic; and in another five (Hanot and Luzet, 1890; Glenn, 1893; Zange-"meister, 1898; Mosher, 1923; Pettavel, 1911) platelet counts were not given for either mother or child. Aetiological factors responsible for producing purpura in the mothers included rheumatic fever, quinine, syphilis, severe sepsis, and toxoaemia of pregnancy. Although the overall mortality among the babies was 57.1%, it must be noted that no infant deaths occurred among the 'acceptable' cases, i.e. those in which there were thrombocytopenia in both mother and child. Male infants were more frequently affected in this group of secondary purpuras, in the ratio of 9:3. Purpuric manifestations appeared within 24 hours of birth in the great majority of cases and the average duration of purpura was 11 days.

The lack of data, which casts some doubt on all but four cases in this group, seriously reduces the amount of information which can be derived from a study of these cases. The principal point of interest is that secondary or symptomatic maternal thrombocytopenia can apparently be transmitted to the child just as the idiopathic variety may be. The features of the disease in the children in the 1.A and 1.B groups may be tentatively compared (Tables 1, 2, and 4). There is a suggestion that the secondary type carries a greater mortality than does the idiopathic. This is perhaps to be expected since many of the symptomatic causes carry heavy intrinsic mortality rates. The sex incidence does not show the female preponderance found in the idiopathic group, and there is only slight suggestion of a higher death rate among male babies than among female. The duration of the disease in the
child appears to be somewhat longer than that in the idiopathic group, though there is no apparent difference in the situation or extent of the bleeding manifestations.

Group 2. Thrombocytopenic Purpura in Infants of 'Normal' Mothers

Twenty-one cases have been reported in which a child with thrombocytopenia was born of an apparently healthy mother. The details of these cases are shown in Table 3, and salient features are summarized in Table 4. Of these 21 cases, the data provided were considered adequate in six instances, and inadequate in the remaining 15. In the six acceptable cases, three were male infants, three were female, and one of the latter died (mortality 17%). If all the mothers in this group are accepted as being normal, the sex incidence of the purpuric infants is 14 males and seven females, with a total mortality of six (29%), three females and three males. The appearance of purpura within the first 24 hours was recorded in only 66%, and the average duration of the disease was six days.

This group of cases is one of considerable potential interest, and the lack of adequate data in so many instances is all the more unfortunate. If the mothers in this group are accepted as being normal, a comparison between this group and that previously discussed in which the condition appears to be transmitted from the mother might be expected to prove interesting. It may be seen from Table 4 that, as regards overall mortality, onset, duration and manifestations of the disease, there is close similarity between the group of children born of normal mothers and those whose mothers suffered from idiopathic thrombocytopenic purpura (Group 1.A). In the latter group, however, there was a striking preponderance of females affected by the disease and a heavy mortality among male babies. These features are not reproduced among the infants born of normal mothers; in these respects they more closely resemble the infants whose mothers had secondary purpura (Group 1.B).

Pathogenesis of Thrombocytopenia in the Newborn

A plausible explanation of the cause of thrombocytopenia in the newborn infants of mothers suffering from idiopathic or from secondary thrombocytopenic purpura is that the factor or influence at work in the mother is transmitted to the child. There is some support for this idea. The condition is generally mild and transient in character, spontaneous recovery usually takes place, and the severity of the disease in the child is roughly proportional to the severity in the mother.

It is of some practical importance to note that
CONGENITAL AND NEONATAL THROMBOCYTOPENIC PURPURA

TABLE 3

Purpura in Infants of 'Normal' Mothers

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author</th>
<th>Maturity</th>
<th>Sex</th>
<th>Age at Onset</th>
<th>Distribution of Lesions</th>
<th>Duration (days)</th>
<th>Platelets (thousands per c.mm.)</th>
<th>Outcome</th>
<th>Age</th>
<th>Parity</th>
<th>Type of Delivery</th>
<th>Platelets (thousands per c.mm.)</th>
<th>Outcome</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>Barclay, 1945</td>
<td>F.T.</td>
<td>M.</td>
<td>2 days</td>
<td>Skin, bowel</td>
<td>14</td>
<td>6</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Schefrin and Shechtman, 1949</td>
<td>F.T.</td>
<td>F.</td>
<td>Birth</td>
<td>Skin</td>
<td>3</td>
<td>67</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Landolt, 1948</td>
<td>F.T.</td>
<td>M.</td>
<td>Birth</td>
<td>Skin, C.N.S.</td>
<td>2</td>
<td>70</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>McAlenney and Kristan, 1949</td>
<td>F.T.</td>
<td>F.</td>
<td>2 hours</td>
<td>Skin</td>
<td>4</td>
<td>66</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Bluestone and Maslow, 1949</td>
<td>F.T.</td>
<td>M.</td>
<td>Birth</td>
<td>Skin, bowel</td>
<td>9</td>
<td>8</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Robson, 1949</td>
<td>Post.</td>
<td>F.</td>
<td>3 weeks</td>
<td>Skin, C.N.S.</td>
<td>6</td>
<td>10</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Greenwald and Sherman, 1929</td>
<td>F.T.</td>
<td>M.</td>
<td>6 days</td>
<td>Skin</td>
<td>12</td>
<td>30</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Lightwood, 1931</td>
<td>F.T.</td>
<td>M.</td>
<td>5 weeks</td>
<td>Skin</td>
<td>9</td>
<td>38</td>
<td>R</td>
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<td></td>
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<tr>
<td>50</td>
<td>Landolt, 1948</td>
<td>F.T.</td>
<td>F.</td>
<td>12 hours</td>
<td>Skin</td>
<td>150</td>
<td>7</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>McAlenney and Kristan, 1949</td>
<td>F.T.</td>
<td>M.</td>
<td>Birth</td>
<td>Skin</td>
<td>1</td>
<td>183</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Bayer, 1931</td>
<td>M.</td>
<td>1 day</td>
<td>Bowel</td>
<td>6</td>
<td>120</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>M.</td>
<td>3 days</td>
<td>Bowel, C.N.S.</td>
<td>4</td>
<td>90</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>M.</td>
<td>4 days</td>
<td>Bowel, C.N.S.</td>
<td>3</td>
<td>45</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>M.</td>
<td>2 days</td>
<td>Skin, bowel</td>
<td>2</td>
<td>50</td>
<td>D</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>F.</td>
<td>2 days</td>
<td>Bowel</td>
<td>3</td>
<td>60</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>57</td>
<td>F.</td>
<td>Birth</td>
<td>Skin</td>
<td>3</td>
<td>48</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>58</td>
<td>M.</td>
<td>Birth</td>
<td>Skin</td>
<td>3</td>
<td>66</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>M.</td>
<td>5 days</td>
<td>Skin, C.N.S.</td>
<td>6</td>
<td>80</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>M.</td>
<td>5 days</td>
<td>Skin, C.N.S.</td>
<td>6</td>
<td>80</td>
<td>D</td>
<td>S.D.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>61</td>
<td>F.</td>
<td>Birth</td>
<td>Skin</td>
<td>3</td>
<td>66</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
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<tr>
<td>62</td>
<td>Wyatt et al., 1950</td>
<td>F.T.</td>
<td>M.</td>
<td>5 days</td>
<td>Skin, bowel</td>
<td>91</td>
<td>80</td>
<td>R</td>
<td>S.D.</td>
<td></td>
<td></td>
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<tr>
<td>63</td>
<td>F.</td>
<td>F.</td>
<td>Birth</td>
<td>Skin</td>
<td>35</td>
<td>23</td>
<td>D</td>
<td>S.D.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Cases of doubtful diagnosis

Notes:
- F.T. = full term
- Prem. = premature
- B = breast
- Bl = blood transfusion
- R = recovered
- D = died
- S.D. = spontaneous delivery
- F = forceps
- Ind. = induced labour
- P = in puerperium
- P.M. = Post-mature

F.T. = forceps; Ind. = induced labour; P = in puerperium; P.M. = Post-mature.

TABLE 4

Summary of Salient Features of Reported Cases

<table>
<thead>
<tr>
<th>Group 1: Infants of Purpuric Mothers</th>
<th>Group 2: Infants of Normal Mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Idiopathic</td>
<td>B. Secondary</td>
</tr>
<tr>
<td>Accepted Cases</td>
<td>Accepted Cases</td>
</tr>
<tr>
<td>Sex</td>
<td>Total</td>
</tr>
<tr>
<td>Sex</td>
<td>d</td>
</tr>
<tr>
<td>Number</td>
<td>7</td>
</tr>
<tr>
<td>Deaths</td>
<td>3</td>
</tr>
<tr>
<td>Mortality</td>
<td>21%</td>
</tr>
</tbody>
</table>

Proportion of cases in which purpura was noted within 24 hours of birth

89% | 82% | 100% | 86% | 66% | 43%

Average duration of purpuric manifestations (days)

5 | 10 | 11 | 13 | 6 | 17

Average initial platelet count (thousands per c.mm.)

46 | - | 19 | - | 38 | -
breast-feeding is not contra-indicated in these infants. Of the nine cases in Group 1.A stated to be breast-fed, eight made a good recovery. (The overall mortality in this group was 25%). Furthermore, in the third case described here, milk from the mother was fed to another infant without causing any significant alteration in platelet levels. It has been suggested, however (Gates, 1946), that thrombocytopenic purpura may be a hereditary condition, and certain features lend credence to this possibility. An affected mother may give birth to a normal child (Finn, 1944). An affected mother may have dissimilar twins, one affected and one not (Goldstein, 1947). A healthy mother may bear affected children (cases in Group 2), and a healthy mother has been reported as producing dissimilar twins, one affected and one not (Bayer, 1931). These phenomena are suggestive of a sex-linked genetic disorder, but much more evidence is required. Careful study of the families of sufferers from idiopathic thrombocytopenic purpura and long-term follow-up of cases of congenital thrombocytopenic purpura would seem indicated.

The pathogenesis of the thrombocytopenia arising in infants whose mothers were stated to be normal is less readily explained. The features of such cases bear some resemblance to those whose mothers were suffering from idiopathic thrombocytopenic purpura in regard to total mortality, onset, and duration of the disease, and resemble those whose mothers were suffering from secondary purpura (Group 1.B) in regard to sex incidence and sex mortality. It might be suggested that these cases of thrombocytopenia arising de novo in the newborn are of two types, one similar to the idiopathic type in the adult, and the other secondary to some disorder in the child itself. Study of the cases in Group 2 suggests that this might be so. The case reported by Greenland and Sherman (1929), both cases of Landolt (1948), and the second case recorded here all showed congenital abnormalities of various types together with aplasia of the bone marrow. Thrombocytopenia could certainly be considered as secondary in type when it is due to such bone marrow aplasia. Aplasia is not found in the marrow in idiopathic thrombocytopenia in the adult, where the accepted picture is that of a normal or even hyperplastic state. It might be expected that the bone marrow in the infant born of a mother with idiopathic thrombocytopenic purpura would show the same appearance. In the case reported by Morrison and Samwick (1945) and in one of the cases reported by Whitney and Barritt (1942) the bone marrow of the infant was normal or hyperplastic. On the other hand, in a second case reported by Whitney and Barritt, and in the cases of Finn (1944) and Guttfreund (1933) hypoplasia or aplasia was found. The findings in case 3 reported here were also suggestive of marrow aplasia. It would appear, therefore, that, until more information is available about the appearance of the bone marrow in infants suffering from thrombocytopenia, it cannot be assumed that aplasia excludes the possibility of the thrombocytopenia being idiopathic in type. The existence as a separate entity of a type of congenital thrombocytopenia due to aplasia of the bone marrow as suggested by Landolt (1948) and Hauser (1948) must be regarded as uncertain.

The two cases reported by Wyatt, Saxton, Lee, and Pinkerton (1950) are of considerable interest. Virus inclusion bodies were demonstrated in cells in many organs of both these children, who were thrombocytopenic and whose mothers were stated to be normal. These inclusion bodies were also found in cases of bronchopneumonia, hepatitis, and enteritis, and the authors suggest that they were examples of a specific viral infection which can be acquired, either transplacentally or directly by the infant postnatally. The infection may be subclinical when inclusion bodies may be found in the salivary glands, but the severe infection may give rise, among other things, to a haemorrhagic diathesis (Farber and Wolbach, 1932). Pettavel (1911) described a case of congenital purpura in which inclusion bodies were found in the thyroid gland. In his case, the mother is stated to have suffered from purpura, but no indication is given of the type of purpura in either mother or child. Thrombocytopenia resulting from virus infection could certainly be regarded as secondary in type, as in measles or smallpox.

As regards the remainder of the cases of thrombocytopenia in infants whose mothers were stated to be normal, it might be suggested that these were idiopathic, and that there are three possible explanations for the occurrence of such cases. First, the mothers of such children may not in fact have been normal. A woman may suffer from idiopathic thrombocytopenic purpura, but be symptom-free and in remission during pregnancy, and yet give birth to a thrombocytopenic infant (Urbanski and Hutner, 1942; Finn, 1944; Sanford, Leslie, and Crane, 1936). A single postnatal examination may be insufficient to reveal the presence of the disease. A second explanation might be that idiopathic thrombocytopenia is a genetic fault, in which the apparently normal mothers (or fathers) are carriers of the condition. There is as yet, however, no direct evidence to support this idea. Thirdly, it may be that these infants are developing the disease known in adults as idiopathic thrombocytopenic purpura at a very early age. This has been reported
CONGENITAL AND NEONATAL THROMBOCYTOPENIC PURPURA

as occurring in the first year of life (Wintrobe, 1946). The present theories of the aetiology of idiopathic thrombocytopenic purpura are not incompatible with the disease manifesting itself at such an early age. Many authors believe that the condition is due to over-production by the spleen of a factor which causes arrest of platelet formation by the megaloblasts (Dameshek and Miller, 1946), or which gives rise to capillary abnormality (Robson, 1949). Other writers have adduced evidence of a coagulation defect in this condition (Allen, Bogardus, Jacobson, and Spurr, 1947; Alexander and de Vries, 1949; Quick, 1949). In the light of these theories, the cases reported by Bayer (1931) are of considerable interest (Table 3). This writer studied capillary resistance and blood coagulation in the newborn, and reported 49 cases of haemorrhagic disease, all of which showed capillary fragility. Nine of these cases in addition were markedly thrombocytopenic, and have therefore been included in Group 2, since the mothers were said to be normal. It is interesting to note that five of these cases had melaena, but did not show any skin manifestations of purpura. In the absence of careful blood examination such cases could easily be mistaken for examples of melaena neonatorum due to hypoprothrombinaemia. This might account for the small proportion of cases of melaena neonatorum which do not respond to vitamin K therapy. It seems reasonable to suggest that careful investigation of the relationship between capillary function, platelet levels, and the coagulation mechanism in all types of purpura in the newborn might go far towards elucidating the problem of congenital and neonatal purpura.

Summary

A comprehensive survey of the literature reveals that 52 cases of congenital or neonatal thrombocytopenia have now been reported. Three further examples are recorded*. These cases have been critically reviewed, and classified.

We wish to thank Professor R. W. B. Ellis and Professor L. S. P. Davidson for their advice and criticism; Mr. R. W. Mathews of E. & S. Livingstone, Ltd. for the illustration of Case 2; and Dr. Agnes MacGregor for the post-mortem report.

* The mother of Case 1, since the presentation of this paper, has had another baby (a girl) who developed congenital thrombocytopenic purpura of the skin three hours after birth. This case also belongs to Group Ia; platelet counts 45,000-60,000 per c.mm. Marrow blood only obtained showing few megaloblasts. The infant was breast-fed and doing well when last seen.

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Congenital and Neonatal Thrombocytopenic Purpura

H. N. Robson and C. H. M. Walker

Arch Dis Child 1951 26: 175-183
doi: 10.1136/adc.26.126.175

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