STUDY II

GLUCOSE TOLERANCE

As part of an extensive investigation into the blood sugar levels of normal and sick children, Svensgaard, (1931-32) studied the glucose tolerance of 8 normal newborn babies during the first and second weeks of life. A standard dose of glucose was given by mouth after a fast of 5 hours and frequent blood specimens were taken. In each case the glucose tolerance was greater during the first week.

Intention

The original intention of this study was to test the glucose tolerance of babies of both non-diabetic and diabetic women during the first and second weeks of life in order to find if any correlation exists between the changing blood glucose and eosinophil levels, the involution of the foetal adrenal cortex and glucose tolerance. The technical difficulties encountered make the value of the achieved observations doubtful, but the study led to some simple observations upon the immediate post-natal glucose tolerance of infants born to diabetic women and upon the glucostatic theory of appetite.

The Glucose Tolerance of Normal Babies

Method

The limitations of the oral glucose tolerance test are well /
well known, but because of the ethical and technical problems concerned in conducting intravenous tests in normal babies, an attempt was made to use the oral route in the present study. Bottle feeding of the babies with the 10 per cent glucose solution proved to be much too slow, however, for the infant had often failed to take all of it by the time the first post-prandial blood sugar was due.

Attempts at giving the dose by rapid gavage were unsatisfactory as the babies frequently lost varying quantities of the solution by vomiting. Intravenous injection of the volumes required was impossible without exposing a vein and this could not be justified. The glucose solution was given therefore by deep intramuscular injection. A standard dose of one gramme of glucose was used and the 5 ccs. of fluid were given either as one injection or as two divided simultaneous doses. The babies had fasted for eight hours before being tested on the third and tenth days of life. Specimens were taken fasting and at 15, 30, 45, 60, 90 and 120 minutes. They were analysed in duplicate by the method of Ramsay (Appendix III). Only normal babies of non-diabetic women were used.

RESULTS

The results are given in Table 25 and 26. The one-hour sample was not found to be useful and it was soon abandoned in favour of a specimen taken at two hours.

Because of the difficulty in comparing glucose tolerance curves /
### TABLE 25

**GLUCOSE TOLERANCE OF NORMAL NEWBORN INFANTS ON THE THIRD DAY OF LIFE**

**THIRD DAY TEST**

<table>
<thead>
<tr>
<th>Administration of glucose g. 1.0 intramuscular injection</th>
<th>Case</th>
<th>Blood sugar in mg. %</th>
<th>Hours after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fasting</td>
<td>$\frac{1}{4}$</td>
</tr>
<tr>
<td>Simultaneous divided doses</td>
<td>1</td>
<td>74.5,76</td>
<td>98.5,100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>53.5,54</td>
<td>82.5,85</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>51,53</td>
<td>66.4,65.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>62,62</td>
<td>95,96.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>70.5,69.5</td>
<td>93.5,95.5</td>
</tr>
<tr>
<td>Single dose</td>
<td>6</td>
<td>60,61.5</td>
<td>85.5,85.5</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>75,75</td>
<td>102.5,102.5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>75,76</td>
<td>103.5,105.5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>67,68.5</td>
<td>97.5,97.5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>59,59</td>
<td>90,90.5</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>56.5,57.5</td>
<td>69,5,69</td>
</tr>
</tbody>
</table>

* N.V. - the numerical value of the curve
**TABLE 26**

**GLUCOSE TOLERANCE OF NORMAL NEWBORN INFANTS ON THE TENTH DAY OF LIFE**

**TENTH DAY TEST**

<table>
<thead>
<tr>
<th>Administration of glucose g. 1.0 intramuscular injection</th>
<th>Case</th>
<th>Blood sugar in mg.%</th>
<th>Hours after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneous divided doses</td>
<td></td>
<td>Fasting</td>
<td>1/4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>86.5,87</td>
<td>109.5,109</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>62,62</td>
<td>96,92.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>76/5,78.5</td>
<td>87,86.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>91,90.5</td>
<td>106,18.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>76.5,78.5</td>
<td>111.5,111.5</td>
</tr>
<tr>
<td>Single dose</td>
<td>6</td>
<td>71,72.5</td>
<td>101.5,101.5</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>82,82.5</td>
<td>115.5,118.5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>72,74</td>
<td>93.5,95.5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>94,96.5</td>
<td>135,137</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>74.5,78</td>
<td>113,116</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>86.86</td>
<td>110.5,112</td>
</tr>
</tbody>
</table>

* N.V. - the numerical value of the curve
curves almost all of which begin from a higher fasting level at the second test, an attempt has been made, at the suggestion of Dr. C.P. Stewart, to put a numerical value on each constructed curve. This is done by selecting sugar values at the same time intervals for each pair of curves. These are then drawn and lines are projected, from the fasting levels of each, parallel to the horizontal axis. The area enclosed by each curve and its "base" is then measured and the result in square millimetres represents the numerical value of the glucose tolerance (the work was done in 1952 before the description of the increment index by Amatuzio, Stutzman, Vanderbildt, & Nesbitt, 1953).

All of the babies who received two simultaneous injections of 0.5 g. glucose each had a higher numerical value for the first curve, indicating an apparent increase in tolerance from the third to the tenth days. Because of possible unequal absorption from the glucose depots in the gluteal muscles, six further babies received only one injection of one gramm. Of these, three had a higher numerical value in the second week (indicating a decrease in tolerance from the third to the tenth day), one showed a decrease in the numerical value and, in two, the figure did not alter significantly.

These wide differences in tolerance during the first and second weeks of life fail to confirm Svensgaard's finding. The irregularity of some of the curves suggests that the speed of absorption of hypertonic glucose from gluteal /
gluteal muscles varies. Because of this, and because of the variability in the results no certain interpretation of them can be achieved. No attempt was made, therefore, to test the glucose tolerance of babies of diabetic women, but intravenous glucose tolerance tests have been carried out on a small number of such infants by Read (1951).

The Glucose Tolerance of Babies born to Diabetic Women

Read claimed that the intravenous glucose tolerance of newborn infants of non-diabetic women does not differ between the first and second weeks of life and that there is no evidence of increased tolerance in babies of diabetic women during the immediate post-natal period. Scrutiny of his statistical evidence, however, shows that his conclusions are scarcely justified and that his results have no bearing upon what happens during the first few hours of life when the babies of diabetic women in particular are likely to be hypoglycaemic. He failed to mention the intravenous dose used, the basis on which a dose was calculated, the weight, the maturity or the route of delivery of the babies in his "normal group". The first curve was obtained at ages which ranged from 16 to 66 hours and the second was about one week later. Less than ten normal babies were included in the first week curve, there were no more than six in the second, and the number of points plotted at each time-interval on his time-trend diagrams shows a steady decrease. Individual curves are not shown, but upon this small series of cases Read /
Read calculates a standard deviation (S.D.) and the range of ± 2 S.D. about the mean over the ninety-minute interval. There is reason to doubt the accuracy of the calculation of the S.D. and the "normal" range extends roughly from 108 to 190 mg.% at ten minutes from 75 to 160 mg.% at twenty minutes and from 50 to 135 mg.% at one hour. Only one baby was examined in his attempt to show that the tolerance of all prematurely born babies lies within normal limits.

Only four babies of diabetic women were studied, their weight ranged from 2 to 4.8 kilogrammes and their maturity from 33 to 38 weeks. In this case Read plotted the individual curves and found them to lie within what he believed to be the normal range.

Serial blood sugar levels on the first day of life were determined by Komrower (1954) on two groups of babies born to diabetic women. One group was given 2.0 grammes of glucose (50% solution) by mouth during the first eight hours and the other received none. Although the mean curve of the blood sugar is rather higher in the "glucose group" than in the other (his figure 4), it is clear (from his table 2) that hypoglycaemic levels developed even when glucose was given e.g. falls of 130 to 10, 110 to 18, and 90 to 14 milligrammes blood sugar per cent. in two hours.

A number of babies who were born between 1948 and 1951 in the present series received glucose during the first few hours. It was given by mouth until the risk of inhalation became apparent. Some babies were then given injections into /
# Table 27

## Blood Sugar Level Response to Administration of Glucose in First Few Hours of Life

<table>
<thead>
<tr>
<th>Case</th>
<th>Wt. in Kg.</th>
<th>Blood Sugar Levels and Doses of Glucose Given</th>
<th>Hours After Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Birth</td>
</tr>
<tr>
<td>3</td>
<td>4.5</td>
<td>66 (2) 15 50 (15) 70 (15) 100</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.8</td>
<td>180 (4) 34</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.4</td>
<td>120 (1) 70 (8.5) 60 (7.5) (10) 64</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4.5</td>
<td>60 (5) 74 (7.5) 74 (7.5) 138</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2.9</td>
<td>182 (2.5) 124 (7.5) 138</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>2.8</td>
<td>254 (1) 180 (1) 86 (8) 52</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>2.8</td>
<td>52 (2) 132 (6.5) 74 (7.5) 74 (1) 78</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>1.6</td>
<td>153 (2) 88 (0.5) 70 (0.5) 58 (0.5) 56 (0.5) 56</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>4.7</td>
<td>102 (2.5) 94 (1) 104 (1) 44</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.8</td>
<td>94 (2.5) 72 (6.5) 62 (6.5) 66</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>2.7</td>
<td>108 (2.5) 98 (6.5) 80 (1) 50</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>4.1</td>
<td>102 (2.5) 58 (1) 72 (1) 42 (1) 55 (1.5) 55 (1.5)</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>3.7</td>
<td>114 (1) 117 (1) 48 (1) 57 (1) 60 (1) 60 (1) 60 (1)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>2.7</td>
<td>43 (1) 51 (1.5) 57 (1.5) 42 (1.5) 53 (1.5) 53 (1.5)</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>3.3</td>
<td>76 (2.5) 69 (1.5) 55 (1.5) 55 (1.5) 55 (1.5) 55 (1.5)</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>3.5</td>
<td>90 (1) 103 (1) 121 (1) 53 (1.5) 53 (1.5) 53 (1.5)</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>4.3</td>
<td>60 (1) 54 (1) 54 (1) 54 (1) 54 (1) 54 (1) 54 (1)</td>
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</tr>
<tr>
<td>46</td>
<td>3.3</td>
<td>60 (1) 54 (1) 54 (1) 54 (1) 54 (1) 54 (1) 54 (1)</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>2.4</td>
<td>70 (2) 82 (2) 69 (1.5) 69 (1.5) 69 (1.5) 69 (1.5)</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>3.3</td>
<td>49 (1) 42 (1) 34 (1) 34 (1) 34 (1) 34 (1) 34 (1)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>2.6</td>
<td>150 (1) 117 (1) 117 (1) 117 (1) 117 (1) 117 (1) 117 (1)</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>-</td>
<td>51 (1) 47 (1) 47 (1) 47 (1) 47 (1) 47 (1) 47 (1)</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>2.8</td>
<td>40 (1) 20 (1) 46 (1) 46 (1) 46 (1) 46 (1) 46 (1)</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>3.7</td>
<td>56 (1) 42 (1) 35 (1) 35 (1) 35 (1) 35 (1) 35 (1)</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>3.8</td>
<td>92 (1) 100 (1) 78 (1) 78 (1) 78 (1) 78 (1) 78 (1)</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>3.8</td>
<td>84 (1) 82 (1) 82 (1) 82 (1) 82 (1) 82 (1) 82 (1)</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>3.8</td>
<td>62 (1) 160 (1) 54 (1) 48 (1) 79 (1) 79 (1) 79 (1)</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>3.7</td>
<td>51 (0.5) 24 (1.5) 18 (1.5) 18 (1.5) 18 (1.5) 18 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

* The figures in brackets represent grammes of glucose given. Where underlined once the oral route of administration was used, where underlined twice the dose was intravenous. Otherwise the glucose was given by intramuscular injection.
into the umbilical vein, but the majority received intramuscular injections of 25 to 50 per cent. glucose after initial trials had shown this to be safe. Blood sugar levels were determined sporadically according to the appearance of the child and to the time available. The results are recorded in Table 27. The blood sugar level, the dose of glucose and the route of administration are all shown against a time-scale. As in Komrower's experience, the blood sugar fell in many cases during the first 3 to 4 hours and a trend toward spontaneous correction by six hours occurred.

THE CORRELATION OF THE BLOOD SUGAR LEVEL AND SIGNS OF HUNGER

The experimental studies of Hetherington & Fanson (1939) and of Brobeck (1946 & 1957) suggest that appetite may be governed by accurately located areas in the hypothalamus for which the term "feeding centres" has been suggested.

At least three explanations of the control of these centres have been advanced. Brobeck believes that a delicate sensitivity to the temperature-rise which follows absorption of food is important. Kennedy (1953) suggests that the level of fat in the body may affect the hypothalamus, possibly through the concentration of some circulating metabolite of fat. Mayer believes that the control of appetite is glucostatic (Mayer et al, 1951; Mayer, 1953 & 1951). He suggests that chemoreceptors in the hypothalamus are sensitive to variations in the blood-glucose level and that increased utilisation of glucose will stimulate appetite. Proof of this /
this theory in adults is made more difficult because of the psychic stimuli which may increase or oppose appetite.

During one of the first glucose tolerance tests which were attempted in the present study, the baby was obviously hungry before the fasting glucose level was obtained. Evidence of hunger quickly subsided when intramuscular glucose was given and at 15 minutes the infant was asleep. Signs of restlessness and of hunger reappeared as the blood sugar level began to fall. These observations suggested a possible relationship between a change in the blood sugar level and the expression of hunger. Reid, De Costa & Allweiss (1950) when writing about the newborn infant of the diabetic mother stated that "their rapidly developing hypoglycaemia is not attended by any clinical evidence of the dangerously low blood sugar except for an early and continuing suckling reflex".

The clinical state of the baby was, therefore, recorded before each sample of blood was taken during a series of glucose tolerance tests.

One gramme of glucose was given by intramuscular injection about 5.30 a.m. in each case. The results are recorded in Table 28. No constant relationship exists between the blood sugar level and sleep or the expression of hunger either in the first or second week of life. For example, Cases 1, 3 and 10 in the first week, and 8, 12 and 14 in the second seemed to respond to a rising blood sugar level with decreased evidence of hunger, quietness or sleep, although in Case 12 the /
### TABLE 28
CORRELATION OF THE BLOOD SUGAR LEVELS WITH SLEEP AND HUNGER

<table>
<thead>
<tr>
<th>Age in days</th>
<th>Blood sugar in mgms.%</th>
<th>¼</th>
<th>½</th>
<th>¾</th>
<th>2 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(fasting)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>75,76 ACH</td>
<td>103.5,105.5 S</td>
<td>101.5,101.5 S</td>
<td>95.5,98 S</td>
<td>76,74.5 AQ</td>
</tr>
<tr>
<td>3</td>
<td>67,68.5 S</td>
<td>97.5,97.5 AC</td>
<td>109,110 AC</td>
<td>105,106 AC</td>
<td>82,5,82 AQ</td>
</tr>
<tr>
<td>3</td>
<td>59,59 ACH</td>
<td>90,90.5 ACH</td>
<td>111,111.5 S</td>
<td>109.5,106.5 S</td>
<td>83,83.5 S</td>
</tr>
<tr>
<td>3</td>
<td>56.5,57.5 ACH</td>
<td>69.5,69 ACH</td>
<td>74.73.5 ACH</td>
<td>81,85.5 AQ</td>
<td>74,72 S</td>
</tr>
<tr>
<td>3</td>
<td>58,60 S</td>
<td>78.5,78.5 AQ</td>
<td>75.5,73.5 S</td>
<td>65.5,67 S</td>
<td>68.5,71 S</td>
</tr>
<tr>
<td>3</td>
<td>59,59 ACH</td>
<td>90,90.5 ACH</td>
<td>111,111.5 S</td>
<td>109.5,106.5 S</td>
<td>83,83.5 ACH</td>
</tr>
<tr>
<td>10</td>
<td>71,72.5 ACH</td>
<td>101.5,101.5 ACH</td>
<td>99,99 ACH</td>
<td>94,95.5 AC</td>
<td>79.5,79.5 ACH</td>
</tr>
<tr>
<td>10</td>
<td>82,82.5 ACH</td>
<td>115,118.5 ACH</td>
<td>116,116 AQ</td>
<td>104,5,106 S</td>
<td>83,5,84 S</td>
</tr>
<tr>
<td>10</td>
<td>72,74 ACH</td>
<td>93.5,95.5 ACH</td>
<td>105,103.5 ACH</td>
<td>91.5,92 ACH</td>
<td>82,83.5 ACH</td>
</tr>
<tr>
<td>10</td>
<td>94,96.5 ACH</td>
<td>135.5,137 S</td>
<td>132,141 AQ</td>
<td>142.5,141 S</td>
<td>130,131.5 ACH</td>
</tr>
<tr>
<td>10</td>
<td>75,76 ACH</td>
<td>89,5,90 S</td>
<td>91,91 ACH</td>
<td>90.5,90 S</td>
<td>94,94.5 S</td>
</tr>
<tr>
<td>10</td>
<td>73,75.5 ACH</td>
<td>84.5,84.5 S</td>
<td>84,83 S</td>
<td>81,81 S</td>
<td>96,94.5 S</td>
</tr>
<tr>
<td>11</td>
<td>75,75 ACH</td>
<td>84,86.5 AG</td>
<td>84,84 AQ</td>
<td>80,5,79 AC</td>
<td>77,75 S</td>
</tr>
<tr>
<td>13</td>
<td>86,86 ACH</td>
<td>110.5,112 ACH</td>
<td>124,120.5 S</td>
<td>114,110.5 S</td>
<td>94,91.5 S</td>
</tr>
</tbody>
</table>

**The symbols used mean—**

A, awake; S, asleep; Q, quiet; C, crying;
H, hungry as judged by fist, blanket or tongue sucking.
the increase in blood sugar was relatively small. Cases 2 and 6 in the first week and 7 and 9 in the second week failed to show any response, although a very adequate rise in the blood sugar occurred.

These observations were made in 1952 before Mayer's work had been noted and they were not, therefore, designed to test his glucostatic theory of appetite. They removed, however, the personal impression that a baby showed evidence of hunger because the blood sugar level had fallen and that he stopped feeding and returned to sleep when the blood sugar rose. More recently, Bernstein & Grossman (1956) have conducted similar but more complex experiments on adult subjects and these have failed to support the glucostatic hypothesis of Mayer.
The eosinopenic response to stress has been recognized since Zappert (1893) described its occurrence in certain infections, and in recent years it has been included among the phenomena of the alarm reaction (Selye, 1949). It was also shown that a decrease in the number of circulating eosinophils followed the injection of corticotrophin or cortisone, and Hills, Forsham and Finch (1948) concluded that stress induced eosinopenia by the release of these hormones.

Thorn, Forsham, Prunty and Hills (1948) demonstrated that the secretion of the adrenal cortex was essential if eosinopenia were to be produced, and from this devised the Thorn test. Following the determination of the absolute eosinophil count an adult receives 25 mg. of corticotrophin and the percentage decrease in four hours is found. Thorn et al believed that a decrement of 50% or more should occur in the presence of healthy adrenal cortex.

The significance of the results is dependent upon the stability of the eosinophil count in normal people over a similar time interval, and it has been shown by Swanson, Bauer and Ropes (1952) from a review of the literature and from a small but carefully studied series of their own that spontaneous variations of this magnitude may in fact occur at /
at certain periods of the 24 hours in adults.

The test has been employed also in newborn infants, but no careful study of hourly changes in the absolute eosinophil level at that age can be found. It was decided, therefore, to undertake an evaluation of the test in the neonatal period by determining the nature of the spontaneous variation over a four-hour interval and to note any relationship that might exist between eosinophil change and disturbance of the baby.

The second part of the investigation was planned to determine what responses could be obtained by the injection of varying doses of corticotrophin and cortisone. Finally it was hoped to determine whether the magnitude of the response varied with the age of the infant.

**Method**

**Part I**

Three groups of newborn infants, conforming to the criteria of normality previously employed (Study 4) were selected at random. The first- and third-day groups each contained 15 infants and there were 16 in the tenth-day group. Six hours were allowed to elapse before studying infants on the first day in order to avoid the rapid eosinophil changes previously described as occurring in that period.

The first count was carried out at 9.30 a.m. in the majority, but at 10.30 a.m. in a few, and thereafter at intervals of one hour until 3.30 p.m.

The infants were fed at 9.45 a.m. and 1.45 p.m. so that all /
all were fed once in the first four hours, or just before
starting in a few, and twice in the six hours.

The infant's reaction to the pain of heel-stabbing was
also noted and graded as follows: (1) Cried when stabbed
and for some time thereafter; (2) cried when stabbed;
(3) restless and whimpered when stabbed; (4) no response.

The technique of eosinophil counting was that described
by McArthur, Smart, MacLachlan, Terry, Harting, Gautier,
Godly, Swallow, Simeone, Zygmuntowicz, Christo, Crepeaux,
Point and Benson (1954), details of which are given in
Appendix 4.

Part II

Varying dosages of corticotrophin and cortisone were
injected into different groups of normal newborn infants at
9,30 a.m. and the percentage change induced in the eosinophil
count was determined.

The infants in some of the groups were given the same
dosage of the hormone on the first, third and tenth days, so
providing serial studies of response in individuals. Lest
the response to a third injection after the interval of a
week might be influenced by the infant's having received two
injections previously separate groups were given the same dose
on days one and three and on days three and ten.

Both the corticotrophin and cortisone were fresh and
taken from the same batches. The corticotrophin was later
checked favourably against another batch by the same manu-
facturer and a further batch by another manufacturer. A
tuberculin /
Figure 60

HOURLY EOSINOPHIL COUNTS OF NORMAL NEWBORN INFANTS

Day 1

HOURLY OBSERVATIONS ON THE EOSINOPHIL COUNTS OF NEWBORN INFANTS

DAY 1

follows grade I response
follows grade II response
follows grade III response
follows grade IV response
Figure 61

HOURLY EOSINOPHIL COUNTS OF NORMAL NEWBORN INFANTS

Day 3

HOURLY OBSERVATIONS ON THE EOSINOPHIL COUNTS OF NEWBORN INFANTS

DAY 3

follows grade I response
follows grade II response
follows grade III response
follows grade IV response
Figure 62

HOURLY EOSINOPHIL COUNTS OF NORMAL NEWBORN INFANTS

Day 10

HOURLY OBSERVATIONS ON THE EOSINOPHIL COUNTS OF
NEWBORN INFANTS

DAY 10

follows grade I response
follows grade II response
follows grade III response
follows grade IV response
### TABLE 29.

**DAY ONE**

<table>
<thead>
<tr>
<th>Case</th>
<th>Eosinophils/cu.mm. at hourly intervals</th>
<th>Percentage variation 0 - 4 hours</th>
<th>Maximum percentage variations in 4 hours</th>
<th>Maximum percentage variations in 6 hours</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>2</td>
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<td>4</td>
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<td>265 (2)</td>
<td>290 (2)</td>
<td>209 (2)</td>
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<tr>
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<td>-</td>
<td>393 (1)</td>
<td>373 (1)</td>
<td>398 (1)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>265 (2)</td>
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<td>106 (1)</td>
<td>106 (1)</td>
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<td>95 (1)</td>
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<td>105 (3)</td>
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<td>69 (3)</td>
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<td>73 (3)</td>
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<td>175 (1)</td>
<td>175 (1)</td>
<td>169 (1)</td>
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<td>44 (1)</td>
<td>44 (1)</td>
<td>48 (1)</td>
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<tr>
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<td>-</td>
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<td>640 (1)</td>
<td>638 (1)</td>
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<td>11</td>
<td>173 (2)</td>
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<td>179 (4)</td>
<td>178 (4)</td>
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<tr>
<td>12</td>
<td>360 (1)</td>
<td>409 (1)</td>
<td>360 (1)</td>
<td>364 (1)</td>
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<td>323 (3)</td>
<td>373 (3)</td>
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<td>309 (2)</td>
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<tr>
<td>15</td>
<td>270 (1)</td>
<td>261 (3)</td>
<td>257 (1)</td>
<td>264 (1)</td>
</tr>
</tbody>
</table>

The figure in brackets indicates the nature of the infant's response to "stabbing". (see text).
<table>
<thead>
<tr>
<th>Case</th>
<th>Eosinophils/cu.mm. at hourly intervals</th>
<th>Percentage variation 0 - 4 hours</th>
<th>Maximum percentage variations in 4 hours</th>
<th>Maximum percentage variations in 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>234 (2) 253 (2) 237 (3) 226 (3) 234 (3) 251 (3)</td>
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</tr>
<tr>
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<td>-6.7</td>
<td>4</td>
</tr>
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<td>+13.1</td>
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<td>-15.3</td>
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<td>-11.8</td>
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<td>-16.9</td>
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</tr>
<tr>
<td>23</td>
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<td>-5.8</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
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<td>-10.6</td>
<td>-14.1</td>
<td>3</td>
</tr>
<tr>
<td>25</td>
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<td>-19.5</td>
<td>-19.5</td>
<td>4 &amp; 6</td>
</tr>
<tr>
<td>26</td>
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<td>-5.2</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
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<td>+3.3</td>
<td>3</td>
</tr>
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<td>28</td>
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<td>-24.1</td>
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<td>29</td>
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<td>-3.6</td>
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</tr>
<tr>
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<td>-0.9</td>
<td>-17.8</td>
<td>3</td>
</tr>
</tbody>
</table>

The figure in brackets indicates the nature of the infant's response to "stabbing". (see text).
<table>
<thead>
<tr>
<th>Case</th>
<th>Eosinophils/cu.mm. at hourly intervals</th>
<th>Percentage variation 0-4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Maximum percentage variations in 6 hours at hour</td>
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<tr>
<td></td>
<td></td>
<td>% at hour</td>
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<td>31</td>
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<td>170 (1)</td>
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<tr>
<td>32</td>
<td>173 (2)</td>
<td>172 (2)</td>
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<tr>
<td>33</td>
<td>169 (2)</td>
<td>167 (2)</td>
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<td>35</td>
<td>286 (2)</td>
<td>285 (2)</td>
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<td>534 (2)</td>
</tr>
<tr>
<td>46</td>
<td>493 (1)</td>
<td>534 (2)</td>
</tr>
</tbody>
</table>

The figure in brackets indicates the nature of the infant's response to "stabbing". (see text).
tuberculin syringe was employed for the injection of cortisone in order to achieve more accurate dosage.

RESULTS

Part I

It may be seen (Figures 60 - 62 and Tables 29 - 31) that there was little spontaneous change in the eosinophil counts of individuals during the same six-hour period on the first, third and tenth days of life.

Of the 15 cases studied on the first day there was insignificant hourly variation in 10, a moderate downward trend in three, a slight downward trend in one and the count fluctuated a little in one. Only six of the 15 infants studied on the third day had very stable eosinophil counts. Four showed a slight and two a moderate downward trend, two a slight upward trend, and some fluctuation occurred in one. On the tenth day the count was stable in 11 of the 16 infants, two showed a slight and one a moderate downward trend, and in two there was a little fluctuation.

In 35 of the 46 infants the spontaneous change in four hours was either an increase or a decrease of less than 10 per cent. In only two of the 46 did the decrease exceed 20 per cent (Figure 63 and Tables 29 - 31).

It may also be seen from Figures 60 - 62 that there was no correlation between the reaction of the baby to the taking of blood and the change in the eosinophil count over the next hour.
Figure 63

EOSINOPHIL LEVELS OF NORMAL NEWBORN INFANTS
SPONTANEOUS CHANGE IN FOUR HOURS ON DAYS 1, 3 and 10 OF LIFE

EOSINOPHIL LEVELS OF NEWBORN INFANTS
SPONTANEOUS CHANGE IN FOUR HOURS
ON DAYS 1-3-10 OF LIFE

[Diagram showing the spontaneous change in eosinophil levels on days 1, 3, and 10 of life.]
hour, nor were the changes related to the time of feeds.

**Part II**

**Induced Change by Corticotrophin.** The scatter of changes (expressed as percentages) in the eosinophil counts of the infants studied on the first, third and tenth days of life as the result of injecting 1, 2.5 or 5 mg. of corticotrophin is shown in Figures 64-66 & Tables 34-36. Two groups were given 10 mg. of corticotrophin, one receiving it on the first and third days and the other on days three and ten, and as the results on day three were almost identical in the two groups, the figures for that day from the first group were used in Figures 64-66. Similarly, two groups were given 5 mg. corticotrophin in addition to the serial study and again there was little difference between them in the response on the third day.

**Eosinophilic Responses.**

The injection of 1 mg. of corticotrophin resulted in a substantial increase in the number of circulating eosinophils in four of the 15 cases the first day and a small increase occurred in a further two. One of the infants given 1 mg. on the third day also showed an increase in eosinophils.

The injection of 2.5 mg. provoked an increased eosinophil count in different cases on days one, three and ten, whereas only one small increment followed the injection of 5 mg. in a bigger series and none at all after the giving of 10 mg.

**Eosinopenic Responses.**

The eosinopenic responses to the different doses of corticotrophin /
THE EOSINOPENIC RESPONSE OF NORMAL NEWBORN INFANTS TO VARYING DOSES OF CORTICOTROPHIN AND CORTISONE IN FOUR HOURS

Day 1

Figure 64

DAY 1 EOSINOPHIL LEVELS OF NEWBORN INFANTS RESPONSE IN 4 HOURS TO VARYING DOSES OF CORTICOTROPHIN AND CORTISONE

- CORTICOTROPHIN
- CORTISONE
Figure 65

THE EOSINOPENIC RESPONSE OF NORMAL NEWBORN INFANTS TO VARYING DOSES OF CORTICOTROPHIN AND CORTISONE IN FOUR HOURS

Day 3

DAY 3 EOSINOPHIL LEVELS OF NEWBORN INFANTS RESPONSE IN 4 HOURS TO VARYING DOSES OF CORTICOTROPHIN AND CORTISONE

○ CORTICOTROPHIN
▲ CORTISONE

CHARGE
THE EOSINOPENIC RESPONSE OF NORMAL NEWBORN INFANTS
TO VARYING DOSES OF CORTICOTROPHIN AND CORTISONE IN FOUR HOURS

Day 10

Figure 66

EOSINOPHIL LEVELS OF NEWBORN INFANTS
RESPONSE IN 4 HOURS TO VARYING DOSES
OF CORTICOTROPHIN AND CORTISONE

% CHANGE

100 -
90 -
80 -
70 -
60 -
50 -
40 -
30 -
20 -
10 -
0 -

10 mg ACTH 2.5 mg ACTH 5 mg ACTH 10 mg ACTH 10 mg C 20 mg C
corticotrophin may be seen in Figures 64-66. The scatter of
response to each dose is considerable on each day, but from
the graphs and from the frequency distribution table (Table
32), which takes into consideration larger groups of infants,
it may be seen that in general the greater the dose of corti-
cotrophin the greater the fall in the eosinophil count.

The mean percentage changes with the varying doses are
recorded in Table 33, but when these means are re-calculated
after the removal of the large positive values on day one it
may be seen from Figure 67 that the regression lines of the
means indicate that a rough arithmetic relationship existed
between the degree of change and the dose of corticotrophin
injected.

The scatter of response to the varying doses overlaps
widely, however, and by comparing Figure 63 with Figures 64-66
it may be seen that an appreciable number of the healthy
infants studied had a spontaneous eosinolysis in four hours
as great as that which in some followed the injection of
corticotrophin. Certainly, with doses 2.5 mg. or less, so
many of the eosinopenic responses lay within ±20% that such a
result would have no significance in individual cases. With
5 mg. a minority of the responses was less than ±20%, but
only with 10 mg. was there almost universal response beyond
that figure.

From the groups studied no significant evidence can be
found to indicate that the response to corticotrophin was any
more /
## TABLE 32

**FREQUENCY DISTRIBUTION OF EOSINOPHIL RESPONSES**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Dose (mg.)</th>
<th>Day</th>
<th>Positive response</th>
<th>Negative Response (%)</th>
<th>No. of infants studied</th>
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</thead>
<tbody>
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<td></td>
<td></td>
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<td>10-19</td>
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<td>1</td>
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<tr>
<td>10</td>
<td></td>
<td>4</td>
<td></td>
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</tr>
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</table>
TABLE 33

MEANS OF EOSINOPHIL CHANGES

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Dose (mg)</th>
<th>% Change in four hours</th>
<th>No. of infants in group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td>Nil (i.e. 'spontaneous change')</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>-</td>
<td>-1.5</td>
<td>-5.7</td>
</tr>
<tr>
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<td>-20.6</td>
</tr>
<tr>
<td>Serial study 2</td>
<td>2.5</td>
<td>-20.8</td>
<td>-19.7</td>
</tr>
<tr>
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<td>5</td>
<td>-30.0</td>
<td>-34.6</td>
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<tr>
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<tr>
<td>Comparative groups 20</td>
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<td>-45.7</td>
<td>-53.0</td>
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<tr>
<td>Cortisone 10</td>
<td></td>
<td>-23.6</td>
<td>-19.5</td>
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<td>Comparative groups 24</td>
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<td>-24.4</td>
<td>-21.5</td>
</tr>
<tr>
<td>Comparative groups 18</td>
<td></td>
<td>-17.4</td>
<td>-24.7</td>
</tr>
</tbody>
</table>
Figure 67

AVERAGE PERCENTAGE DECREASES INDUCED IN NORMAL NEWBORN INFANTS BY VARYING DOSES OF CORTICOTROPHIN ON DAYS 1, 3 AND 10 OF LIFE

AVERAGE PERCENTAGE DECREASES INDUCED BY CORTICOTROPHIN ON DAYS 1, 3 AND 10 OF LIFE

% DECREASE

CORTICOTROPHIN mg.

DAY 3
DAY 10
DAY 1
more or less efficient on any of the three days.

**Induced Changes by Cortisone.** The results of injecting cortisone may be seen also in Figures 64-66 and in Tables 37-41.

Only one significant eosinophilic response was obtained, and unlike those from corticotrophin it occurred on the tenth day.

As with corticotrophin there was considerable individual variation in eosinopenic response, and over the four-hour interval the response of the cortisone group as a whole was appreciably less than the response of the groups receiving half the dosage (by weight) of corticotrophin.

It may be seen also that the responses of the group receiving 20 mg. of cortisone were on the whole smaller than those of the group receiving 10 mg. The mean change on the third day with the greater dosage is in fact larger, but this is due to the influence on the mean of four decrements which fall well below the main scatter of responses.

**DISCUSSION AND INFERENCES**

Spontaneous variations sufficiently great to invalidate the Thorn test were described by Rud (1947) in adults, but he used an acetone stain which has been recognized as being capable of introducing error into eosinophil counting.

Swanson et al (1952) undertook a careful study of the hourly spontaneous changes in adult absolute eosinophil values, and substantiated that diurnal variation did occur and that it was sufficiently great in the mornings to invalidate the test if /
if carried out then. They concluded, however, that the eosinophil count was sufficiently stable in the afternoons to justify Thorn testing even although spontaneous decrements of up to 40% were found. It was postulated that the stress of wakening and the relaxation of sleep might exert an important effect on the number of circulating eosinophils and would explain why the spontaneous changes are commoner and greater in the morning. Tatai and Ogawa (1951) studied normal sedentary adults and found that the absolute eosinophil count was maximum at night during sleep and minimum in the waking daylight hours.

Following the adjustments made by the infant to the start of extra-uterine life he is subjected to fewer stresses than the adult and his day is not divided into the same compartments of stress and relaxation. Much of his 24 hours is spent asleep protected from sudden changes in environmental temperature and with the sole disturbance of regular feeding. It was important, therefore, to determine whether the diurnal variation obtaining in adults occurred in newborn infants and whether feeding, with the associated processes of weighing and changing, or the painful stimulus occasioned by the taking of blood, were able to induce eosinophil decrements greater than 50%.

Leucocyte counts at 15 minute intervals over three or four hours following bottle feeds were carried out by Mitchell (1951), and variations in the number of white cells were found. No particular attention was paid to eosinophils and there was no /
no proof that the process of digestion was really responsible for the fluctuations. Washburn (1934) performed serial total white cell and differential counts on infants over the interval 9 a.m. to 5 p.m. and failed to find any pronounced variation in the total number of leucocytes. Those which did occur were produced largely by lymphocytic changes and were not related to ingestion, digestion, sleep, increased activity, or minor external disturbance. No absolute figures for eosinophils were given in the paper but the line of the hourly eosinophil values is depicted on the graphs of several infants, and, although they appear fairly stable, they are close to the base-line and the small fluctuations which do appear may amount to decrements of 30% or more.

In the present groups studied on the first, third and tenth days of life considerable stability of the eosinophil count over the same six hours in individual infants was found. Particular attention was paid to such spontaneous changes as might occur in the time interval zero to four hours for comparison with the eosinopenic responses to corticotrophin and cortisone. Usually at four hours the eosinophil count fell within the range ± 10% of the original value; in only two of the 46 individuals (4%) were the decrements in excess of 20% and in neither did they amount to 30%.

There is a tendency for eosinophil values to be higher on the third day than at any other time in the first 10 days with the exception of birth (Study 8). The evidence suggesting under-activity of the adrenal cortex following upon the immediate /
Immediate response to the stress of birth has been reviewed (Study 10), but no correlation between day-to-day eosinophil and blood glucose change was found to substantiate the suggestion that the explanation of the group trend toward rising eosinophil counts and falling blood glucose levels in the first few days might be that the production of glucocorticoids was depressed at that time.

White and Sutton (1950) observed the eosinopenic responses of infants to adrenaline, accepted decrements of 35% or greater as implying normal adrenocortical response and regarded anything less than a 30% decrease as abnormal. Employing these criteria they concluded that the pituitary-adrenal response in healthy, full-term infants was normal, but no attention was paid to the age of the subject in days. Since the publication of their paper, however, the use of adrenaline in the test has fallen into disrepute in view of such inconsistent results as those demonstrated by Kark and Muehrcke (1952) among others.

The Thorn test employing corticotrophin has been shown to be of value in the assessment of the efficiency of the pituitary-adrenal mechanism in adults, provided it is remembered that 'it is subject to the limitations common to most laboratory tests' (de Mowbray and Bishop, 1953), and provided that the test is carried out in the afternoon to avoid the greater spontaneous variations occurring in the morning.

Klein and Hanson (1950) employed corticotrophin in the Thorn test on older children and seldom induced decrements much /
much greater than 37%. Employing this as their standard of normality they carried out the test on newborn infants. The infants of one group were tested once in the first three days and again in the second week with much better and more consistent falls in the latter. Two other groups were studied, one in the first week and the other in the second, with similar results. With 1 mg. or less of corticotrophin fewer "positive" Thorn tests were obtained than when the dose was increased to 2-12 mg. and the 1 mg. dose was considered to be the more sensitive in demonstrating adrenocortical hypofunction. Venning (1950), however, employed much larger doses of corticotrophin in a small series and induced greater eosinophil responses in the second than in the first week.

In the present study doses of 2.5 mg. or less of corticotrophin were inadequate to provoke eosinopenic responses beyond the range of spontaneous change and appeared in some cases to induce an eosinophilia. The injection of 5 mg. was followed by an eosinopenia beyond the spontaneous range in the majority of cases, but only with 10 mg. was such a response consistently obtained.

In the groups studied, therefore, the dose of corticotrophin required to provoke eosinopenic responses greater than 20% in newborn infants was two-fifths as great as that required to induce a decrease of over 50% in the normal adult although the body weight of the infant was only about one-twentieth of the adult weight. Furthermore, even with this relatively high dose of corticotrophin decrements of 50% or greater occurred in about half the subjects only. The magnitude /
magnitude of the response was roughly proportionate to the
dose given, but the dosages were so high relative to body
weight that impotence of the particular batch of corticotro-
phin might be suspected had it not been excluded by comparison
with others. These observations provide further suggestive
evidence that relative inefficiency of the adrenocortical
response to corticotrophin exists at this age.

White and Sutton (1950) found that adrenaline was rela-
tively ineffective in provoking eosinopenia in premature
infants, and, in order to exclude the possibility that this
might be due not to functional under-activity of the adrenal
but to abnormal resistance of the eosinophils to cortisona,
they injected six infants with whole adrenal cortical extract
and obtained an adequate eosinopenic response in all. They
concluded that there was inability on the part of the prema-
ture infant to elaborate sufficient amounts of adrenal corti-
cal hormone in response to corticotrophin. Klein and Hanson
(1950) injected whole adrenal extract into 11 infants in the
first two days of life with a view to excluding eosinophil
resistance and obtained eosinopenic responses greater than
37% in eight of them in four hours.

In the present study cortisone was employed in preference
to lipo-adrenal extract and proved to be less effective in
inducing eosinopenia than half the dose by weight of corti-
cotrophin. This at first appears to suggest eosinophil
resistance. Evidence in favour of the suppression of
adreno-cortical /
adreno-cortical function by cortisone was published by McIntosh and Holmes (1951), and the more likely explanation of the poorer response to 20 mg. is that the injection of cortisone depressed endogenous adreno-cortical function and the resulting total of available cortisone was less than would have followed a smaller dose of corticotrophin.

The absolute eosinophil levels in Part I of this investigation were rather higher on the tenth than on the third day and so differed from the figures in Study 8 and the figures from which the eosinopenic responses were calculated in Part II of this study, both of which series were larger and showed higher absolute values on the third day. It had been considered possible that applying the Thorn test to newborn infants on the third day would show that the eosinopenic responses indicated a relative degree of adrenal cortical hypofunction compared with those induced on the first and tenth. The comparison of the group responses to corticotrophin on the three days, however, shows no significant difference between them, and if there is any doubtful trend at all it is toward rather better responses on the third day.

The Thorn test is of little value in the assessment of the health of the pituitary-adrenal axis in newborn infants because, unlike in adults where the great diurnal variation is the handicap, the response to relatively great doses of corticotrophin is so poor that it may be within the range of spontaneous variation.

In /
In these conditions it is almost impossible to define what the normal eosinopenic response of a normal newborn infant to corticotrophin should be, but from the experience of this study it appears that the criteria might be a decrement of 30% or greater when 10 mg. are injected.

SUMMARY AND CONCLUSIONS

The literature referring to the Thorn test in adults and newborn infants is briefly reviewed.

The evaluation of the test in the newborn infant depends upon (a) the range of spontaneous eosinophil change, and (b) the range of eosinopenic response to varying doses of corticotrophin.

Serial hourly studies of eosinophils in healthy infants showed considerable stability of absolute levels, and such fluctuations as did occur were unrelated to feeding and minor upsets.

Increasing doses of corticotrophin induced a proportionate increase in the mean eosinopenic response. There was, however, a considerable range of response to each dose on each day, and 10 mg. of corticotrophin were required to induce decrements greater than 30% consistently.

There was no significant difference in the nature of the response to the varying doses on the first, third and tenth days of life.

The Thorn test at this age is of little value because the poor eosinopenic responses to corticotrophin may fall within the range of spontaneous change. A normal response might be defined /
defined as a decrement of 30% or greater when a 10 mg. dose is injected.
TABLE 34

RESULTS OF INJECTION 1 mgm. CORTICOTROPIN (ACTH)

<table>
<thead>
<tr>
<th>Case</th>
<th>Day one</th>
<th>Day three</th>
<th>Day ten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>4h.</td>
<td>% change</td>
</tr>
<tr>
<td>215</td>
<td>70</td>
<td>195</td>
<td>+178.6</td>
</tr>
<tr>
<td>216</td>
<td>425</td>
<td>686</td>
<td>+61.4</td>
</tr>
<tr>
<td>217</td>
<td>109</td>
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<td>+73.4</td>
</tr>
<tr>
<td>218</td>
<td>213</td>
<td>197</td>
<td>-7.5</td>
</tr>
<tr>
<td>219</td>
<td>55</td>
<td>245</td>
<td>-345.5</td>
</tr>
<tr>
<td>220</td>
<td>345</td>
<td>363</td>
<td>+5.2</td>
</tr>
<tr>
<td>221</td>
<td>55</td>
<td>28</td>
<td>-49.1</td>
</tr>
<tr>
<td>222</td>
<td>150</td>
<td>139</td>
<td>-7.3</td>
</tr>
<tr>
<td>223</td>
<td>163</td>
<td>153</td>
<td>-6.1</td>
</tr>
<tr>
<td>224</td>
<td>145</td>
<td>133</td>
<td>-8.3</td>
</tr>
<tr>
<td>225</td>
<td>153</td>
<td>55</td>
<td>-64.1</td>
</tr>
<tr>
<td>226</td>
<td>528</td>
<td>483</td>
<td>-8.5</td>
</tr>
<tr>
<td>227</td>
<td>445</td>
<td>398</td>
<td>-10.6</td>
</tr>
<tr>
<td>228</td>
<td>214</td>
<td>217</td>
<td>+1.4</td>
</tr>
<tr>
<td>229</td>
<td>277</td>
<td>234</td>
<td>-15.5</td>
</tr>
</tbody>
</table>

Mean percentage change for group  
+32.6  
-19.7  
-16.0
### Table 35

**RESULTS OF INJECTION OF 2.5 mgm. CORTICOTROPHIN (ACTH)**

<table>
<thead>
<tr>
<th>Case</th>
<th>Day one</th>
<th>4h.</th>
<th>Day three</th>
<th>4h.</th>
<th>% change</th>
<th>Day ten</th>
<th>4h.</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>204</td>
<td>234</td>
<td>69</td>
<td>391</td>
<td>186</td>
<td>-70.5</td>
<td>153</td>
<td>134</td>
<td>-46.0</td>
</tr>
<tr>
<td>205</td>
<td>55</td>
<td>69</td>
<td>194</td>
<td>56</td>
<td>-71.1</td>
<td>248</td>
<td>124</td>
<td>-5.1</td>
</tr>
<tr>
<td>206</td>
<td>294</td>
<td>255</td>
<td>167</td>
<td>123</td>
<td>-26.3</td>
<td>234</td>
<td>222</td>
<td>-4.6</td>
</tr>
<tr>
<td>207</td>
<td>113</td>
<td>100</td>
<td>167</td>
<td>98</td>
<td>-4.3</td>
<td>277</td>
<td>98</td>
<td>-8.0</td>
</tr>
<tr>
<td>208</td>
<td>45</td>
<td>33</td>
<td>58</td>
<td>50</td>
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<td>266</td>
<td>-8.0</td>
</tr>
<tr>
<td>209</td>
<td>44</td>
<td>399</td>
<td>134</td>
<td>134</td>
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<td>297</td>
<td>264</td>
<td>-11.5</td>
</tr>
<tr>
<td>210</td>
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<td>261</td>
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</tr>
<tr>
<td>211</td>
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<td>191</td>
<td>141</td>
<td>103</td>
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<td>208</td>
<td>186</td>
<td>-8.0</td>
</tr>
<tr>
<td>212</td>
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<td>144</td>
<td>144</td>
<td>0</td>
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<td>27</td>
<td>119</td>
<td>119</td>
<td>-8.0</td>
<td>138</td>
<td>138</td>
<td>-24.5</td>
</tr>
</tbody>
</table>

**Mean percentage change for group:** -20.8

**% change:** -19.7
### TABLE 36

**RESULT OF INJECTION OF 50 mgm. (ACTH) EOSINOPHIL LEVELS**

<table>
<thead>
<tr>
<th>Group and number</th>
<th>Day</th>
<th>Change</th>
<th>Day</th>
<th>Change</th>
<th>Day</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gp. A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-30.0</td>
<td>4h.</td>
<td>0</td>
<td>4h.</td>
<td>-34.0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-39.6</td>
<td>4h.</td>
<td>0</td>
<td>4h.</td>
<td>-39.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gp. B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-36.1</td>
<td>4h.</td>
<td>0</td>
<td>4h.</td>
<td>-36.1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>-48.7</td>
<td>4h.</td>
<td>0</td>
<td>4h.</td>
<td>-48.7</td>
</tr>
</tbody>
</table>

**Mean percentage changes for different groups:**

- Gp. A: 16 babies (24 changes) for 16 babies
- Gp. B: 24 babies (24 changes) for 24 babies
### TABLE 37

RESULTS OF INJECTION OF 10 mgm. ACTH

<table>
<thead>
<tr>
<th>Case</th>
<th>Eosinophil Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day one</td>
</tr>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>144</td>
<td>197</td>
</tr>
<tr>
<td>145</td>
<td>519</td>
</tr>
<tr>
<td>146</td>
<td>134</td>
</tr>
<tr>
<td>147</td>
<td>69</td>
</tr>
<tr>
<td>148</td>
<td>181</td>
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<tr>
<td>149</td>
<td>342</td>
</tr>
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<td>150</td>
<td>336</td>
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<td>152</td>
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<td>153</td>
<td>194</td>
</tr>
<tr>
<td>154</td>
<td>339</td>
</tr>
<tr>
<td>155</td>
<td>66</td>
</tr>
<tr>
<td>Case</td>
<td>Day three</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>156</td>
<td>95</td>
</tr>
<tr>
<td>157</td>
<td>178</td>
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<tr>
<td>158</td>
<td>97</td>
</tr>
<tr>
<td>159</td>
<td>223</td>
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<tr>
<td>160</td>
<td>711</td>
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<td>331</td>
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<tr>
<td>162</td>
<td>289</td>
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<td>166</td>
<td>163</td>
</tr>
<tr>
<td>167</td>
<td>305</td>
</tr>
<tr>
<td>Day 0</td>
<td>4h</td>
</tr>
<tr>
<td>------</td>
<td>----</td>
</tr>
<tr>
<td>292</td>
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</tr>
<tr>
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<td>490</td>
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</tr>
<tr>
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</table>

**RESULTS OF INJECTION OF 10 mgm. CORTISONE**

**EOSINOPHIL LEVELS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>4h</th>
<th>14h</th>
<th>24h</th>
<th>48h</th>
</tr>
</thead>
<tbody>
<tr>
<td>GpA</td>
<td>967</td>
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<td>106</td>
<td>104</td>
</tr>
<tr>
<td>GpB</td>
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<td>123</td>
<td>124</td>
</tr>
<tr>
<td>GpC</td>
<td>134</td>
<td>137</td>
<td>139</td>
<td>141</td>
<td>143</td>
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</table>

Note: Changes indicate the difference from the baseline at Day 0.
<table>
<thead>
<tr>
<th>Case</th>
<th>Day one</th>
<th>Day three</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4h</td>
</tr>
<tr>
<td>168</td>
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<td>70</td>
</tr>
<tr>
<td>169</td>
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<td>173</td>
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<td>174</td>
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<td>176</td>
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<tr>
<td>185</td>
<td>156</td>
<td>127</td>
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</tbody>
</table>
TABLE 41

RESULTS OF INJECTING 20 mgm. CORTISONE ON DAYS THREE AND TEN

<table>
<thead>
<tr>
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<th>Day ten</th>
</tr>
</thead>
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<tr>
<td>203</td>
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</table>
STUDY 13

THE 24-HOUR URINE VOLUMES OF BABIES BORN TO DIABETIC AND NON-DIABETIC WOMEN

Intention

The intention of this study was to measure the 24-hour urine volumes of babies born to diabetic and non-diabetic women in order to find if the oedematous appearance of infants of diabetic mothers is indeed associated with the diuresis described by White (1952) and others.

Method

The groups.

The infants of diabetic women were delivered by caesarean section and so two control groups of babies born to non-diabetic mothers were studied. The first consisted of those born spontaneously by the vagina at full term and the second of infants born prematurely (average about 38 weeks) by caesarean section for such reasons as placenta praevia and disproportion. The majority of infants in the diabetic group and all of those in the control groups were males.

The collection of urine.

The collection of 24-hour volumes of urine from newborn infants is difficult. The small size of the genitals makes the accurate fitting of an appliance awkward and the possible inhalation by the baby of one of his early feeds makes dangerous immobilisation of the infant on a frame. This risk can be justified in the test group, the babies of which
Figure 68

APPARATUS FOR THE COLLECTION OF URINE FROM MALE INFANTS

Diagram showing the apparatus for collecting urine from male infants.
will neither be fed nor taken to their mothers for a few days. The babies of the control groups, however, must be taken to their mothers every three or four hours for feeding. This involves a good deal of handling during which an appliance may be disturbed. For these reasons special apparatus was designed. The collections were started immediately after birth.

**Female infants.** Urine was collected by catheterisation. A Foley self-retaining catheter of 10 F.G. with a 3 ml capacity balloon was made by Messrs William-Warner & Co. Ltd. specially for this study. The possible risk of introducing infection by catheterisation excluded the inclusion of females in the control groups, and after the occurrence of a troublesome urinary infection in a baby of the diabetic group no further girls were studied.

**Male infants.** The apparatus for the male was simple, but effective (Figure 68). It consisted of a finger cot (d) which was rolled over and strapped on to the infant's penis. The finger cot was then attached to a glass tube (c) and this was inserted into a glass 6 in. by 1 in. test tube (A) for about 1½ in. and connected to it by latex colostomy tubing (F). A small piece of polythene tubing (B) was pushed through a pin prick in the latex tubing and strapped to the glass connecting tube. The former opened about one inch nearer to the baby than the latter, so that leakage of urine was avoided. A long length of polythene tubing (E) was passed to the bottom of the test-tube through another /
Figure 69

DAILY URINE VOLUMES OF NEWBORN INFANTS

DAILY URINARY OUTPUT IN NEWBORN INFANTS.

- ○ DIABETIC
- □ NORMAL (VAGINAL DELIVERIES)
- X NORMAL (CAESAREAN DELIVERIES)

Urine Volume
ML./24 HR.

Day One  Day Two  Day Three
another puncture in the latex, and the external end was occluded by an accurately fitting cannula and stilette. The infants were nursed in such a position that voided urine flowed easily into the test-tube, air being displaced through tube B. The urine was immediately aspirated from the test-tube by means of a syringe attached to the metal cannula and it was kept in the refrigerator. (see Study 14).

Splint.

In order to reduce the risk of displacing the appliance the legs of the baby were kept in abduction by a small butterfly splint. This was well padded and covered in soft leather. It was fitted to the ankles by crepe bandage and it kept the feet four inches apart. (The splints were made in the Royal Infirmary of Edinburgh).

RESULTS

The daily urine volumes of the infants born to diabetic women were higher than those of infants in the control groups (Figure 69 , Table 42 ). This difference was most obvious during the first 48 hours when the average volumes excreted by babies in the diabetic and control groups were 47 ml. and 22 ml. respectively. By the third day the urine volumes were indistinguishable. No big difference is apparent between the volumes passed by the two control groups, but the infants born by caesarean section possibly passed more urine during the first 24 hours. The volumes passed by the vaginally /
TABLE 42

24-HOUR URINE VOLUMES (IN MILLILITRES)
OF BABIES BORN TO DIABETIC AND NON-DIABETIC WOMEN

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
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<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
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<td>30</td>
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<tr>
<td></td>
<td>h</td>
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<tr>
<td></td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>j</td>
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</tr>
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<td></td>
<td>k</td>
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<td>17</td>
</tr>
<tr>
<td></td>
<td>l</td>
<td>5</td>
<td>16</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>m</td>
<td>12</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Normal (caesarean section)</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>o</td>
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</tr>
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<tr>
<td></td>
<td>123</td>
<td>60</td>
<td>20</td>
<td>35</td>
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</tbody>
</table>

* in 16 hours (baby died)
vaginally delivered babies, however, are at the lower end of the range described Thomson (1944).

**COMMENT**

The simplest explanation of the difference between the urine volumes of the diabetic and the control groups is that the movement of control babies to and from their mothers displaced the collecting apparatus and caused leakage of urine. This would invalidate not only this study but also Study 14 which depends upon it. The urine collections were kept under continuous observation, however, by the author and by a number of most conscientious paediatric house officers (who saw the babies hourly by day and usually more than once between midnight and breakfast) as well as by co-operative nurses. Leakage is very easily recognised and a number of babies have been excluded because it was reported. The urine volumes of those retained in the present study are believed to be correct.

The difference between the two groups is made more significant by the fact that none of the babies in the diabetic group were fed until the third to the fifth day, whereas all babies in the control groups were given fluid from the first day.

**SUMMARY**

The babies of diabetic women are said to have a diuresis during the first few days of life. Their 24 hour volumes /
volumes have been measured and they do exceed those of rather more mature infants born by caesarean section and of mature babies born spontaneously to non-diabetic women.
STUDY 14

THE DAILY URINARY EXCRETION OF FORMALDEHYDOGENIC STEROIDS AND 17-KETOSTEROIDS

Intention

The intention of this study was to show, if possible, that hyperadrenocorticism exists at birth in the infants of diabetic women (see pages 51-56).

Method

The opportunity of assessing adrenocortical function more directly than by counting eosinophils arose in 1954 when Dr. C.P. Stewart offered to determine in his laboratory the formaldehydogenic steroid and 17-Ketosteroid excretion of diabetic and control groups.

The provision of an acceptable control group proved to be an almost insurmountable obstacle. The diabetic pregnancies in this series were terminated usually about the 36th. week by elective caesarean section, and the number of non-diabetic pregnancies which are terminated similarly is very small. A study of the records of the Simpson Memorial Maternity Pavilion has shown that of over 3,000 annual deliveries there are only about six elective caesarean sections between the 35th. and 37th. weeks of gestation. Because of the risk of introducing infection by indwelling catheters in baby girls, only male infants were eligible for inclusion in the control study.

The available alternatives were to study a group of infants /
infants who were delivered vaginally at full term and a group of infants delivered by caesarean section at from 36 to 41 weeks. Small groups of each of these have been used.

The difference in gestation between the diabetic and non-diabetic groups in this study is less of a bar to their comparison than the route of delivery, for Bjorklund (1954) has shown that the urinary secretion of adrenocortical steroids by prematurely born infants is significantly less than in those born at full term. The demonstration, therefore, of significantly higher levels of such steroids in the urine of a less mature group (the babies of diabetic women) than in the full-term control group would be of added importance. It is questionable if caesarean section is a less stressful event for the foetus than vaginal delivery, but the baby who is delivered by section is much less likely to show evidence of the labouring mother's increased adrenocortical activity, and so the demonstration of higher levels of corticosteroids in his urine might be of greater significance.

The technique of urine collection has been described in Study 13. The urine was aspirated from the collecting tube as soon as it was voided, and it was then transferred to a polythene bottle. This was kept in a nearby refrigerator in the early cases, but to reduce the risk of losing the specimen, the polythene collecting bottle was later kept in a vacuum cylinder packed with ice and kept beside the infant's cot.

The /
SERIAL DAILY URINARY EXCRETION OF ACID STABLE FORMALDEHYDEGENIC STEROIDS

**Figure 70**

**INFANTS OF DIABETIC WOMEN**

**INFANTS OF NORMAL WOMEN**

**Figure 71**

**INFANTS OF DIABETIC WOMEN**

**INFANTS OF NORMAL WOMEN**

**Diabetics**

- Normal •
- Dyspnoeic ●
- Cyanotic Att. ○

**Normals**

- All Cases ◆
- Normal Course
The acid-stable formaldehydogenic steroids in the urine were determined. The acid-stable formaldehydogenic substances in the urine were determined quantitatively by a modification of the method of Tompsett (Tompsett and Smith, 1954). The 17-Ketosteroids were measured by the M.R.C. method (Medical Research Council, 1951).

RESULTS

The number of babies in each group is small and the results are unsuitable for statistical analysis.

Acid-stable formaldehydogenic steroids.

The horizontal lines on the graphs in Figure 70 have been drawn empirically at the level of 0.5 mg. of acid-stable formaldehydogenic steroids (A.S.F.S.) daily. From these and from Table 43, the urinary excretion of A.S.F.S. can be seen to be greater in the abnormal than in either group of normal infants on the first day of life. The A.S.F.S. excretion of the abnormal group probably remained above normal on the second day, but the difference, in the fewer cases studied, was less obvious by the third day.

There is probably no significant difference between the A.S.F.S. excretion of infants born spontaneously and by caesarean section to non-diabetic women.

In the abnormal group the A.S.F.S. excretion increased from the first to the second day in 11 babies and it decreased in 3. In the vaginal control group the excretion increased in /
<table>
<thead>
<tr>
<th>Group</th>
<th>Case Number</th>
<th>Absolute Excretion (mg./24 hr.)</th>
<th>DAY 1.</th>
<th>Excretion per m²</th>
<th>DAY 2.</th>
<th>Excretion per m²</th>
<th>DAY 3.</th>
<th>Excretion per m²</th>
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<tbody>
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<td><strong>NORMAL spontaneous vaginal births</strong></td>
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<td></td>
<td>0.57</td>
<td>3.06</td>
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<td></td>
<td>i</td>
<td>0.19</td>
<td>1.04</td>
<td></td>
<td>0.26</td>
<td>1.42</td>
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<td></td>
</tr>
<tr>
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<td>j</td>
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<td>0.1</td>
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<td>p</td>
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<td>0.51</td>
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</table>

**TABLE 43 (a)**

**URINARY EXCRETION OF ACID-STABLE FORMALDEHYDOGENIC STEROIDS**
**TABLE 43(b)**

**URINARY EXCRETION OF ACID-STABLE FORMALDEHYGENIC STEROIDS**

<p>| Group | Case Number | DAY I. | | DAY 2. | | DAY 3. | | | | |
|-------|-------------|--------|--------|--------|--------|--------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th></th>
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<th>Absolute Excretion (mg./24 hr.)</th>
<th>Excretion per m²</th>
<th>Absolute Excretion (mg./24 hr.)</th>
<th>Excretion per m²</th>
<th>Absolute Excretion (mg./24 hr.)</th>
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</tbody>
</table>

* in 16 hrs. (baby died)
### Table 1

**Urinary Excretion of 17-Ketosteroids**

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Group</th>
<th>Day</th>
<th>Absolute Excretion (mg/24 hr.)</th>
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<tr>
<td>21</td>
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</tbody>
</table>

**Notes:**
- Excretion per m²
- Day 1
- Day 2
- Day 3
- Group number
- Case number
in all 7. In the caesarean control group it increased in 5, remained constant in 2 and decreased slightly in 1.

Of those babies in whom the urine collection was continued for three days the A.S.F.S. excretion increased from the second to the third day in two of the abnormals and decreased in five, as compared with an increase in three of the normals and a decrease in two. In this study, therefore, the infants born to diabetic mothers excreted more A.S.F.S. on the first day than those born to non-diabetic women, but the latter groups showed a rising trend and by the third day of life there was little difference between them.

17-Ketosteroids.

The 17-Ketosteroids were determined in the abnormal and in the spontaneous vaginal control groups only. Reference to Figure 71 and Table 44 shows that there is no apparent difference of 17-Ketosteroid excretion between the two groups on any of the three days studied. In the abnormal group eight showed an increase and four a decrease in excretion from the first to the second day, whereas three showed an increase and three a decrease over the same period in the normal group.

From the second to the third day three of the abnormal group showed an increase, two a decrease and one no change, whereas one of the normals showed an increase and four a decrease.

Excretion/Body surface area.

Although the babies of diabetic women are generally abnormally /
Figure 72

The relationship between body surface area and the daily excretion of A.S.F.S. on the first day of life
Figure 73

THE RELATIONSHIP BETWEEN THE DAILY URINARY VOLUME AND THE DAILY EXCRETION OF A.S.F.S.

- Normal group
- Abnormal group

![Graph showing the relationship between daily urinary volume and daily excretion of A.S.F.S.](image-url)
abnormally large for their gestational age there was no appreciable difference in the size of the infants making up the normal and the abnormal groups in this study, as those of the latter were delivered prematurely.

It was decided, however, to compare the excretion of A.S.F.S. and 17-Ketosteroids by the abnormal and the spontaneous vaginal control groups on the basis of unit surface area as well as in the absolute terms used above. The surface area of each infant was found from the monograms of Crawford, Terry and Rourke (1950), but unfortunately only the birth weight was available as the urine collection interfered with weighing on the second and third days. This means that the figures for hormone excretion on these two days should be a little higher than those given, for the surface area then would be less than at birth.

On the basis of surface area the excretion of A.S.F.S. was again higher in the abnormal than in the normal vaginal group on day 1, less obviously so on day 2, and it was no different from the normal on day 3, whereas there was no difference in the excretion of 17-Ketosteroids in the two groups on any day. It may be seen from Figure 72 that no very definite correlation existed between the body surface area of infants in either group and the absolute excretion of A.S.F.S. on day 1 so that the higher excretion seen in the babies of diabetic mothers could not be explained on the basis of greater size.

Daily urine volume.

The /
The daily urine volume of the infants born to diabetic women was higher than that of the control group (Study 13). The excretion of A.S.F.S. on day 1, however, in the abnormal group was unrelated to the volume of urine passed (Figure 73). The lower volumes of urine passed by the control group in the first 24-hour period particularly did not prevent the 17-Ketosteroid excretion of these babies from equalling that of the infants in the abnormal group. In neither group was an increase or a decrease in urine volume from day to day necessarily accompanied by a corresponding increase or decrease in the excretion of A.S.F.S. or 17-Ketosteroids.

**Correlation of Hormone Excretion with Clinical Behaviour in Infants of Diabetic Women.**

The excretion figures have been correlated with the clinical courses of the babies. Prolonged dyspnoea occurred in three of the infants for whom the A.S.F.S. excretion was known. One of these died after having shown a high excretion of A.S.F.S. but one perfectly asymptomatic infant in the abnormal group had excreted more. A second of these dyspnoeic babies had high excretion and a third showed a rapid increase in excretion from the first to the second day and improved clinically over the same period. None of these three infants showed a decrease in the amount of A.S.F.S. excreted. Infants who had cyanotic attacks are scattered through the group and their behaviour bears no consistent relationship to the amount of A.S.F.S. excreted or to increases or decreases in excretion. In the two very symptomatic infants for whom the 17-Ketosteroid excretion was
was known there was an insignificant decrease to death in one and a steep increase in output in the other over the period of progressive clinical improvement. There was no consistent relationship between the occurrence of brief cyanotic attacks and the excretion of 17-Ketosteroids.

**COMMENT**

It has been mentioned that the study of hormonal disturbances in such infants is beset with difficulties. The acid-stable formaldehydogenic steroids probably represent only a proportion of the excreted corticosteroids (Page 95) and may not be the most satisfactory index of adrenocortical activity. It is unfortunate that the urinary volumes of some of the infants in the normal group on the first day of life were at the lower end of the range described by Thomson (1944) but the volumes passed by the caesarean controls were more normal in distribution. In any case, no relationship has been found between the volume of urine passed and the excretion of A.S.F.S. The absence of any significant difference in 17-Ketosteroid excretion in the two groups, although different from the results of Bjorklund and Jensen (1955) makes it unlikely that there was any unobserved or unreported loss of urine in the control group. The difference between the A.S.F.S. excretion of the two groups is made more significant if it is remembered that the individuals in the abnormal group are some weeks less mature than those in the normal group, for Bjorklund (1954) has shown that the less /
less mature the foetus the smaller is his urinary corticoid excretion. No relationship exists in this series between the A.S.F.S. excretion figure and the clinical behaviour of the baby, i.e. high excretion does not correlate with severe upset or freedom from disturbance. Of the three babies who had respiratory embarrassment on the first day of life, two showed some rise in A.S.F.S. excretion in the next 24-hour period, but one, whose course ended in death, showed no change. It is of doubtful importance that the latter infant had unilateral renal vein thrombosis. Similar fluctuations in excretion in other infants were unaccompanied by clinical disturbance. It is equally important to note that abnormal neonatal behaviour did not coincide with or follow a sudden fall in A.S.F.S. excretion.

It should be remembered that qualitative differences may exist between the hormones of the intra-uterine (foetal) adrenal cortex and the extra-uterine (permanent) cortex. Such a difference would explain the apparent pre-natal incompleteness of the eosinolytic mechanism. The hypoglycaemia in the infant is of such short duration that it is unlikely to be the stimulus provoking increased glucocorticoid secretion on the first few days of life. No relationship was found to exist between eosinophil and hormonal levels or changes in levels and neonatal behaviour.

**SUMMARY**

The urinary excretion of acid-stable formaldehydogenic steroids /
steroids was employed as an index of adrenocortical activity. The infants of diabetic women showed a higher A.S.F.S. excretion than those of the controls on the first day, but this difference was lost by the third day. The 17-Ketosteroid excretion of the two groups was very similar.
STUDY 15

ADRENAL HAEMORRHAGE IN THE NEWBORN
"PSEUDOPNEUMONIA INFANTUM"

Intention

The intention of this study is to examine the evidence advanced for the belief that adrenal failure in the newborn may produce a clinical picture resembling pneumonia described by Goldzieher and Gordon (1932).

Method

The literature dealing with adrenal haemorrhage has been reviewed briefly and the clinical features and autopsy findings of a group of neonatal deaths at the Simpson Memorial Maternity Pavilion have been examined.

RESULTS

The literature.

The principal feature of "Pseudopneumonia Infantum" is said to be dyspnoea but there may be associated pyrexia, cyanosis, shock and hypoglycaemia. The authors of the original description referred to animal experiments in which respiratory embarrassment followed bilateral adrenalectomy and was relieved by the giving of adrenocortical extracts. A fall in the respiratory rate of an affected newborn infant from 60 to 30 a minute half an hour after an injection of adrenal cortical extract was reported by Goldzieher and Greenwald (1928) but spontaneous alterations of this magnitude are not uncommon at that age.
The clinical presentation of adrenal haemorrhage in adults was classified into three types by Arnaud (1900). The peritoneal type resembles an acute abdominal emergency with abdominal pain, tenderness, frequent vomiting and shock. The asthenic type causes progressive weakness and death within a few days and, in the nervous type, the patient is generally found in convulsions or coma. Examples of the various types and of mixtures of types have been described several times and the literature has been reviewed by Dewhurst (1951). He added four cases where the condition occurred in pregnant women in three of whom respiratory distress was present.

The literature dealing with unilateral adrenal haemorrhage in newborn infants has been reviewed by Emery & Zachary (1952). To 14 cases which had been published since 1900 they added two others. Although there is some variation in the symptomatology they were able to discern a general pattern. "The baby appears to be normal at birth after an uneventful pregnancy and a straightforward delivery. A few hours, or at most a few days, after birth the baby becomes ill, will not take feeds and becomes noticeably pale. There is invariably some pyrexia, sometimes of extreme degree. The baby may be restless, but in the later stages becomes weak and comatose. A mass is often palpable in the loin. Death may occur with dramatic suddenness". The authors found no evidence from the literature to support the belief that adrenal haemorrhage caused neonatal dyspnoea. They were not, however,
however, dealing with bilateral haemorrhage.

Observations on S.M.M.P. cases.

The case records were obtained of eleven live-born infants who had died at the Simpson Memorial Maternity Pavilion, and in whom obvious macroscopic adrenal haemorrhage was found at autopsy. Such clinical information as appeared on the infant's charts has been summarised (Table 45). Massive haemorrhage was predominantly unilateral in six (Cases 1, 2, 6, 7, 9, & 11) but in none was it the only abnormal finding. In three it was associated with a birth weight of less than 2268 grammes. Although respiratory signs (gasping, cyanotic attacks, dyspnoea, cyanosis) were present in eight and just might have been interpreted as "Pseudopneumonia Infantum" in several of these, the facts are that four did have pneumonia (two frank consolidation and two on histological examination), two had pulmonary haemorrhage, one was extremely premature and atelectatic, and one had inhaled meconium. Of the five cases with bilateral adrenal haemorrhage, all had respiratory symptoms, but all had pulmonary lesions at autopsy. In six of the eleven babies no record of temperature has been kept but the clinical notes do not mention pyrexia. In one it was 95° and in two it ranged from 96 to 98°. In only two was the temperature 100 to 103°. One of these babies had pneumonia and the other had Kernicterus and many polymorphs in the affected adrenal.

SUMMARY /
SUMMARY

The published literature states that adrenal haemorrhage may cause dyspnoea, but there is no convincing evidence that, as an isolated lesion, it causes dyspnoea in the newborn. There is, therefore, no reason for believing that functional adrenal failure at this age produces a pseudopneumonic disturbance or that the respiratory symptoms of the newborn infants of diabetic women are due to hypoadrenocorticism.
<table>
<thead>
<tr>
<th>Date of birth</th>
<th>Birth wt. in grammes</th>
<th>Temp. °F.</th>
<th>Survival time</th>
<th>Clinical signs</th>
<th>Autopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.6.47 Quinn</td>
<td>4196</td>
<td>N.R.</td>
<td>&quot;minutes&quot;</td>
<td>Gasping respiration only.</td>
<td>Massive haemorrhage right adrenal with retroperitoneal haemorrhage. Microscopic examination - inhalation of meconium.</td>
</tr>
<tr>
<td>7.11.47 Burnett</td>
<td>1814.4</td>
<td>N.R.</td>
<td>20 hrs.</td>
<td>Poor general condition. Very poor air entry to lungs. Deeply cyanosced.</td>
<td>Bilateral pneumonia. Haemorrhage destroying half left adrenal. Two smaller haemorrhages in right adrenal.</td>
</tr>
<tr>
<td>8.2.48 McAllum</td>
<td>2127</td>
<td>95-97.2°</td>
<td>3½ weeks</td>
<td>&quot;cerebral irritation&quot;. Severe dyspnoea with rib recession for 48 hrs. Vomiting and diarrhoea.</td>
<td>Naked eye appearance bilateral pneumonia but microscopic examination showed congestion only. Extensive bilateral adrenal haemorrhage. No evidence of gastro-enteritis.</td>
</tr>
<tr>
<td>19.6.49 Reid</td>
<td>3175.1</td>
<td>96.8-97.8° (terminal 103°)</td>
<td>3 days</td>
<td>Icterus gravis neonatorum</td>
<td>Erythroblastosis foetalis. Kernicterus. Haemorrhagic destruction of left adrenal in which many polymorphs were found on microscopic examination. Infection? &quot;Aspiration of meconium and early bronchopneumonia&quot;. Haemorrhagic destruction of both adrenals.</td>
</tr>
<tr>
<td>28.10.54 McQuire</td>
<td>4196</td>
<td>98-97</td>
<td>4 hrs.</td>
<td>Severe cyanotic attack at 7 hours with twitching of right arm and mouth. Followed by frequent cyanotic attacks, general deterioration and death.</td>
<td>Early pneumonia. Central venous thrombosis with haemorrhage of the left adrenal.</td>
</tr>
</tbody>
</table>

N.R. = NOT RECORDED ON INFANT'S CHART OR NOTES
STUDY 16

ELECTROCARDIOGRAPHY

The dyspnoea, cyanotic attacks and cardiac arrhythmias which were observed by Bjorklund (1953) led him to study the electrocardiograms of 15 infants of diabetic mothers and to compare these with those of a control group of 37 normal babies in the birth weight range 2.8 to 5.5 kg. The electrocardiograms of all those in the control group were judged to be normal by Ziegler's criteria, although the Q-T interval was short in some. The T wave was iso-electric or positive with the exception of only one case and the S-T segments were on the iso-electric line. Among infants of diabetic women, however, the electrocardiograms of 11 of 15 were classed as abnormal by the same criteria. The S-T segment was suppressed or "sagged", T waves were pathologically negative, the Q-T interval was prolonged and the U waves were abnormal. A ventricular tachycardia was noted in two cases. No relationship was found between the duration of the maternal diabetes or the gestational age of the baby and the electrocardiograms. The abnormalities disappeared within the first 15 days of life and usually within the first five. The E.C.G. changes were found both in the presence and in the absence of such disturbances as collapse, cyanosis, arrhythmia or dyspnoea, but in none of the children with any of these disturbances was the E.C.G. normal.

Because /
Because of these E.C.G. tracings, which suggested hypokalaemia (Figures 24 and 25), Bjorklund investigated serum potassium levels and found them to be low by the standards he employed. In three of his cases (6, 11 and 14) the E.C.G. was normal although the serum potassium was low. The levels which he found are not outside the normal range given recently by Hill (1954).

**Intention**

The intention of this study is to examine the electrocardiograms of a consecutive number of live-born babies of diabetic women and to relate these to any observed clinical disturbance.

**Method**

If the case was not an urgent one the electrocardiograms were carried out by Miss C. Brydone, from the Royal Hospital for Sick Children and reported upon by Dr. R.A. Miller. Latterly, however, if the baby was unwell, or if Miss Brydone was unavailable the electrocardiograms were carried out by a member of the Royal Infirmary cardiological department and reported upon there. (This explains the difference in quality of the reproductions, the Royal Infirmary apparatus being much more suitable for this purpose).

**RESULTS**

The individual electrocardiograms are reproduced in Figures /
Figures 74 to 91. Of the 11, ten babies showed low T waves, or depression of the ST segment. No consistent relationship was found between the ECG abnormality and the clinical disturbances noted.

Case 98 /
Figure 74

CASE 98

E.C.G. AT AGE ONE HOUR
CASE 98

E.C.G. AT AGE TWO DAYS
CASE 98

E.C.G. AT AGE THREE DAYS
CASE 99
E.C.G. AT AGE ONE HOUR

[Electrocardiogram tracings]
CASE 99

E.C.G. AT AGE ONE DAY
CASE 99

E.C.G. AT AGE FOUR DAYS
Figure 80

CASE 100

E.C.G. AT AGE ONE HOUR
CASE 100

E.C.G. AT AGE THREE DAYS

Figure 81

333
Case 98

This infant had one cyanotic attack only and this occurred on the first day of life (see Appendix I). ECG's were obtained on the first and second days of life and they were reported by Dr. R.A. Miller.

**Day 1. (Figure 74)** "This ECG is probably abnormal in that the T wave in leads I, II, & III is almost flat. Moreover in lead V4 the T wave is diphasic".

**Day 2. (Figure 75)** "The ECG shows low voltage T waves in leads I, II & III. The T wave in V4 is down. Such a feature is probably abnormal".

Case 99

This baby had four cyanotic attacks on days 4 and 5 (see Appendix I). Two were associated with feeding and two with pharyngeal collections of mucus. ECG's were obtained on the first, second and fifth days of life and they were reported by Dr. R.A. Miller.

**Day 1. (Figure 77)** "In lead III there is a small R deflexion and deep S deflexion. In lead V4 there is depression of the ST segment. The significance of such a finding is obscure".

**Day 2. (Figure 78)** Lead III is possibly abnormal in that there is a small R deflexion and deep S deflexion".

**Day 5. (Figure 79)** "There is no definite abnormality in this ECG".

Case 100

This baby's course was normal. ECG's were obtained on days 1 and 4 and they were reported by Dr. R.A. Miller.

**Day 1. (Figure 80)** "The T waves in leads I, II & III do not exceed 1 mm. In lead V4 the T wave is down. The significance of this finding is obscure".

**Day 4. (Figure 81)** In lead I the T wave measures 0.5mm. In leads II & III the T wave is down. The T wave is diphasic in lead V4".

Case 101
CASE 101

E.C.G. AT AGE ONE HOUR
Case 101

E.C.G. at age 24 hours
CASE 102

E.C.G. AT AGE SIX HOURS
Figure 85

CASE 104

E.C.G. AT AGE ONE HOUR
CASE 104

E.C.G. AT AGE TWO DAYS
Case 101

This baby's course was normal. ECG's were obtained on days 1 and 3 and they were reported by Dr. R.A. Miller.

**Day 1.** (Figure 82) "The T waves in leads I & II are down. In lead III the T wave is almost flat. In lead V4 the T wave is down. The significance of these findings is obscure".

**Day 3.** (Figure 83) "The QT interval measures 0.32 of a second. The T waves in leads I, II & III do not exceed 1.2 mm. There is no depression of the ST segment".

Case 102

This baby was a classical big puffy-looking baby (birth weight 4508 grammes at 35 weeks). He became dyspnoeic after 3 hours and he died at 41 hours (see Appendix I). At autopsy unilateral renal thrombosis was the apparent cause of death. Pancreatic islet hyperplasia was obvious (Figure ).

An ECG was obtained on the first day and it was reported by Dr. R.A. Miller.

**Day 1.** (Figure 84) "The T waves in leads I-III are of low voltage. Leads VI - V4 are normal. This is a normal ECG".

Case 104

This baby had only one cyanotic attack and this was associated with feeding on the 6th day (see Appendix I). ECG's were obtained on the first and fourth days and they were reported by Dr. R.A. Miller.

**Day 1.** (Figure 85) "The T waves in leads I & II are flat. In lead III it measures about 0.25 mm. No other unusual feature was noted. It is just possible that the low voltage T waves signify some pathological condition".

**Day 4.** (Figure 86) "The T waves are flat in leads I & II while in lead III the T wave is down. The significance of the low voltage T waves is obscure".

Case 105
Figure 87

CASE 105

E.C.G. AT AGE ONE DAY
Figure 88

CASE 109

E.C.G. AT AGE THREE DAYS
CASE 119

E.C.G. AT AGE ONE DAY

Figure 89
This mongol baby had only one cyanotic attack on the fourth day. It was associated with feeding. There was no evidence of congenital heart disease. An ECG was obtained on the first day and it was reported by Dr. M.F. Oliver.

**Day 1.** (Figure 87) "Sinus tachycardia, rate approximately 136 per minute. PR interval 0.12 of a second. There is marked right axis deviation. In lead I there is a tiny Q, moderate R, moderate S which is not slurred and low upright T. In lead II there is a tiny Q, moderate R, small S and low upright T. In lead III there is a tiny R, tiny S, moderate R and diphasic T. In aVR there is a tiny R, small S, small R and low inverted T. In aVL there is a small Q, small R, moderate S and diphasic T. In aVF there is a moderate R, small S. and diphasic T. In VI there is a moderate R, notched on the upstroke and upright T. In V2 R and S are approximately equal and the T wave is upright. V4 and V6 are similar. The appearances are probably not abnormal for a baby of one day old."

**Case 105**

This baby was well until the fourth day when he developed cyanosis (see Appendix I). The baby made a good recovery. An ECG was obtained on the fourth day and it was reported by Dr. F. Simpson.

**Day 4.** (Figure 88) "Sinus tachycardia, rate 165 per minute. PR interval 0.10 of second. The record is within normal limits for a baby of this age."

**Case 109**

This baby was dyspnoeic during the first four days and was very ill (see Appendix I). ECG's were obtained on the first and second days of life. The first was reported by Dr. M.F. Oliver and the second by Dr. F.0 Simpson.

**Day 1.** (Figure 89) "Sinus tachycardia, rate 136 per minute. PR interval 0.10 of a second. In leads I and II the T wave is low inverted. In lead III it is diphasic. In aVL and aVF the T wave is flat. In V2 it is diphasic and in V4 it is low inverted. It was possible to take only two chest leads because of the size of the baby. The actual QT interval measures 0.30 of a second compared with a calculated QT interval of 0.27 of a second. This is probably not significant."
Case 119 (Contd.)

significant. The T wave changes are similar to those seen in hypokalaemia in an adult but it is not known whether this could be a normal variant for a newborn baby”.

Day 2. (Figure 89) "Comparison with previous record shows persistence of sinus tachycardia. The heart rate is now about 160 per minute. There has been slight change in the position of the heart. There is now less right axis deviation. The ventricular complexes are within normal limits for a baby of this age. The T waves remain flat to low inverted throughout. The significance of this is uncertain”.

This baby had normal serum potassium levels and she recovered spontaneously without potassium being given. She was found later to have a patent ductus arteriosus which required ligation at the age of two years.

Baby Thomson (date of birth 12.1.56).

This baby is not a member of the present series.


Well at birth but one hour later his respiration became slightly distressed. A detergent mist and oxygen were begun and he quickly improved. No treatment was required after the first 24 hours. An ECG was obtained at the age of 4 hours and it was reported by Dr. R.M. Marquis.

Day 1. (Figure 90) "Sinus tachycardia, rate 115 per minute. PR interval 0.12 of a second. There is well marked right axis deviation with low inversion of the T waves in leads II, III and aVF. In VI a moderate R wave of 8 mm. is the sole initial deflection. T wave is low upright. The transitional zone is in V2. In V4 and V6 a moderate R wave is the main initial deflection. T waves are flat to low diphasic. The QT interval appears prolonged at 0.36 of a second. The form of the ventricular complex in VI suggests the presence of right ventricular hypertrophy which may well be within normal limits for a baby of this age. The T wave changes in V4 and V6 are abnormal but non-specific and in association with QT could be due to a metabolic disturbance”.

Baby Long /
Figure 90

BABY T. - Date of Birth 11/1/56

E.C.G. AT AGE 7 HOURS
Figure 91

BABY L. - Date of Birth 11/5/56

E.C.G. AT AGE 12 HOURS
Baby Long (date of birth 11.5.56)

This baby is not a member of the present series.


Well at birth and remained so. An ECG was obtained at the age of 12 hours and it was reported by Dr. R.M. Marquis.

Day 1. (Figure 91) "Sinus tachycardia rate 125 per minute. PR interval of a second. There is right axis deviation with the normal right ventricular preponderance of this age group. In addition to these changes, however, there is ST depression with predominant inversion of the T waves in V3 R and V2. The significance of the ST/T wave change in the right chest leads is not clear but is an occasional finding in the ECG of infants in whom no abnormality, cardiac or otherwise, is apparent at birth or during subsequent follow-up. The ST depression usually disappears within the first few months of life.

SUMMARY

Low T waves and depression of ST were found in 10 of a series of electrocardiograms obtained in 11 symptomatic and asymptomatic infants. Although serum potassium levels were not studied routinely, the abnormality existed in an ill baby whose potassium was normal and who recovered without potassium treatment.
The high incidence of congenital malformation in these babies reported by White (1952) was widely quoted and generally accepted until such work as that of Gardell (Page 108) suggested that it might be otherwise. The present study was at first an attempt to explain a high incidence, but it developed into an enquiry into whether it is high at all.

POSSIBLE CAUSES OF AN INCREASED INCIDENCE OF CONGENITAL MALFORMATIONS.

(1) Inheritance

There is no doubt that heredity plays some part in the aetiology of diabetes mellitus (Page 119). Inheritance appears to be "the most logical explanation" of a high incidence of congenital malformations in the babies of diabetic mothers according to White (1952). Although the arterial degeneration associated with diabetes possibly may be inherited (le Compte, 1957) there is no clear evidence that diabetic patients have a higher incidence of congenital deformities than do non-diabetics. The possible linkage of the gene carrying predisposition to diabetes with one responsible for an apparently distinct disease is illustrated by a family which attended the Royal Edinburgh Hospital for Sick Children, and which has been reported by Duncan & Scott (1957). Three girls in a family of twelve children developed diabetes mellitus at the ages of 7, 8 and 6 years.
6 years. A fourth died of it in infancy. The three survivors and the mentally defective son of one of them went on to develop idiopathic nerve deafness and optic atrophy. Although they have had diabetes for periods ranging from 6 to 19 years, none of them has the slightest evidence of diabetic retinopathy.

(2) Hypoglycaemia.

The observations of Duraiswami (1950) suggest that maternal hypoglycaemia early in diabetic pregnancy may cause malformation of the foetus. An analysis of the maternal case records of this series shows, however, that, although the mother of Case 26 (hemivertebrae and bifid rib) did suffer from infrequent mild hypoglycaemic incidents in pregnancy, the mothers of children with bilateral congenital cataract (Case 30), sacrococcygeal agenesis (Case 36), mental deficiency (Case 55), double thumb (Case 71), torticollis (Case 104), mongolism (Case 105) and patent ductus arteriosus (Case 119), had no significant hypoglycaemia.

Because the psychotic pregnant woman may have functional amenorrhoea or be ignorant of the fact that she is pregnant, such women, it was thought, might sometimes receive treatment in early pregnancy with insulin coma. A foetus with optic atrophy, hypertelorism and mental defect was, in fact, born to a mother who had received insulin treatment in pregnancy (Wickes, 1954). Enquiries were made of a number of mental hospitals where efficient insulin therapy units exist. The records /
records of the Royal Edinburgh Hospital for Mental Disorders, the Crichton Royal Institution at Dumfries, the Department of Experimental Psychiatry at the University of Birmingham, St. Ebba's Hospital at Epsom and St. Andrew's Hospital at Northampton were examined, but the particulars of only two such cases were obtained. Dr. T.A. Munro of the Royal Edinburgh Hospital found no record of any pregnant women who had been treated with insulin. Dr. W. Mayer-Gross of Birmingham stated that "The trouble is that schizophrenia very rarely starts during pregnancy and early schizophrenics often feel as well during pregnancy as normal women". He recalled only one girl who had skilfully concealed her pregnancy and who had received insulin coma treatment. He believed that the baby was normal, but the case record was unavailable.

Dr. P.K. McCowan of Dumfries stressed that insulin coma is never given intentionally to a pregnant woman, but he agreed that routine pregnancy diagnosis tests are not used before female schizophrenics are treated. He knew of only one pregnant girl who had received therapy. This patient (M.S.) was an unmarried student with a two-year history of increasing withdrawal symptoms. She received 57 insulin comas in eleven weeks from the eighth week of her pregnancy. She was discharged at twenty weeks and followed no further. The girl's family doctor, however, stated that he had attended her /
her from the time of her hospital discharge. Her abdomen seemed enlarged and an obstetrician diagnosed hydramnios and possible foetal abnormality. Labour was induced and she was delivered of an "oedematous" female infant of 3 lb. 9 oz. weight. The baby was atelectatic and died after a few hours. No external malformations were observed and no autopsy was carried out.

The chance of finding further similar cases seemed so small that the study was abandoned.

(3) Cortisone

The experimental production of congenital deformities with cortisone is interesting in view of the evidence suggesting that adrenal activity is increased abnormally in diabetic pregnancy.

Using the house mouse, an animal in which "spontaneous" cleft palate (without hare-lip) is rare, Baxter & Fraser (1950) gave cortisone to pregnant females and produced cleft palates in 44 per cent. of the foetuses. This was confirmed by Fraser, Fainstat & Kalter (1953) and in rabbits by Fainstat (1954). Both an excess and a deficiency of vitamin A during pregnancy may cause congenital malformations of the brain in the rat foetus.

Although the giving of a daily dose of cortisone to pregnant rats failed to cause congenital deformities, when it was added to hypervitaminosis-A it raised the incidence /
incidence of gross malformations of the foetal brain and calvaria from 7.8 per cent. to 36.6 per cent. (Miller and Woollam, 1957). In the case reported by Harris and Ross (1956), a human foetus with cleft palate was born to a woman who had received 300 mg. cortisone daily from about the 38th. day of pregnancy and through the time during which the palatal processes would normally have been fusing. The cleft palate could not, of course, be ascribed undoubtedly to cortisone.

Corticosteroid production increases considerably in normal human pregnancy, but not until after the period of foetal organogenesis and the fact that none of the babies born after the prolonged cortisone treatment of Rhesus sensitised women (Page 55) had cleft palate could be explained in this way if cortisone were known to be harmful.

Cortisone may cross the placenta in several animal species (Steward, 1913); Stewart and Rogoff, 1925); Rogoff and Stewart, 1927); Ingle and Fisher, 1938); but there is some evidence that it cannot cross the human one (Page 55). In any case not one of the babies in the present series had a cleft palate.

COMPARISON OF CONGENITAL MALFORMATIONS IN CHILDREN OF THIS SERIES AND IN A CONTROL GROUP.

The previously reported studies (Page 107) have been very different not only in their results, but in the way by which these were obtained. Some refer to live children and some to /
to autopsies, some refer to newborn infants and others to older children and some seem to count every trivial deviation from the normal in children of diabetic women, but to record only the serious malformations in the controls. Some may have examined only a "diabetic" group and have taken the "normal incidence" from studies by other people.

The importance of re-examining both groups again beyond the newborn period is illustrated well by the fact that in the "diabetic group" the bilateral congenital cataract and the torticollis were not diagnosed in the early weeks, the mental defect was not apparent until after six months, the patent ductus arteriosus was not suspected until the follow-up examinations at eighteen months and the cause of the scoliosis was not determined until the child reported for her first review at the age of five years. Similarly in the control group, the short oesophagus, for example, was not diagnosed until 6 weeks and the coarctation of the aorta and other cardiac murmurs were noted for the first time at ages ranging from 3 to 10 years.

The discovery of every existing malformation in each member of a series is clearly impossible. The selection of a particular system or anatomical site for detailed study, e.g. the eye, may be grossly misleading if the system or structure is not susceptible to injury by, for example, hypoglycaemia or hyperadrenocorticism. Because the incidence of congenital malformations is influenced by maternal age and parity, any control group should take these into consideration.
consideration.

The children in this study were therefore matched from the records of the Simpson Memorial Maternity Pavilion as closely as possible with children of non-diabetic woman for month and year of conception and for maternal age and parity. The final control group represents only about one-third of the group to whom appeals for assistance had been sent. Because of the danger that the parents of mentally deficient or physically handicapped or deformed children might refuse to co-operate without explaining their reasons, the homes of all "refusals" were visited. All of them refused because they either resented interference, or because they feared that they would commit their child to an upsetting experiment. All of these parents, with the exception of two doctors, responded favourably to explanation and to a personal invitation. The only reason eventually for having to contact a group three times greater than that required was because of changes of address. Some of these children were traced by Medical Officers of Health and Health Visitors. (The general practitioners of all children in the abnormal and control groups were also contacted. Not one objected to a patient being examined).

Both groups were then examined personally and the important malformations were recorded (Figures 92 to 99).

One baby (Case 30) died at home aged 4 weeks. Although this infant's death was certified by the general practitioner as /
as being caused by congenital heart disease, there is no proof that such was the case and it has been omitted. The baby's course had been normal in hospital and no malformations had been found. He remained apparently well until the day of his death when he was found collapsed and distressed in the morning and died shortly after the general practitioner arrived. A terminal systolic murmur was the only criterion upon which the diagnosis of congenital heart disease was based. No other signs were found and no autopsy was carried out.

No obvious difference in the incidence of congenital malformations was found and no further investigations were undertaken.
COMPARISON OF PHYSICAL ABNORMALITIES PRESENT SINCE BIRTH IN INFANTS OF DIABETIC AND NON-DIABETIC WOMEN

<table>
<thead>
<tr>
<th>Physical Abnormalities</th>
<th>Diabetic group</th>
<th>Non-diabetic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacral agenesis</td>
<td>1</td>
<td>Club foot</td>
</tr>
<tr>
<td>Congenital cataracts</td>
<td>1</td>
<td>Hypertrophic pyloric stenosis</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1</td>
<td>Coarctation of aorta</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>1</td>
<td>Cardiac murmurs, &quot;organic&quot;</td>
</tr>
<tr>
<td>Mongolism</td>
<td>1</td>
<td>Mental defect, mild diplegia</td>
</tr>
<tr>
<td>Mental defect</td>
<td>2</td>
<td>Short oesophagus</td>
</tr>
<tr>
<td>Scoliosis (hemi vert.)</td>
<td>1</td>
<td>Inguinal Herniae</td>
</tr>
<tr>
<td>Extra thumb</td>
<td>1</td>
<td>Mod. funnel sternum</td>
</tr>
<tr>
<td>Fused central incisors</td>
<td>1</td>
<td>Cong. absence one nail</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>13 children</td>
</tr>
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</table>
Figure 93

X-RAY OF CASE 26

Scoliosis, bifid ribs and vertebral deformity
Figure 94

X-RAY OF CASE 26

Scoliosis, bifid ribs and vertebral deformity
Figure 95

X-RAY OF CASE 26

Vertebral deformity
Figure 96

X-RAY OF CASE 36

Sacral agenesis
Figure 97

JULY 1955 - X-RAY OF CASE 108

INTRAVENOUS PYELOGRAM SHOWING LEFT HYDRONEPHROSIS
RETROGRADE PYELOGRAM CONFIRMING THE
PRESENCE OF LEFT HYDRONEPHROSIS AND HYDROURETER
Figure 99

X-RAY OF CASE 119

Patent ductus arteriosus
PART C

APPENDIXES
APPENDIX I

CASE SUMMARIES OF BABIES WHO
SUFFERED FROM DYSPNEA OR CYANOTIC ATTACKS
APPENDIX I

CASE SUMMARIES OF DYSPNOEIC BABIES

1. Male. Caesarean section delivery (C/S). Birth weight (B.W.) 3175 g. Maturity 36 weeks. Difficulty was experienced with the mother's anaesthetic of pentothal, cyclopropane and oxygen. Ten minutes elapsed after birth before the baby's respiration was established. Breathing was shallow and "murmuring" in character for 6 hours but was normal by 16 hours.

2. Female. C/S. B.W. 4493 g. Maturity 35 weeks. The baby cried well at birth and was given glucose by intravenous and intramuscular injection. Oral glucose was given at 20 minutes, and at one hour she regurgitated, inhaled and became distressed. This was ascribed wrongly to hypoglycaemia, and more glucose was given by mouth at 3 hours. Inhalation recurred with consequent dyspnoea and cyanotic attacks. She improved gradually during the remainder of the first day.

4. Female. C/S. B.W. 3792 g. Maturity 35 weeks. Well at birth. Glucose (50% solution) was given at 1, 3½ and 4½ hours. The baby regurgitated and inhaled. Respiratory distress was acute and many moist sounds were audible throughout the chest. This infant was not observed personally, and the condition was ascribed not to inhalation but to "the pulmonary oedema of hypoglycaemia". More urgent treatment seemed to be indicated, and glucose was given intravenously at short intervals /
intervals from 6 until 18 hours. Gradual improvement occurred over this period. The blood sugar values recorded were no more abnormal than those recorded in quite asymptomatic infants, but the substitution of intravenous for oral glucose saved the baby from further inhalation.

6. Female. Assisted breech. B.W. 1928 g. Maturity 32 weeks. Glucose was given by intramuscular injection and by mouth at birth. The baby regurgitated, inhaled and respiration remained distressed for a few hours but then improved rapidly.

2. Female. C/S. B.W. 2764 g. Maturity 37 weeks. The infant's respiration was shallow, rapid and "murmuring" in character during the first few hours, but it was well-established by 4 hours. Soluble sulphathiazole and penicillin were prescribed and given by intramuscular injection for 3 days as a prophylactic measure. She seemed well for 5 days, but her temperature then fell from normal to 95.2° F. and she fed rather poorly. On the 8th day she vomited and aspirated a feed. Respiration ceased and the heart sounds were inaudible. The trachea was intubated, partially cleared by suction and coramine was injected into the heart. She responded a little and bronchoscopy was carried out. Dyspnoea persisted, however, and she died two hours later. Bilateral bronchopneumonia was found at autopsy and was so well developed that it had clearly preceded the aspiration of vomitus.
14. Female. C/S. B.W. 2941 g. Maturity 37 weeks. The baby's condition was excellent at birth. Three hours later the blood sugar had fallen from 182 mg.% to 72 mg.%, and glucose by oesophageal tube was ordered. Some minutes later the baby vomited and inhaled. Respiration was stridorous and she became deeply cyanosed and limp. Auscultation of the chest revealed many bilateral coarse moist sounds. She remained thus for some hours but then gradually improved. Feeding was reattempted 8 hours later and 3-hourly thereafter with smaller volumes of 10% glucose. Vomiting took place on each occasion until the second day of life, but aspiration did not recur.

15. Male. Breech delivery with forceps to the after-coming head. B.W. 2806 g. Maturity 36 weeks. Respiration was established with difficulty and remained shallow during the first hour. Slight improvement occurred then but moist sounds were audible throughout the chest, and attempts at feeding the infant with glucose were unsuccessful. The dyspnoea was more pronounced at 20 hours, costal indrawing was obvious and he was cyanosed in oxygen. He remained in poor condition and collapsed suddenly at 46 hours. He appeared moribund but improved a little only to die suddenly at 68 hours. Massive bilateral adrenal haemorrhage was found at autopsy. The glands had ruptured into the perirenal tissue on each side. The lungs which had appeared to be expanded normally showed areas of collapse /
collapse on microscopy. Unfortunately consent for autopsy of the trunk only was obtained. The brain may have been damaged in view of the nature of the delivery.

12. Female. C/S. B.W. 2807 g. Maturity 34 weeks.

Asphyxiated at birth but responded to intravenous lobeline. The infant remained dyspnoeic for 4 hours and during much of this time rib indrawing was severe. The cry had improved by $5\frac{1}{2}$ hours, but indrawing was unchanged until 12 hours. Respiration then became easier, and the infant was well by 48 hours.


The baby cried at birth and seemed well, but within an hour respiration became laboured and "murmuring". Air entry was poor. Respiration suddenly ceased at $5\frac{1}{2}$ hours but recommenced after coramine was given. He remained in extremis, and by 10 hours only gasping respirations were present although stimulants had been given. He died one hour later. The lungs were bulky and airless at autopsy. Severe pulmonary hyaline membrane disease was confirmed at autopsy.

35. Female. Assisted breech delivery. B.W. 1644 g.

Maturity 30 weeks. Apart from extensive bruising of the buttocks and legs, the baby's immediate post-natal condition was satisfactory and respiration was established quickly. During the first day the baby became dyspnoeic and severe indrawing of the ribs and sternum was /
was present. She died suddenly at 22\(\frac{1}{2}\) hours, and at this time she was noted to be rather yellow. The serum bilirubin was not determined. Only 5 mg. of vitamin K had been given. Autopsy revealed a large unruptured subependymal haemorrhage in the wall of the left ventricle where fluid blood and blood clot were also found. Bleeding extended into the rest of the ventricular system and the subarachnoid space. The meninges and the cerebral cortex, but not the basal ganglia, were slightly yellow. Neither serological nor histological evidence of haemolytic disease existed, and death was ascribed to prematurity and cerebral haemorrhage. The route of delivery may have been responsible in part.

27. Male. C/S. B.W. 4841 g. Maturity 34 weeks. The baby cried at delivery but then became apnoeic and deeply cyanosed. He responded slowly to resuscitative measures and was dyspnoeic for one hour. Rapid improvement followed.

40. Male. C/S. B.W. 2693 g. Maturity 38 weeks. The infant cried before the cord was clamped but he was then apnoeic for 10 minutes. He was deeply cyanosed and the heart was very slow. He then gasped in response to intravenous lobeline, and rhythmic respiration was established. He did not cry, however, and he "murmured" continuously. Scattered moist sounds were heard throughout the chest. Three and a half hours /
hours after delivery the baby's temperature rose steadily to 106° F. No other abnormality was found, but at 4 hours rhythmic respiration was replaced by intermittent gasping. Stimulants were ineffective and he died 10 minutes later. The cause of death was not found at autopsy nor at review of the histological sections in 1957. Unfortunately the brain was not examined in detail. This was the only infant in the whole series to develop hyperpyrexia.

45. Female. Spontaneous deliver (S/D). B.W. 4309 g.
Maturity 38 weeks. The baby cried well at birth, but respiration was extremely rapid for 2 hours (pulse : respiration ratio of 1:1). She then improved quickly.

46. Female. C/S. B.W. 3296 g. Maturity 36 weeks. The baby cried at birth but after a few minutes respiration became difficult and associated with "murmuring" in expiration. This continued intermittently but always with improvement, and she was normal by 24 hours.

62. Male. C/S. B.W. 3820 g. Maturity 36 weeks. The baby cried strongly at birth and respiration was established at once. Rapid respiration and indrawing of the ribs was noted at one hour, but he was active and acyanotic. He became more dyspnoeic, however, and at 2 hours moist sounds were audible throughout his chest. At 9 hours the respiratory rate was 80 to 110 / minute, and this persisted during the first and second days. The heart rate never exceeded 140 to 160 / minute, and there /
there was no evidence of cardiac failure. At 48 hours, air entry to the lungs was still poor. As no meconium had been passed, a finger was slipped into the rectum for a few moments through a tight sphincter. Copious meconium was then slowly released. A portable X-ray of the chest was of poor quality but revealed no gross abnormality. Streptomycin was begun by intramuscular injection. At 72 hours some improvement was noted, but the respiratory rate remained at 80 to 100 / minute, the heart rate was 160 / minute, and he became cyanosed when taken out of oxygen. His temperature, which had been raised to 100° F. during the first 24 hours only, remained normal. Tube feeding with glucose was begun without incident at 72 hours and followed by bottle feeding 2 days later. The dyspnoea gradually disappeared on the fourth day and oxygen was discontinued. Progress from then was normal. Streptomycin was given for four days only.

84. Male. C/S. B.W. 1701 g. Maturity 37 weeks. The growth of the foetus had been very slow in the 3 or more weeks before birth, and trouble in the post-natal period was anticipated. His condition was good at birth, and the rib-indrawing noted was not abnormal at his birth weight. This became more obvious after a few hours, however, and respiration suddenly ceased at 16 hours. Resuscitative efforts were unsuccessful. Both cerebral hemispheres were flattened at autopsy. Blood clot was present in the left lateral ventricle and
and clot had grossly distended the right lateral ventricle and had extended into the surrounding hemisphere. Blood was present throughout the ventricular system and in the subarachnoid space. Much of each lung was airless, and hyaline membrane was found on microscopic examination.

93b. Female. Breech delivery. Second of twins. B.W. 850 g. Maturity 37 weeks. The baby's condition was very poor at birth. Respirations were feeble and lung expansion was poor. Gastric oxygen was not helpful. During the first 3 hours some lung expansion was achieved, but rib and sternal indrawing were very severe. Irregular respiration was replaced with a period of gasping respiration at 14 hours. She improved and relapsed from then until her death at 48 hours. Mild jaundice appeared on the second day. At autopsy death was ascribed to extreme prematurity. The pulmonary tissue was very immature, but there was no evidence of hyaline membrane.

102. Male. C/S. B.W. 4508 g. Maturity 35 weeks. The infant's immediate condition was good, but after 3 hours the respiratory rate increased and at 3½ hours a brief cyanotic attack occurred. Respiration remained rapid and shallow, and crepitations were audible at both lung bases. Streptomycin by intramuscular injection was begun. Respirations were still rapid and shallow at 24 hours, mild to moderate costal recession.
recession was present and a tinge of cyanosis was visible when the infant was taken out of oxygen. Moderate lung expansion appeared to have taken place, but some degree of hyaline membrane was suspected. At 41 hours respiration ceased without warning and cardiac arrest followed within a few minutes. Resuscitative measures were unsuccessful. An E.C.G. (see Figure 84) on the first day had shown only low voltage T waves in leads I to III. At autopsy the heart was enlarged to about 1 \(\frac{1}{2}\) times the normal for that body weight, and both ventricles were involved equally. No other heart abnormality was found. A large ovoid mass in the area of the right kidney was at first thought to be an adrenal haemorrhage. It extended into the retroperitoneal tissue, the right iliac fossa and even to the left side of the abdomen. On microscopic examination, however, it proved to be a haemorrhagic infarction of the left kidney with only small surviving areas of renal tissue. The larger left renal veins contained ante-mortem thrombus. The right kidney was normal. (The urine had been collected from birth for formaldehydogenic steroid determination and contained no visible blood.)

106. Male. S/D. B.W. 2892 g. Maturity 37 weeks. The baby's respiration became distressed within 4 hours of birth and he was cyanosed. Treatment with oxygen and a detergent mist was begun. Multiple harlequin reactions were observed from 8 to 12 hours, but he gradually /
gradually improved and was much better at 24 hours. The detergent mist and oxygen were withdrawn after 2 days and his further progress was satisfactory.

109. Male. C/S. B.W. 2792 g. Maturity 37 weeks. The baby's condition was good at first, and only slight irregularity of respiration and rib-indrawing was noted during the first 24 hours. On the second day two short cyanotic attacks occurred. Toward the end of the third day respiration became shallow, and on the morning of the fourth day further cyanotic attacks occurred. Between these his condition was very poor. Deterioration was rapid and alarming. The resident paediatrician believed that the baby was moribund, administered oxygen and gave him cortisone, glucose and streptomycin at different sites by intramuscular injection. The baby was seen personally within 30 minutes of the onset of this deterioration. He was very limp, showed early dehydration and deep physiological jaundice. Respiration was shallow but became deeper on stimulation. A few moist sounds were audible in the left lower and mid zones. The only other abnormality was the presence of a firm mass with a rounded lower pole deeply palpable in the left side of the abdomen. There was no other evidence of infection. During the examination the infant had a Harlequin reaction. The latter taken with the multiple cyanotic attacks were thought to be evidence of central immaturity only. The mass appeared to be renal /
renal and thrombosis of the renal vein was considered. Alternatively it was felt that the kidney might have been displaced downward by massive adrenal haemorrhage. Urinalysis revealed only a physiological quantity of albumin, the blood urea nitrogen was 24 mg.%, X-rays of chest and abdomen (portable machine) revealed no abnormalities, and the E.C.G. was normal. Cortisone and streptomycin were continued. The infant's condition deteriorated gradually throughout the day and, between cyanotic incidents, respiration remained slow and difficult. Hydration was now poor but intravenous therapy was considered to be inadvisable. A slow rectal drip of warmed 6% glucose was therefore given through a self-retaining catheter. During the next 12 hours slow improvement in general condition took place, respiration became more regular and less difficult, and cyanotic attacks ceased. Cortisone was discontinued. Progress was maintained from this point. The left kidney was no longer palpable. Harlequin reactions persisted on the sixth day but oral feeding was tolerated, and next day oxygen and streptomycin were discontinued. He was discharged apparently well on the 26th day. (SEE ALSO UNDER CYANOTIC ATTACKS.)

119. Female. C/S. B.W. 2551 g. Maturity 37 weeks. The baby's immediate condition was good and respiration was established easily. Within an hour, however, "murmuring", shallow respiration and rib-indrawing appeared. The infant's colour was good in oxygen, and no signs were /
were detectable in the chest or elsewhere. She was nursed in a detergent mist, and intramuscular streptomycin was begun. X-ray of the chest was negative. E.C.G. showed low inverted T waves in leads I and II and diphasic T wave in lead III. In aVL and aVF the T wave was flat. No potassium was given. The serum potassium was 27.4 mg.% but the specimen had been slightly haemolysed. The blood sugar was 96 mg.%. During the remainder of the first 24 hours respiration was at 60 / minute (heart 130 / minute) and both costal and sternal recession were present. Air entry was poor but no adventitious sounds were audible in the chest. At 24 hours a repeat X-ray of chest was negative. The E.C.G. showed a sinus tachycardia of 160 / minute, there was less right axis deviation, the ventricular complexes were within normal limits but the T waves remained flat to low inverted throughout. The serum potassium was at that point 29 mg.% and the blood sugar was 73 mg.%. Her respiratory embarrassment remained unchanged until the third day, from which point slow improvement took place. Oxygen and the detergent mist were discontinued on the fourth day and streptomycin on the fifth. Deep physiological jaundice appeared on the fourth day and deepened to the seventh day when the serum bilirubin was 28 mg.%. On the eighth day it had decreased to 20.5 mg.% and jaundice quickly cleared. Temperature was normal throughout. She was discharged well at 3/52, but was readmitted in her second year for ligation of a patent ductus arteriosus.
23. Female. S/D. B.W. 1601 g. Maturity 37 weeks. The baby was well until the fourth day when she suffered from two brief cyanotic attacks. Her further progress was uneventful.

29. Male. C/S. B.W. 3657 g. Maturity 36 weeks. The baby was well until the third day when a brief cyanotic attack occurred during feeding. His further progress was uneventful.

42. Female. C/S. B.W. 3345 g. Maturity 36 weeks. Well until the second night after birth when she suddenly became blue and was noted to be apnoeic. Mucus was aspirated from the pharynx. Respiration recommenced and cyanosis cleared. Her further progress was uneventful.

51. Female. C/S. B.W. 2757 g. Maturity 37 weeks. The baby cried well at birth but respiration was "murmuring" in character during the first few hours. No real dyspnoea was noted. Feeds of glucose water were given from 12 hours, and during the first 3 of these she had brief cyanotic attacks. Her further progress was uneventful.

52. Male. C/S. B.W. not recorded, but about 3200 g. (calculated from weight on day 5). Maturity 35 weeks. The baby cried at birth and remained fairly well until
8 hours old when he had a sharp cyanotic attack. Mucus was aspirated from his pharynx and he improved. Feeds of glucose water were begun on the second day, and during the first of these he had two mild cyanotic attacks. His further progress was uneventful.

56. Female. C/S. B.W. 2948 g. Maturity 37 weeks. The baby was well at birth and remained so until the fourth day. Feeding was begun on the third day. During a feed on day 4 the baby had a sharp cyanotic attack. Mucus was aspirated from the pharynx and before the resident paediatrician had reached the ward the infant had recovered completely. Her further progress was uneventful.

74. Female. C/S. B.W. 3402 g. Maturity 35 weeks. The baby was well until the fifth day when a brief cyanotic attack appeared during the first feed, but it passed off spontaneously. Her further progress was uneventful.

85a. Male. C/S. B.W. 2438 g. Maturity 35 weeks. This baby was one of dissimilar twins. Partial placenta praevia had caused slight ante-partum haemorrhage. The baby was well until the third day when he had a sharp cyanotic attack (omitted in error from Figure 5). He recovered quickly, but had further less severe incidents on days 6 and 8. His further progress was uneventful.
86. Male. C/S. B.W. 3912 g. Maturity 37 weeks. The baby was well on the first day, but on the second he had a brief cyanotic attack. Mucus was aspirated from his pharynx and he returned to normal at once. His further progress was uneventful.

88. Female. C/S. B.W. 2445 g. Maturity 34 weeks. The baby was well at birth, but during the first night she had a brief cyanotic attack. Mucus was aspirated from her pharynx and she recovered. She remained well until the third day when she had 3 further mild cyanotic attacks. Her further progress was uneventful.

98. Female. C/S. B.W. 3104 g. Maturity 35 weeks. The baby cried at birth but, apart from infrequent gasps, respiration was not established for 7 minutes. She remained well until 12 hours, when she suddenly became deeply cyanosed. Her heart rate was 60 / minute, and respiration was reduced to infrequent gasps. She was quite toneless. A considerable amount of mucus was aspirated from her pharynx, her feet were "flicked" and oxygen was given. After an interval of 2 minutes respiration recommenced, her colour improved and the heart rate returned to normal. Her further progress was uneventful.

99. Female. C/S. B.W. 2693 g. Maturity 36 weeks. The baby was well until the fourth day. Immediately after the first feed had been given a sharp cyanotic attack occurred. This was treated with aspiration of the pharynx /
pharynx, sensory stimulation and oxygen, and after one minute the attack passed off. Another developed, however, immediately before the next feed. It also lasted for one minute, during which time a little mucus was cleared from the baby's pharynx. Early on the fifth day she turned blue, and respiration was noted to be shallow and infrequent. As soon as this was noted the heart rate was found to be 50 to 60/minute. The baby looked quite inert; she was limp and the tendon reflex could not be elicited. A little mucus was aspirated from the pharynx, and the usual resuscitative measures were employed. After two minutes the respiratory rate increased, although breathing remained shallow. Her colour improved, and the heart rate immediately increased to 80/minute, and 5 minutes later it was 130/minute. A few hours after this a further cyanotic attack occurred during a feed. It lasted for some seconds only and was followed by a series of harlequin colour changes. She remained well out of oxygen after this, but the resident paediatrician noted wide and sudden changes in heart rate which were quite unrelated to respiration (e.g. from 130 to 60/minute). Where respiration was normal, however, the bradycardia was unassociated with cyanosis. Her further progress was uneventful.

103. Female. S/D. B.W. 2013 g. Maturity 31 weeks. The baby was well except for one brief cyanotic attack at 17 hours. Her further progress was uneventful.
383

104. Female. C/S. B.W. 3019 g. Maturity 38 weeks. The baby was well except for a brief cyanotic attack during a feed on the sixth day. Her further progress was uneventful.

105. Male. C/S. B.W. 2899 g. Maturity 36 weeks. This mongol baby had a cardiac murmur. His condition was otherwise satisfactory until the fourth day when he developed a brief cyanotic attack during a feed. His further progress was uneventful.

107. Male. C/S. B.W. 3005 g. Maturity 36 weeks. The baby was well until 9 hours when a bout of crying was followed by deep cyanosis and arrested respiration for 30 seconds. This was followed by irregular respirations for several minutes. The heart rate was not noted. He showed many Harlequin reactions, but remained well till day 4 when he had a cyanotic attack lasting one minute. Three hours later, during his first feed, he became deeply cyanosed and atonic. Apnoea was so prolonged that the experienced sister-in-charge of the unit thought that he was dead. The incident lasted between 3 and 4 minutes, and toward the end of this time when the resident paediatrician arrived, the infant was noted to twitch a little and to have a heart rate of 100 to 110 / minute (base-line 120 to 130). Very little mucus was aspirated from the pharynx. Oxygen and sensory stimulation were given and he slowly recovered. His chest was quite normal. Harlequin reactions /
reactions were frequent until the end of the sixth day. His further progress was uneventful.

108. Female. C/S. B.W. 3395 g. Maturity 39 weeks. The baby cried well at birth, but this was followed by apnoea for about 2 minutes. During the first few hours her abdomen became greatly distended. A stomach tube was passed in an attempt to relieve this, and a cyanotic attack of moderate severity occurred. Her further progress was complicated by two brief convulsions on the 14th day, when a urinary tract infection was found. This responded slowly to treatment, and she was later found to have a left hydronephrosis (see Congenital Malformations).

109. See summaries of dyspnoeic babies. This infant had a number of classical cyanotic attacks superimposed upon his dyspnoea. The following description was recorded by the resident paediatrician:

"....the attacks have assumed a constant pattern. They are preceded either by a diffuse pink vasodilation or by a Harlequin colour change. One half minute or so later the baby emits a series of shrill cries and then becomes generally stiff and apnoeic without any clonic jerking. As apnoea persists the baby gradually develops a greyish cyanosis, becomes quite limp and appears moribund. At this stage the heart rate is 160/minute." Sensory stimulation of the feet "coincides with a gradual return of respiration in/
in the form of irregular slow gasps which give way to normal rhythm."
Between these attacks "he is very reactive; the slightest sensory stimulus produces a generalised twitching of arms and legs."

Such cyanotic attacks differ from the common pattern and may be truly epileptic.

122. Male. C/S. B.W. 4614 g. Maturity 36 weeks. The baby was well until the third day when he had a brief cyanotic attack. His further progress was uneventful.
APPENDIX II

AUTOPSY REPORTS

(a) Neonatal deaths

(b) Intra-uterine deaths
APPENDIX II

AUTOPSY REPORTS ON NEONATAL DEATHS

CASE 9.

The body was that of a rather small female infant weighing 5 lb. 12 oz. P.M. lividity was not marked. There was fairly good growth of hair for this stage of development.

Thorax: Pharynx, oesophagus healthy. Thyroid and thymus glands showed no abnormality. There was some milk clot at the lower end of the oesophagus. Trachea and bronchi moderately congested. A few flecks of milk were present in the upper part of the trachea. The major bronchi were clear. Fleura was clear and glistening and there was no free fluid in the pleural sacs. Lungs were quite well expanded but both lower lobes were rather bulky and small purple patches of collapse were present over both upper and lower lobes. The right middle lobe was reddish-pink in colour and appeared to be normal. On section, both lower lobes were found to be rather congested and small quantities of yellow material could be expressed from the cut ends of the intra-pulmonary bronchi. The appearance was rather suggestive of an early broncho-pneumonia. Pericardium was clear and glistening and there was no free fluid in the pericardial sac. Heart was of normal size and shape. Chambers had a normal appearance. Endocardium was healthy. Both foramen ovale and ductus arteriosus were patent and no congenital abnormalities were present.

Abdomen: Peritoneum clear and glistening and there was no free fluid in the peritoneal sac. Stomach was of normal size and shape and there was nothing of path. interest in the remainder of the intestinal tract. Liver was of normal size and shape. Capsule smooth. On section, the organ had a normal appearance. Spleen was of normal size and shape. Capsule smooth. On section, no abnormality was found. Adrenal glands normal. Pancreas and the stomach bed and stomach itself were preserved intact for further examination. Kidneys small and showed a marked degree of foetal lobulation. Capsule was smooth and stripped easily, and on section both cortex and medulla were healthy. There was nothing of pathological interest in the remainder of the urinary tract.

Head: Dura mater and pia-arachnoid perfectly healthy and both falx and tentorium were intact. Brain showed rather immature gyral pattern but was quite firm in consistence, and on section no intra-cerebral lesion was found.

"A.E.C."

Microscopic /
Microscopic report:

Kidney: Capsule normal. Outer layer of cortex consists of primitive renal tissue. The glomerular epithelium and the capillary loops have a normal appearance. The tubules are healthy. There is marked vascular congestion.

Liver: The capsule is normal. The liver cells are mainly healthy. A few show early fatty change. The portal tracts are normal, and the bile ducts healthy. A few foci of extra-medullary erythropoiesis, normoblastic in character, are present and are not excessive for this stage of development. There is considerable vascular congestion.

Lungs: Pleura is normal. Lungs poorly aerated and widely consolidated. The alveolar walls are swollen and congested and many contain a fibrinous exudate with numerous polymorphonuclear and eosinophils. The bronchi are healthy and their membrane is intact. A few contain a fibrinous exudate and some polymorphs, but the majority clear. Some areas of over-distension surrounded the consolidated zones. Some intrapulmonary haemorrhage has also occurred.

Spleen: Capsule and trabeculae normal. The pulp is cellular and very congested. The Malpighian bodies are well developed and have a normal appearance.

Summary: Bilateral pneumonia.

"A.E.C."

Add. Micro. Report:

Pancreas: In sections from the head, body and tail shows very numerous islets. These are on the average much larger than in a normal infant of comparable age and occasionally amount to 5 or 6 times the average normal size. The islets are mostly of the usual round or oval form, but occasionally consist of two contiguous masses of tissue. They are made up of mixed A- and B-cells, mainly the latter, and devoid of any path. change. The small pancreatic ducts are conspicuously gathered in groups throughout the pancreatic structure and the acinar tissue, apart from very slight infiltration with round cells, is normal.

"R.F.O."

CASE 18.

The body was that of normally-built, well-nourished infant weighing 2,780 gms. and measuring 45 cm. long. A short segment of dried cord was attached to the umbilicus.

Thorax: Thyroid gland was normal. Pericardial and pleural sacs healthy.

Heart /
Heart normal.
Larynx, trachea and bronchi healthy.
Lungs were fully expanded and oedematous.

Abdomen: Peritoneal sac normal.
Stomach contained some bile and mucus.
Intestines normal.
Liver was of average size, shape and consistence, but abnormally pale.
Spleen was average in size, shape and consistence, and on section showed a congested surface.
Pancreas (1.98 gms.) was normal externally and on section.
Kidneys were average in size, shape and consistence, but abnormally pale.
Pelvis, ureters and bladder healthy.

Both adrenal glands were markedly swollen and fluctuant and consisted on section of large masses of blood clot in which remnants of cortex were embedded. Blood in the left gland had ruptured anteriorly and inferiorly to infiltrate the peri-renal tissue in that region, while the haemorrhage in the right gland had perforated to cause widespread infiltration of the soft tissues behind the kidney.

Brain was not examined.

Microscopic report:

Heart: Shows generalised congestion and hydrops of the myocardial cells, probably post-mortem in origin.

Lungs: Exhibit moderately marked collapse and oedema. Bronchi, apart from their content of serous fluid, are normal.

Pancreas: Shows very numerous islets. These are on the average distinctly larger than the normal and occasionally amount to giant forms about 8 times greater than the average normal. The islets are roughly round or oval in shape and never show any peripheral budding. They are structurally normal apart from a slight increase in the fibrous framework of the giant types. The interstitial tissue of the ordinary parenchyma is diffusely infiltrated with polymorphs and round cells indicating a sub-acute or chronic pancreatitis.

Kidneys: Congested, but otherwise normal.

"R.F.O."

CASE 32.

The body was that of a fairly well-developed male infant weighing 5 lb. 14 oz. Post-mortem lividity was present over posterior trunk and limbs. No congenital abnormality was seen on external examination.

Head: /
Head: Dura and pia-arachnoid were perfectly healthy. Falx and tentorium were intact. Brain was rather soft but no intra-cerebral lesion was found.

Thorax: Pharynx and oesophagus, thyroid and thymus glands were healthy.
   Trachea and bronchi were healthy.
   Pleura was clear and glistening. There was no free fluid in the pleural sac.
   Lungs were rather bulky and dark red in colour. On section they were found to be almost airless and some whitish fluid could be expressed from the cut ends of the intra-pulmonary bronchi.
   Pericardium was clear and glistening. There was no free fluid in the pericardial sac.
   Heart was of normal size and shape. Chambers had a normal appearance. Endocardium was healthy. Foramen ovale and ductus arteriosus patent. No congenital abnormality was present.

Abdomen: Peritoneum was clear and glistening. There was no free fluid in the peritoneal sac.
   Stomach was small and contained a little thick mucus. There was nothing of path. interest in the small or large bowel.
   Liver was of average size and shape. Capsule smooth. On section, no abnormality was seen.
   Gall bladder small and contained some thin watery bile.
   Bile ducts healthy.
   Spleen small. On section, it was seen to be rather soft. Adrenal glands of average size.
   Pancreas had been removed in bloc for detailed exam.
   Kidneys were of average size and showed foetal lobulation. Capsule smooth and stripped easily. On section, cortex and medulla healthy. There were depositions of uric acid crystals on the pyramids of both kidneys.
   There was nothing of path. interest in the remainder of the urinary tract.

"A.E.C."

Microscopic report:

Lungs: Pleura healthy. Lungs slightly expanded and deeply congested. Many alveoli contain acidophil vernix membrane. Bronchi are healthy and their epithelium is intact. A few contain vernix caseosa. There is no pneumonia.

Liver: Capsule normal. Liver cells are healthy and the lobular pattern is preserved. There are numerous foci of haemopoiesis, mainly normoblastic in character, throughout the parenchyma and in the portal tracts. The organ is congested and the sinusoids are full of red cells. The bile ducts are healthy.

Adrenal /
Adrenal gland: Cortex and medulla showed no abnormality.

Thyroid gland: The acini are well-developed and many contain acidophil colloid.

Spleen: The capsule and trabeculae are normal. Pulp is cellular and congested. The Malpighian bodies are well-developed and have a normal appearance.

Kidneys: There is a neogenic zone of primitive renal tissue in the outer cortex. The glomerular epithelium and capillary loops have a normal appearance. The tubules are healthy. The organs are congested.

Summary: Evidence of aspiration of vernix caseosa.

"A.E.C."

Pancreas: Shows numerous islets scattered throughout the acinar tissue. The islets are of the usual round or oval shape, but abnormal in respect of size in that many are distinctly larger than normal. The nuclei, particularly in the hypertrophied islets, are also frequently enlarged and sometimes hyperchromatic. The ducts and acini are normal, but the periductal and interacinar fibrous framework is locally infiltrated with a few round cells.

"R.F.O."

CASE 35.

The body was that of a small, premature female infant weighing 1,600 gms. The infant was jaundiced, the skin and mucous membranes being bright yellow in colour. No abnormalities found on external examination.

Head: Dura mater and pia-arachnoid healthy. There was slight subarachnoid haemorrhage over left cerebral hemisphere. Brain was immature, soft in consistence and on section some fluid blood and blood clot were found in the left lateral ventricle. Some fluid blood was also present in the 3rd ventricle, aqueduct and 4th ventricle. There was a large unruptured sub-ependymal haemorrhage in the wall of the left lateral ventricle. There was some yellow staining of the meninges and cerebral cortex.

Thorax: Pharynx, oesophagus, thyroid and thymus glands showed no abnormality.

Trachea and bronchi healthy.

Pleura was clear and glistening. There was no free fluid in the pleural sacs.

Lungs were quite well expanded, reddish-pink in colour and on section no abnormality was seen.

Pericardium was clear. No free fluid in the pericardial sac.

Heart /
Heart was very small. Chambers had a normal appearance. Foramen ovale and ductus arteriosus were patent. Endocardium was healthy.

No congenital abnormalities found in the heart.

Abdomen: Peritoneum was clear and glistening. No free fluid in the peritoneal sac.

Stomach was small and contained a little thick mucus. There was nothing of pathological interest in the small or large bowel.

Liver was small, firm and on section showed no abnormality. Gall bladder was small and contained some thin watery bile. Bile ducts were healthy. Adrenal glands and pancreas were healthy. Spleen was of average size for this stage of development, firm, dark red in colour and showed no abnormality on section. Kidneys were small and showed a moderate degree of foetal lobulation. Capsule was smooth and stripped easily. No abnormality on section.

The remainder of the urinary tract showed no abnormality. "A.E.C."

Microscopic report:

Spleen: The capsule and trabeculae normal. Pulp cellular and very congested. Malpighian bodies small.

Liver: Liver cells healthy. There is widespread haemopoiesis in the parenchyma and portal tracts. This is usual for this stage of development. The organ is moderately congested.

Lungs: Pleura healthy. Lungs quite well expanded and moderately congested. Bronchi healthy and their epithelium is intact. There is no pneumonia.

Kidneys: Capsule is normal. There is a neogenic zone of primitive renal tissue in the outer cortex. The glomerular epithelium and capillary tufts have a normal appearance. Tubules healthy. Organs congested.

Summary: Prematurity. "A.E.C."

CASE 40.

The body was that of a well developed male infant weighing 2,660 gms. Post-mortem lividity was pronounced over face, trunk and limbs. No congenital abnormality was found on external examination.

Head: Dura mater and pia-arachnoid were perfectly healthy. Falx and tentorium intact.

Brain was firm in consistence. On section, no intra-cerebral lesion was found.

Thorax:
Thorax: Pharynx and oesophagus were healthy. Thyroid and thymus glands showed no abnormality. Trachea and bronchi were healthy. Pleura was clear and glistening. There was no free fluid in the pleural sacs. Lungs were moderately well expanded and deeply congested. On section, blood-stained fluid could be expressed from the cut surface. The appearance was that of a moderately severe pulmonary oedema. As far as could be judged from macroscopic examination, there was no pneumonia. The pericardium was clear and glistening. There was no free fluid in the pericardial sac. Numerous subpericardial haemorrhages were present over the heart surface. The heart was of average size and shape. The chambers were of normal appearance. Endocardium was healthy. Foramen ovale and ductus arteriosus patent. No congenital abnormality present.

Abdomen: Peritoneum was clear and glistening. There was no free fluid in the peritoneal sac. Stomach was of average size and shape. There was nothing of pathological interest in the small or large intestine. Liver was of normal size. Capsule smooth. On section, no abnormality was seen. Gall bladder was small and contained some dark-brown bile. Bile ducts were healthy. Spleen was small, firm and pale red in colour. On section, no abnormality was found. Pancreas was removed for fuller examination. Adrenal gland had a normal appearance. Kidneys were of average size and shape. Capsule smooth and stripped easily. On section, cortex and medulla were healthy. Ureters and bladder showed no abnormality.

"A.E.C."

Microscopic report:

Lungs: Pleura healthy. Lungs moderately expanded and rather congested. Bronchi healthy and their epithelium intact. There is no pneumonia.

Kidneys: There is a neogenic zone of primitive renal tissue in the outer cortex. The glomerular epithelium and capillary tufts have a normal appearance. The tubules are healthy.

Liver: Capsule is normal. Liver cells are healthy. Numerous foci of haemopoiesis, mainly normoblastic in character, are present. These are not excessive for this stage of development. The portal tracts have a normal appearance. The bile ducts are healthy. The organ is congested.

Spleen: Capsule and trabeculae are normal. Pulp is cellular and congested. Malpighian bodies are well developed and have a normal appearance.

"A.E.C."

CASE 84. /
CASE 84.

The body was that of a male infant weighing 3 lb. 12 oz., smaller than usual considering the gestational age. There was no external deformity.

Head: Meninges - there was an excess of blood-stained fluid in the subarachnoid space around the base of the brain. There was no tearing of either falx or tentorium.

The brain itself showed flattening of the gyri of either cerebral hemisphere. On section, a quantity of blood clot was found in the left lateral ventricle. The right lateral ventricle was grossly distended by a mass of blood clot which extended throughout a considerable part of the surrounding cerebral tissue - the features being those of an intraventricular haemorrhage, with extension throughout the right cerebral hemisphere.

It was impossible to trace any subependymal haemorrhage owing to the disintegration of the cerebral substance.

Section of the hind-brain showed the 4th ventricle also to contain a blood clot.

Thorax: Pharynx and oesophagus healthy. Trachea contained no foreign material. Pleura - either pleural sac contained an excess of clear amber-coloured fluid.

Lungs - a moderate degree of aeration was present in the left upper lobe and part of the right upper lobe. Whilst the aeration of a minor degree was present in the remainder of the lung tissue, both lower lobes, and the lower part of the right upper lobe were firm and relatively airless. No sub-pleural haemorrhages were present.

Pericardial sac contained no excess of free fluids. No subepicardial haemorrhages were present.

Heart was of average size and developmentally normal. There was no congenital defect. No abnormality was noted in the size or capacity of the chambers. The ductus arteriosus showed slight roughening of the intimal surface.

Abdomen: Peritoneal sac healthy.

Liver of average size. Running down the right lobe there was a well demarcated line of demarcation. The right portion of this lobe being pale and the left portion dark and congested. Section showed this demarcation (an apparent physiological division between right and left lobes) to extend throughout the depth of the liver substance. Sections have been taken from right and left lobes and also through the line of demarcation.

Biliary tract normal. Pancreas was removed by Dr. R.F. Ogilvie. Spleen was of usual size and normal size.

Both kidneys were of usual size. They showed on section no apparent abnormality.

The remainder of the urogenital tract showed no pathological condition.

Adrenals were of average size for an infant of this weight. They showed on section no abnormality.

Microscopic /
Microscopic report:

**Lung:** Sections of either lung show only a minor degree of aeration. In particular, areas of patchy alveoli are distended by masses of degenerate squames and amniotic debris considerably in excess of normal. In the unaerated regions the alveoli containing an amorphous acidophil precipitate show an oedematous distension. No infective reaction is present.

**Liver:** Sections from right and left lobes of the liver and through the line of function fail to reveal any histological distinction between the various sections. The amount of haemopoiesis is in keeping with a slightly premature infant.

**Spleen:** No abnormality is present.

**Kidney:** Vestiges of the neogenic zone are still evident, indicative of slight prematurity. No pathological condition is present.

**Heart:** Shows vacuolation of some of the muscle fibres, probably an anoxic effect.

**Abstract:** Intra-cerebral haemorrhage.
- Inhalation of increase quantity of liquor amnii.
- Pulmonary oedema.
- Macroscopic but no microscopic evidence of demarcation between right and left lobes of liver.

"A.D.B."

**Pancreas:** The acinar and islet tissues are irregularly congested, but the acinar material is otherwise normal. The islet tissue is very abundant. A good many of the islets, particularly in head and body, are moderately increased in size and not infrequently include abnormally large cells with correspondingly large nuclei. No degenerative changes, however, are present in the islets.

"R.F.O."

**CASE 93b.**

The body was that of a small female infant weighing 900 gms. There was slight jaundice of the skin, particularly over the face.

**Head:** There was no evidence of meningeal or intra-cerebral haemorrhage.

**Thorax:** Serous sacs were healthy.
- Upper respiratory passages contained no foreign material.
- Mouth /
Mouth, pharynx, oesophagus showed nothing to note.
Lungs were of expected size, but felt slightly more bulky and firmer than normal. They did not, however, have the usual consistency of lungs involved by hyaline membrane. No abnormal material could be expressed from the cut surfaces. Heart was of appropriate size and showed no developmental abnormality.
Thymus gland was normal.

Abdomen: Peritoneal sac was healthy.
Intestinal tract showed no abnormality.
Liver and spleen were of appropriate size and showed nothing of note on section.
Gall bladder and biliary tract were healthy.
Pancreas was removed in toto and weighed 0.73 gms.
Kidneys showed no abnormality.
Urinary tract was healthy.
Adrenals were of appropriate size and bright yellow in colour.

Microscopic report:

Lungs: The pulmonary tissue is very immature. Many of the alveolar ducts are over-distended while the intervening air-spaces are completely atelectatic. There is no excess of squames but some of the alveolar ducts contain small masses of albuminous material mixed in some instances with small numbers of polymorphs. These polymorphs are generally scanty throughout both lungs and the majority appear pyknotic. It is difficult to be certain whether they represent a true inflammatory response in the lungs or whether they have been aspirated from infected liquor amnii. There is no evidence of pulmonary hyaline membrane.

Liver: Extensive haemopoiesis is present in keeping with the degree of prematurity.

Kidney: There is a broad neogenic zone indicative of considerable prematurity.

Spleen: A little haemopoiesis can still be made out.

Adrenals: These show nothing of note.

Summary: Extreme prematurity.
?
Early pneumonia.

"A. MacF."

CASE 102.

The body was that of a male infant aged 40 hrs. and weighing 4080 gms. The crown to heel - 53.5 cm. Crown to rump - 38.5 cm. For a baby of 35 weeks gestation the weight and /
and size were certainly excessive. The baby was moderately jaundiced and a specimen of heart blood was taken post mortem and this was sent to Blood Transfusion Department via Dr. Farquhar. A bluish discolouration of the skin was evident in the left lower limb. This discolouration was linear and followed the course of the saphenous vein, extending from the groins right down to the ankle. Section through the skin showed an area of haemorrhage in the related underlying subcutaneous fatty tissue, which was most probably the result of venous thrombosis.

**Head:** Tentorium and falx were intact. Brain showed no abnormality externally nor on section. Pituitary was of normal size and was removed for microscopy.

**Thorax:** Pharynx and oesophagus were healthy. Trachea contained no foreign material. Pleura was clear and glistening. Both lungs were comparatively well aerated. There was some congestion of the lower lobes, but no other pathological condition. No subpleural haemorrhages were present. Pericardial sac was healthy. Heart was considerably larger than usual, almost $1\frac{1}{2}$ times normal for a baby of this weight. The auricles showed no abnormality. Dissection of the ventricles showed enlargement of the chambers with a corresponding increase in thickness of the walls. The enlargement affected both right and left ventricles. There was no intra-ventricular septal defect. The pulmonary trunk and aorta arose in their respective normal positions, as did the coronary arteries. The ductus arteriosus as might be expected was patent. There was in fact no congenital defect to account for the cardiac enlargement. The myocardium was of normal colour and sections have been fixed in absolute alcohol for glycogen.

**Abdomen:** Peritoneal sac was healthy. Stomach and intestinal tract showed no pathological condition. Liver was considerably larger than usual, it weighed 275 gms. It was of uniform pale brown colour. Biliary tract and pancreas were normal. Spleen was of usual size for a baby of this weight. It was of normal consistence and showed no abnormality on section. Kidneys - in the site occupied by the right kidney and right adrenal there was a large firm ovoid shaped mass apparently the site of a massive haemorrhage. The mass has been fixed prior to section, the adrenal being the most probable site of haemorrhage. Haemorrhage also extended to a considerable extent in the retroperitoneal tissues, whence it was found in the right iliac fossa and over on the left side of the abdomen. The left adrenal was normal. The left kidney showed very marked congestion of the medulla and the cortico-medullary boundary zone. Several small veins in the medulla contained firm, almost certainly ante-mortem thrombus.
The main renal vein was not, however, thrombosed. The remainder of the urogenital tract showed no abnormality.

**Microscopic report:**

**Kidney:** Sections of the left kidney show a massive haemorrhagic infarction with small islands of surviving renal tissue around the interlobular vessels. The large renal veins contain thrombus of recent origin.

The right kidney shows erythropoiesis distributed throughout the medulla and inner cortex. No abnormality is present in tubules or glomeruli.

**Liver:** There is considerably excessive erythropoiesis, this mainly normoblastic.

**Spleen:** There is probably an excess of normoblasts in the pulp. It is impossible to be more certain of this.

**Adrenal:** No abnormality is present.

**Heart:** The myocardium shows no abnormality. A section stained for glycogen shows this substance to be present, but it is doubtful whether it is present in excess of normal.

**Lung:** Shows generalised congestion with patchy areas of intra-alveolar haemorrhage. No thrombosis is present.

**Pituitary:** No abnormality is present.

**Skin:** Sections taken from the left leg fail to include the saphenous or any large venous channels.

In the subcutaneous fatty tissue there is an early polymorph leucocyte infiltration and a few localised areas of haemorrhage.

**Abstract:**

Massive venous infarction of right kidney.

Thrombosis of left renal vein and left saphenous vein.

Enlargement of heart of undetermined origin.

Excessive erythropoiesis in liver.

"A.D.B."

**Pancreas (4.67 g.):** The islets are abundant, particularly in certain regions of the tail. Their average size is slightly increased, but only a few islets can be described as conspicuously enlarged. Some of the cells in the enlarged islets are two or three times the usual size, this feature being particularly evident in the increased size of the nucleus. The parenchyma is normal.

**Note:** The fact that the islets are not as large as they usually are in a diabetic foetus may in this case be related to the unusually large pancreas which is about twice the normal weight.

"R.F.O."
APPENDIX IIB

AUTOPSY REPORTS ON INTRA-UTERINE DEATHS

BABY McC.

The body was that of a macerated male foetus, weighing 2,480 gms. Crown to heel measurement - 1'7"; crown to
rump - 1'2". Weight of pancreas 1.27 gms. The skin showed
patches of epidermal desquamation. No external deformity
noted.

Head: Meninges healthy. No subdural or subarachnoid
haemorrhage present. Brain soft as a result of maceration.
No intracranial haemorrhage present.

Thorax: Pharynx and oesophagus showed no abnormality.
Trachea and bronchi patent. The mucosa of the trachea
showed early haemoglobin staining.

Either pleural sac contained a quantity of blood-stained
fluid. There were numerous scattered subpleural haemorrhages.

Lungs were non-expanded and on section were seen to be
solid in texture and completely airless.

Pericardial sac contained a quantity of blood-stained
fluid.

Heart - there were scattered subepicardial haemorrhages.
The heart was flabby in consistence and somewhat dilated.
On dissection, no congenital abnormality was found. Chambers
were dilated. Endocardium showed haemoglobin staining.

Abdomen: Peritoneal sac contained a considerable quantity of
blood-stained fluid.

Stomach, small intestine showed no abnormality.
Liver was of average size and soft in consistence. On
section, pulp was seen to be pultaceous as a result of
maceration.

Pancreas was removed and given to Dr. R.F. Ogilvie.
Spleen was of average size and usual shape. It was soft
as a result of maceration.

Both kidneys were of normal size and had undergone severe
maceration.

Pelvis, ureters and bladder showed no abnormality.
Adrenals were severely macerated.

Microscopic report:

Sections show some oedematous expansion of the alveoli
with no cornified squamous epithelial cells or debris present.
The bronchial epithelium is entirely desquamated as a
result of maceration.

Liver, spleen and kidneys: The histology of the organs is
completely obscured consequent upon maceration.

Abstract: Maceration. 

"A.D.B."
BABY C.

The body was that of a severely macerated female foetus weighing 2,580 gms. with a complete transverse fracture and separation through the cervical spine.

Head: Meninges were apparently healthy.

Brain was extremely soft and pultaceous as a result of maceration.

Thorax: Pharynx and oesophagus showed no abnormality.

Trachea contained no foreign material within their lumen.

Thorax sac contained a considerable quantity of blood-stained fluid.

Both lungs were completely unexpanded, and on section showed a somewhat soft and autolytic parenchyma.

Heart was of average size and shape, but the myocardium was extremely flabby as a result of maceration. No congenital abnormality was present.

Abdomen: Peritoneal sac contained a large quantity of blood-stained fluid.

Intestinal tract showed nothing to note.

Liver was of average size but extremely soft and macerated.

Pancreas showed nothing to note.

Spleen was of average size and extremely soft in consistency.

Both kidneys were of normal size though they had a very soft autolytic consistence.

Pelvis, ureters, bladder healthy.

Adrenals - these disintegrated on removal being extremely soft and autolytic.

Microscopic report:

Lungs: Bronchial epithelium is desquamated owing to maceration.

The only abnormality apparent is a distension of the alveoli which contain a considerable excess of cornified epidermal cells.

In microscopy of the visceral organs the histology is completely obscured as a result of maceration.

Abstract: Maceration.

"A.D.B."

BABY T.

The body was that of a severely macerated female foetus weighing 1,640 gms.

Head: The brain was merely a pultaceous mass as a result of maceration.

Thorax: /
Thorax: Pharynx, oesophagus and trachea showed no abnormality. 
Phleural sacs contained some blood-stained fluid.  
Lungs were of expected size but severely macerated.  
Heart showed no developmental abnormality.

Abdomen: The abdominal organs, liver, spleen, and kidneys showed no developmental abnormality. All these organs were severely macerated.  
Pancreas was scarcely recognisable owing to maceration.

Microscopic report:

Lung: Lung tissue is very severely macerated, but a considerable excess of cornified epidermal squames is still evident, indicative of an anoxial state.

Summary: Anoxia.  
Macerated (Diabetic mother). 

"A.D.B."

BABY M.

The body was that of a large macerated male foetus weighing 2,780 gms. The epidermis was desquamating over the lower limbs, leaving a raw red surface underneath. No congenital abnormality was found on external examination.

Head: Dura mater and pia arachnoid showed no abnormality. There was some subarachnoid haemorrhage over both temporal poles. 

Brain - 340 gms. Soft. This was apparently the result of maceration and partly the result of severe bilateral intraventricular haemorrhage which had partially destroyed the walls of the lateral ventricles. The source of the haemorrhage was not found. Fluid blood and blood clot were found in the lateral ventricles, third ventricle, aqueduct and 4th ventricle. Some of this fluid blood had reached the subarachnoid space as noted above.

Thorax: Pharynx and oesophagus, thyroid and thymus glands had all suffered slightly from maceration. Thymus glands - 20 gms.  
Phleura was dull and there was a small quantity of blood-stained fluid in the pleural sacs. 
Trachea and bronchi showed haemoglobin staining of the lining mucus. 
The lungs were rather bulky, dark purple in colour, numerous subpleural petechiae were present over the surfaces of both lungs. On section, the lungs were seen to be deeply congested, slightly macerated and whitish fluid could be expressed from the cut surface. This was probably aspirated liquor. Right lung - 60 gms. Left lung - 50 gms.  
Pericardium was dull and there was some blood-stained fluid in the pericardial sac.  
Heart was of the expected size and weighed 50 gms. It was slightly macerated. No congenital abnormality was present.

Abdomen: /
Abdomen: The peritoneum was dull. There was some blood-stained fluid in the peritoneal sac. There was nothing of interest in the alimentary tract. Liver 180 gms.; it was very macerated. Gall bladder was small and contained some thin watery bile. Bile ducts were patent. Adrenal glands weighed 10 gms. each. They were macerated. Pancreas was removed intact for separate examination. Kidneys were very macerated and weighed 50 gms. each. Ureters and bladder showed no abnormality. Spleen was small, firm and slightly macerated, weighing 30 gms.

Microscopic report:

Lungs: Pleura healthy; lungs expanded as a result of aspiration of liquor and moderately congested. Bronchi show desquamation of their lining epithelium as a result of maceration. There is no pneumonia. A number of alveoli contain histiocytes and cornified cells derived from the liquor amnii.

Thymus: Capsule and lymphoid tissue normal. Hassal's corpuscles have a normal appearance. Interstitial tissue shows no abnormality.

Adrenal glands: Capsule normal. Zona glomerulara is relatively intact. Remainder of the glands is severely macerated.

Prostate: Glandular epithelium slightly macerated. Stroma normal.

Testis: Organ is macerated.

Kidneys: Organs severely macerated and only the outline of tubules and glomeruli remains.

Spleen: Capsule and trabeculae show little change. Pulp is severely macerated. The outline of some of the Malpighian bodies is still visible.

Liver: Liver cells have suffered severely from maceration. There are numerous foci of haemopoiesis throughout the parenchyma and in the portal tracts. These are mainly normoblastic in character.

Summary: Maceration. Evidence of aspiration of liquor amnii.

"A.E.C."

BABY K.

The body was that of a rather large female foetus weighing 6 lb. 10 oz. A considerable degree of maceration had occurred and /
and the surface epithelium had desquamated, leaving a raw red surface underneath. No congenital abnormalities were noted on external examination.

**Head:** Dura mater intact. Brain very soft and macerated. No intra-cerebral lesion present.

**Neck and Thorax:** Pharynx and oesophagus healthy. Trachea and bronchi showed haemoglobin staining of the lining mucosa. Thyroid and thymus glands showed slight maceration. Pleura dull and there was some blood-stained fluid in the pleural sacs. Lungs were unexpanded and dark purple in colour. They were rather macerated. Pericardium was dull. There was blood-stained fluid in the pericardial sac. Heart was of average size and shape and was not severely macerated. No congenital abnormality was present.

**Abdomen:** Peritoneum was dull and there was some blood-stained fluid in the peritoneal sac. Stomach was of average size and was empty. There was nothing of interest in the small or large bowel. Liver was of normal size. Capsule smooth. On section the organ was seen to be rather macerated. Spleen was soft and macerated. Gall bladder was small and contained some thin brown bile. Bile ducts were patent. Adrenal glands and pancreas showed early maceration. Kidneys were of average size and showed marked foetal lobulation. They were very soft and macerated. There was nothing of pathological interest in the remainder of the urinary tract.

**Microscopic report:**

**Spleen:** Capsule and trabeculae show little change. Pulp is macerated. A few remnants of Malpighian bodies are visible.

**Kidney:** Capsule is normal. Glomeruli almost completely macerated. A few still retain cellular detail. The medulla is severely macerated.

**Lungs:** Pleura is normal. Lungs show evidence of maceration. The bronchi show desquamation of their lining epithelium.

**Liver:** Organ is very macerated but outline of portal tracts is still visible. A few foci of haemopoiesis were seen.

**Pancreas:** Very macerated.

**Summary:** Severe maceration of all organs. No evidence of haemolytic disease or of congenital syphilis.

"A.E.O."

BABY T. /
BABY T.

The body was that of a rather large extremely macerated female foetus weighing 7½ lb. The surface epithelium was desquamating leaving a raw red surface underneath. No congenital abnormalities were found on external examination.

Thorax: Pharynx and oesophagus were normal apart from maceration.
Thyroid and thymus glands showed little change apart from maceration.
Trachea and bronchi were not abnormal.
Pleura was rather dull and the pleural sacs contained a considerable quantity of blood-stained fluid as a result of maceration.
Lungs were dark purple in colour and quite airless, and on section they were found to be deeply congested but had not suffered severely from maceration.
Pericardium was dull and there was a small quantity of blood-stained fluid in the pericardial sac.
Heart was of normal size and shape. Chambers had a normal appearance and there were no congenital abnormalities present.

All the abdominal organs had suffered severely from the maceration and no structural detail could be made out.

Dura mater and pia arachnoid were perfectly healthy, and the falx and tentorium were intact.
Brain was extremely soft and had suffered severely from maceration.

Microscopic report:
Dobel Sections: No spirochaete present.

"A.E.C."

BABY B.

The body was that of an extremely macerated male foetus weighing 5 lb. 14 oz. The surface epithelium was desquamating leaving a raw red surface underneath. No congenital abnormalities were found on external examination.

Thorax: Pharynx and oesophagus showed slight maceration.
Thyroid and thymus glands had a normal appearance.
Trachea and bronchi were passively congested.
Pleura was dull and there was a small quantity of blood-stained fluid in both pleural sacs.
Lungs were pale pink in colour and quite airless. They had not suffered so severely from the maceration and no structural abnormality was found.
Pericardium was clear and glistening and there was no free /
free fluid in the pericardial sac.  Heart was of normal size and shape.  Chambers had a normal appearance.  Endocardium was healthy.  Maceration was not severe.  Foramen ovale and ductus arteriosus were patent.  No congenital abnormalities were present.

**Abdomen:** Peritoneum was dull and there was a considerable quantity of blood-stained fluid in the peritoneal cavity.  All the abdominal organs had suffered severely from maceration and little structural detail could be made out.  Liver and spleen were not enlarged and there was no evidence of syphilis or erythroblastosis.

Dura mater and pia arachnoid were healthy.  Brain was very soft in consistence.  No intra-cerebral lesion found.

**Microscopic report:**

**Lung:** Pleura normal.  Bronchi have suffered severely from maceration and their mucous membrane has desquamated.  Bronchi and alveoli packed with cells derived from the liquor amnii.

**Liver and Spleen:** Severely macerated.  No structural detail present.

**Dobell Sections:** No spirochaete present.

**Summary:** Maceration.  Evidence of aspiration of liquor amnii.

"A.E.C."
APPENDIX III

SELECTION OF A MICRO-METHOD FOR
THE DETERMINATION OF THE BLOOD SUGAR LEVEL
Clinical laboratory methods of determining the blood sugar depend upon the ability of glucose in hot alkaline solution to reduce either copper to cuprous oxide or potassium ferricyanide to ferrocyanide. The reduction may then be measured by titrimetric or colorimetric methods and compared with that produced by standard glucose solutions. Although many methods are available, the size of the subjects and the frequency with which blood samples were required in this study of newborn infants restricted the choice to one which would yield reliable duplicate analyses on 0.1 ml. of capillary blood. Such a method was described by Haslewood and Strookman (1939) and recommended by King (1951). The protein of 0.1 ml. of whole blood is precipitated by sodium tungstate and copper sulphate, and aliquots of the filtrate are treated with a modified Harding and Down's copper reagent from which the iodate is omitted. The cuprous oxide formed is estimated by the intensity of colour produced with either phosphomolybdic acid or arsenomolybdic acid solution. The method seems simple and, as no other then available yielded duplicate analyses on such a small quantity, it was adopted against the advice of a senior laboratory technician who claimed to have had previous unsatisfactory experience of it.

**EXPERIENCE OF KING'S METHOD**

The method was given a two-month trial but without the desired /
TABLE 46

VARIATION IN RESULTS USING KING'S METHOD

<table>
<thead>
<tr>
<th>Date</th>
<th>Specimen</th>
<th>From same Glucose Standard or Blood Sample Electro-Photometer Readings of Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>17.10.51</td>
<td>Glucose</td>
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<td>&quot;</td>
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<td>&quot;</td>
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<tr>
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<tr>
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<td>&quot;</td>
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<td>&quot;</td>
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<td>&quot;</td>
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</table>
desired standard of accuracy being achieved. Three or more analyses of the same blood sample or glucose standard solution commonly produced results which varied by from 5 to 10%, and errors of 20% occurred too often. Only rarely was the error reduced to less than 5%. With increasing practice and the systematic exclusion of possible technical faults, the error persisted. Examples of the results obtained, selected at random and arranged in chronological order, are given in Table 46. Where three separate analyses were made on the same specimen, the results of two of them commonly agreed, but the third was widely divergent. To be effective, however, any method would have to yield comparable figures on duplicate analyses only. The measures taken to improve accuracy will now be outlined.

Measures Adopted to Improve Accuracy.

The most likely explanation for the failure of a chemical method in the hands of a clinician is the latter's comparative inexperience of laboratory techniques. To him the usefulness of a method lies in its stability and in the ease with which he can learn to use it accurately. The measures taken by myself to improve my results with this method are given in detail in order to show that, although it may be useful to the biochemist, it cannot yield accurate results in the hands of the average clinician without a great deal of practice.

1. Reagents.

All reagents were made and used strictly according to instructions. Several batches were prepared both for and by me.
me. Only analytical quality chemicals were employed. Both phosphomolybdic acid and arsenomolybdic acid reagents were tried. The distilled water was tested regularly for substances which might interfere with colour production.

2. Accuracy of apparatus.

Grade A pipettes only were used to deliver quantities of 1 ml. or more. Grade A volumetric flasks were used in the preparing of solutions, and chemicals were weighed accurately. Several grade A quality micro-pipettes calibrated to contain 0.1 ml. were obtained. A large number of grade B quality micro-pipettes were compared with these for accuracy by a colorimetric method, and only those found to be satisfactory were used for further work.

3. Test-tubes.

Simple test-tubes, measuring 6 x $\frac{3}{4}$ inches and stoppered with cotton wool, were used at first. Particles of cotton wool were frequently found in the solution, however, and they may have supplied a reducing substance or interfered with the electrophotometer reading. "Q and Q" test-tubes with hollow ground-glass stoppers were substituted, but traces of dichromate cleaning solution gained access to small unsealed crevices in the stoppers and this contamination could not be removed by washing. Duplicate analysis of a standard glucose solution yielded photoelectric cell readings of 9 from a tube the stopper of which was contaminated in this way, and 317 from a clean test-tube and stopper.

Solid glass stoppers ("Norgil") were then used but without appreciably improving the variability of the results.
These stoppers produced a deep blue colour with phosphomolybdic acid reagent at first, possibly because of the presence of metallic salts deposited during the grinding process. Rubber stoppers, previously decolourised by prolonged boiling in caustic soda, and glass marbles were tried but without improvement.

Folin and Wu tubes gave no better results, and these are so designed that washing becomes very difficult.

Finally simple test-tubes (6 x 3\(\frac{3}{4}\)) were used again. Each was calibrated accurately to 12 ml. and after the colour development stage the volume in each was made up to the 12 ml. mark with distilled water. The error in results persisted.


All test-tubes were washed first with soap and water (a detergent, 'Teepol', was tried later but without improvement). They were then immersed in clean dichromate solution for 24 hours, following which they were washed with tap water twenty times and with distilled water ten times. They were then stacked in the inverted position in tinned-iron test-tube baskets and dried in an electric oven. They were stored in a drawer which was relined regularly with clean shelf-paper, and they were generally used within 48 hours. Ground-glass stoppers, when used, received the same treatment.

Because of the possibility that the variability in results was due to dichromate solution so combining with glass that its removal by simple washing was incomplete, the effect was observed of immersing the tubes in running water for 12 hours after routine washing. No improvement resulted.

Pipettes /
Pipettes were filled with and immersed in clean dichromate solution for at least 12 hours. They were then washed through twenty times with tap water and ten times with distilled water before being dried with ANALAR quality acetone and with suction. They also were left immersed in water after cleaning and before drying, but this measure failed to improve the results. Because of the possibility that laboratory dust was being sucked into the pipettes during the drying process, positive pressure was tried. After filling the pipette with ANALAR quality acetone, air was blown through it from a compressor by way of a large glass-wool filter. No improvement resulted.

Two laboratory technicians were found to have been making a practice of cooking an evening meal in the drying oven before going to night-classes. Sugar doughnuts featured on the menu when the practice was discovered! Correction of this potential source of contamination, however, failed to effect any significant improvement in the results.

5. Heating of test-tubes.

Uneven heating of test-tubes in a water-bath gives rise to erratic results (Miller and Van Slyke, 1936). A new bath was therefore obtained which had a perforated false floor raised about half-an-inch above the bottom of the bath. Heating was provided by a gas-ring, and the water temperature in all parts of the bath was uniform. Variable results persisted. (It was noted, however, that further heating of the tube after colour-development had taken place resulted in the intensification of colour, e.g. photo-electric readings of 260 and 106 became 300 and 150 respectively on boiling for a further /
further few minutes.)

6. Delay in reading results.

The colour produced on adding phosphomolybdic acid reagent is said to be stable for three hours (King and Garner, 1947), but the colour was found to fade on standing. The following photo-electric readings were obtained on the same sample over a ten-minute period: 352, 348, 345, 342, 339, 337. Fading was not accelerated in other tubes when oxygen was bubbled through the solution after colour development. Colour-fading has also been experienced by Lehman and Silk (1952) in this method. It may be retarded by standing the test-tubes in ice-water. The photo-electric cell readings should then be made as rapidly as possible. This practice, however, did not reduce the variability of results in my experiments, and indeed the colour differences were often apparent to the eye when the tubes were removed from the water-bath.

7. Technique.

(a) The author's skill with pipettes was examined by experienced biochemists without significant faults being found. The fluid delivered by pipettes of various sizes was weighed on an accurate micro-balance under standard conditions, and the variability for each pipette was insignificant.

(b) An 18-inch length of rubber tubing was fitted to the micro-pipettes when taking-up and expelling glucose-standard solution or blood. The lips were carefully dried in order to minimise the risk of contamination from salivary sugar.
(c) All reagents and the glucose standard were delivered as far down in the test-tube as possible without the pipette actually touching the solution which was there already.

(d) The same cells were used for control and test solutions in the Hilger-Spekker electrophotometer. They were always inserted in the same position and they were always clean. All bubbles in the test or control solutions were tapped clear of the cell walls before a reading was taken.

(e) The entire technique was carried through under the continuous observation of one or two biochemists on several occasions. Each stage was checked and passed, but undesirable variability in results persisted.

Summary of Experience.

The variability of results was considered to be too great for the work which was to be done. The error occurred after preparation of the blood filtrate and in the copper reduction - colour production stage. It took the form of poor colour formation, and colour-fading after removal of the test-tube from the water-bath was less important. No way of overcoming this fault was found.

The development of the method was reviewed, particularly with regard to the experience of biochemists.

HISTORY OF THE DEVELOPMENT OF THE COPPER REDUCTION METHODS OF DETERMINING THE BLOOD SUGAR
A review of the literature concerning the evolution of the copper reduction method of determining the blood sugar reveals that opinion about it has varied widely and sometimes bitterly. The alkaline copper solution, the colour producing reagent and the nature of the test-tube to be used have been the particular subjects of modification and criticism until very recently.

Although the methods of Lehmann, Bang and Maclean preceded that of Folin and Wu (1919), the latter may be regarded as the basis upon which the modern copper methods for determining the blood sugar have been developed. The authors employed a phototungstic-phosphomolybdic reagent in order to precipitate the blood proteins. The filtrate was then heated with an alkaline copper solution. On the further addition of a phenol reagent and an alkali, a blue colour developed, the intensity of which depended upon the amount of cuprous oxide formed and therefore upon the level of reducing substance in the filtrate.

They discovered, however, (1920) that the phenol indicator introduced certain inaccuracies, and they substituted a new phosphomolybdic acid - sodium tungstate reagent. They also recommended that the alkaline copper reagent should be siphoned and filtered regularly in order to remove the cuprous oxide which was precipitated spontaneously. Benedict condemned the method because of the "excessive, inevitable and uncontrollable reoxidation of cuprous oxide". On re-examining /
examining the method, Folin and Wu discovered that when test-tubes of 20 mm. or more diameter were employed, then the losses by re-oxidation "became astoundingly high". They believed that convection currents within the solution during heating were sufficient to explain this, and in order to correct this fault they designed a special tube which has since borne their names. This tube is calibrated at 25 ccs. and has a constricted neck of not more than 8 mm. diameter above a bulb of such a size that when 4 ccs. of fluid are placed in it the upper level of the fluid will lie in the constricted portion. They compared the results obtained in 14 blood samples, each of which was analysed by both the original and the modified method. The latter gave slightly lower values than the other, and a further trial showed that, when the modified method was used, higher values were obtained in Folin and Wu tubes than in open test-tubes. The authors concluded that "from a theoretical standpoint the method now appears to be without a flaw".

A similar method was described by Shaffer and Hartmann (1920-21) who confirmed that significant losses of cuprous oxide by re-oxidation occurred when open test-tubes were used. They believed that their method was the best available and that it was both more reliable and more convenient than that of Folin and Wu.

The Folin and Wu copper reagent and its various modifications were criticised by Benedict (1925) who found that it was easily upset by non-sugar substances. He believed that his new alkaline copper reagent gave sugar levels in urine with /
with only one tenth of the error found with the Folin and Wu reagent. A remarkable increase in the quantity of cuprous oxide obtained resulted from the addition of a small amount of sodium bisulphite to the reagent. The bisulphite did not affect the copper solution. He also selected a tungstic-arSENIC-phosphoric acid reagent as his colour producer because it resulted in better and more stable colour formation than did the phosphomolybdic-tungstic acid reagent of Folin and Wu. He rejected the Folin and Wu tube and used simple test-tubes which were graduated at 12.5 and 25 cms. A few drops of benzene were added prior to heating, and the tubes were stoppered with cotton wool. The benzene appeared to favour the precipitation of more cuprous oxide, probably, he thought, because it was in a finer state of division. He obtained results which were 20% lower than those obtained on the same samples by the Folin and Wu method. He stated that "unless we assume an inhibiting substance in the blood (which cannot be demonstrated and which would invalidate all copper methods as applied to blood) we must assume the presence of a slowly reacting interfering compound which causes plus errors of something over 10 mg. per 100 ccs. of blood". He believed that his new method was less upset by this compound and that it reflected more accurately than did Folin and Wu's method the "true sugar" level. Folin (1926) rejected some of Benedict's criticisms, but he went on to propose a modification of his alkaline copper reagent and a new acid molybdate reagent for the estimation of cuprous oxide. With these modifications he was able to obtain significantly lower values /
values than with the original (1920) Folin and Wu method. He further criticised Benedict's method, and the latter (1926) in his reply stated that "Folin's paper leads to the anomalous conclusion that while the Benedict method yields figures which are probably correct, the method itself is quite unsatisfactory". He criticised Folin's modified method and then described a modification of his own which, he believed, would make it both simpler and safer than Folin's. Again the alkaline copper solution was altered so that the reduced copper would be held in solution and the colour development would be more rapid and constant. He dismissed Folin's criticism of his use of simple test-tubes, benzene and cotton wool stoppers as "fanciful and quite incorrect", and he claimed that the Folin and Wu tubes allowed 6 to 7% reoxidation of cuprous oxide. Later in 1926 Folin and Svedberg published a paper comparing results obtained on the same blood samples by the Folin and Wu method, the Folin method and fermentation. They "discovered another weakness in the method which might long have remained undiscovered". The copper solution was found to become progressively alkaline on storage, with resultant introduction of error. Recommendations for overcoming this were made. They were satisfied that Folin's method yielded results which were nearer the fermentable sugar values than those obtained by the Folin and Wu method.

An extensive further modification of the copper method was published by Benedict (1928). The results obtained from his modified method were 22 mg. per 100 ml. of blood lower /
lower than those found by the Folin and Wu technique. The new alkaline copper reagent was made fresh daily by mixing two stock solutions, and to it he added small amounts of sodium bisulphite. He returned, however, to the phosphomolybdic acid colour producer and to the Folin and Wu tubes, both of which he had rejected three years previously. Shortly after this, according to Peters and Van Slyke (1932), Folin abandoned the colorimetric copper method in favour of the ferricyanide method which he described in 1928. He published two papers in 1929, however, the first alone, and the second with Malmros, concerning the various copper methods. In the first he believed that his 1926 solutions were as nearly perfect as they could be made, and he ascribed complaints about errors to "a more or less incorrect way of using the method". He had found, however, that the final colour was subject to fading after dilution, and to overcome this he recommended that a weak molybdate solution should be used for the final dilution in place of water. He was unhappy about results on hypoglycaemic samples. He agreed with Benedict's criticisms concerning the alkaline copper reagent and he too recommended constituting the reagent fresh for use from two stable stock solutions. Even then the reagent could deteriorate in a few hours in sunlight or in a hot room. Finally he modified his acid molybdate reagent further and then revised his method. The second paper, with Malmros, was designed to compare the available blood sugar methods. Although Folin had carried out such a comparison already with Svedberg in 1926, they stated that "The /
"the defects found in the two copper methods would seem to be serious enough to more or less invalidate their comparative results and made a repetition of the work with improved methods imperative". They found that the original Folin and Wu method produced high results. The revised Folin copper method gave the lowest, and the Hagedorn-Jensen and Folin ferricyanide methods gave almost identical results.

Colour-fading was troublesome in the Benedict method, according to Everett (1929), but Benedict firmly denied this in a paper published later in the same year. In 1931 Benedict described his 1928 reagent as "having objections which limit its usefulness". He described a new copper reagent which could be kept as one solution for "reasonable periods of time". The results were correct on average to 3 to 5% when tungstomolybdic acid filtrates were used. He doubted if any more accurate figures could be obtained by any other procedure, however elaborate. He again employed Folin and Wu tubes, but he now added benzene to them before boiling.

A modified tube is recommended for this method by Peters and Van Slyke (1932).

The addition of potassium iodide was found by Shaffer and Somogyi (1933) to stabilise the copper reagent so that spontaneous autoreduction to cuprous oxide on storage and further autoreduction on heating became less likely. They believed that the copper reagents of Folin (1926, 1929) were insufficiently alkaline and that they measured only 75 to 90% of the sugar present. The new method employed straight 8 by 1 inch test-tubes stoppered with glass balls, and it was said to be accurate to within 2 mg.%. 

Harding /
Harding and Downs (1933) were also concerned about the instability of copper reagents, and they claimed that there was no one ideal copper solution for all sugars. They produced another copper reagent which they believed was generally useful. It was made fresh daily from two solutions, each of which was stable for three months. They recommended that the filtrate and the copper solution should be heated in simple test-tubes stoppered with non-absorbent cotton wool. (Many authors have rejected cotton wool because it may contain contaminating reducing substances.) Their copper reagent was used by Haslewood and Strookman (1939) in a phosphomolybdic acid colorimetric method. These authors also recommended 6 by \( \frac{3}{4} \) inch test-tubes stoppered with cotton wool. The reliability of the various Somogyi-Shaffer-Hartmann copper reagents was affirmed by Nelson (1944). The omission of potassium iodide, however, for the colorimetric method made the copper reagent unstable, so that autoreduction took place. He emphasised the need to make up the copper solution just before it was required. He found, however, that when Somogyi's (1937) micro-reagent was employed in this way then "all of the phosphomolybdate reagents tried left much to be desired in reproducibility from time to time and lacked the desired stability of colour". He therefore developed an arsenomolybdic acid reagent which gave better stability and reproducibility of colour, and he also modified the copper reagent again to give improved accuracy at lower glucose readings. He claimed that neither Folin and Wu tubes nor stoppers for test-tubes were required as the high sodium sulphate concentration of the new reagent protected /
protected adequately against reoxidation. The colorimetric method included by King (1951) among his micro-techniques is essentially that of Haslewood and Stookman. The method was examined by King and Garner (1947). They stated that during the war years 1939-45 and subsequently, much difficulty had occurred with colorimetric methods for the determination of the blood sugar. Biochemists had repeatedly complained of the rapid fading of the blue colours, and this had become more obvious since the introduction of photo-electric instruments. This difficulty was ascribed by them to impurities in the reagents and particularly in the sodium carbonate, and they claimed that with analytical reagent chemicals, colour development and proportionality were satisfactory. They found the Harding copper reagent superior to that of Somogyi. The colour was found to remain substantially stable over a three-hour period, and it was more stable when Nelson's arsemomolybdic acid reagent was used.

Because of Nelson's dissatisfaction with phosphomolybdic acid reagent, and because of the recommendation of King and Garner (1947), arsemomolybdic acid solution was used at first in the present study. As a result of a personal visit to the Post-Graduate Medical School at Hammersmith in 1951, however, it was discovered that the use of arsemomolybdic acid reagent had been abandoned in the routine laboratory because it was associated with the development of a turbidity which upset the photo-electric readings and which was attributed to impurities in the chemicals. The technician using /
using the method had an error of approximately 10% on average when carrying out duplicate tests.

Instability of colour production in this method was described by Lehmann and Silk (1952). This difficulty persisted even when the precautions with regard to the purity of chemicals were taken as described by King and Garner (1947). The extent of the fading tended to be greater with deeper colours, but the relationship was not proportional and it was impossible to introduce a correction. Fading was found to be particularly inconvenient when low blood sugar values were measured, and a result of 60 mg.% could give readings corresponding to 35 - 40 mg.% after 20 minutes' delay. They recommended the reintroduction of the Folin and Wu tubes, the immersion of these in ice-water as soon as they had been filled to the mark, the use of a blue or green filter in the colorimeter and that dilution after the addition of phosphomolybdate reagent should be carried out with a modified phosphomolybdate reagent.

This review of the literature provided evidence that skilled chemists had had difficulty with the copper reduction method. The "ideal" copper reagent or colour producing reagent has been produced repeatedly, and expert opinion has varied widely and bitterly on each. Chemical impurities have been blamed for some errors. The simple test-tube and the complicated Folin and Wu tube have displaced one another several times. Others have used test-tubes of varying diameter fitted with wool stoppers, glass stoppers or no stoppers at all, and then in 1952 the Folin and Wu tube was reintroduced.
reintroduced to help prevent the re-oxidation, the very occurrence of which had been denied. The method is simple, it is rapid, and it is eminently suitable for routine use by the relatively inexperienced when a 10% error is of no importance. Undoubtedly it can be accurate to within 2% (Shaffer-Somogyi) but this skill was not acquired personally after a two-month period of continuous effort and under the minute-to-minute supervision of biochemists on many occasions.

The conclusion that the faults were entirely personal might have been inescapable had not complete success resulted from the very first personal trial of the method described by Ramsay (see below).

During an investigation into the differences between normal blood values found by 21 laboratories in the London area the reported values for an unknown stock glucose solution ranged from 80 to 135% of the true value with most of the results falling between 90 and 110% (Wootton and King, 1953). The copper reduction method described by King (1951) was used. Explanations other than unreliability of the method undoubtedly exist and it is interesting to note that the method has been revised completely again by Asatoor and King (1954). An excess of copper is now present in the Somogyi copper tungstate deproteinisation, so that the preparation of an alkaline copper reagent with its inherent danger of error is no longer necessary. The method has been included among the techniques of King and Wooton (1956) without any mention of the criticisms and recommendations of Lehmann and Silk (1952).
THE EVOLUTION OF RAMSAY'S FERRICYANIDE METHOD

The method described by Dr. W.N.M. Ramsay of the Department of Biochemistry, University of Edinburgh, makes use of three previously described methods. These are the cadmium hydroxide precipitation of protein in blood, the reduction of ferricyanide to ferrocyanide by glucose, and the combination of ferrocyanide and an organic material (α-dipyridyl) to form a red ferrous-dipyridyl complex.

The quantitative reduction of potassium ferricyanide by sugar in hot alkaline solution and the iodometric titration of the excess ferric salt from the basis for the extensively employed blood sugar method of Hagedorn and Jensen (1923). The method has been altered very little in the succeeding 25 years. Few exact measurements of reagents are necessary, and after cooling there is no danger of reoxidation of ferrocyanide even if the tubes are allowed to stand for several hours exposed to the air at room temperature (Peters and Van Slyke, 1932). Only the need to have at least 0.2 ml. of blood for accurate duplicate analyses, especially at hypo-glycaemic levels, prevented the use of this method during the present investigation.

According to Peters and Van Slyke (1932) Folin abandoned his copper methods in favour of the colorimetric ferricyanide micro-method which he described in 1928. With the latter he found that precautions against reoxidation were no longer needed and he abandoned his Folin and Wu tubes. He continued, however, to use tungstic acid precipitation of protein rather than the zinc hydroxide method of Hagedorn and Jensen. He modified /
modified the method a little in 1929 to cover a wider range of blood sugar (25 - 400 mg.%) and he introduced a light filter to remove the disturbing effect of excessive ferricyanide. With Malmros (1929) he compared the Folin, Folin and Wu, Folin ferricyanide and Hagedorn-Jensen methods. The Folin method yielded the lowest results. Slightly higher but almost identical results were obtained with the two ferricyanide methods. The Folin and Wu results were the least satisfactory.

Somogyi (1930) knew that when tungstic acid protein-precipitation was used, higher blood sugar results were obtained with a ferricyanide method than with the modified Shaffer-Hartmann copper method. He was surprised therefore to find a seeming contradiction in that the Hagedorn-Jensen ferricyanide method gave, in his hands, results which were no higher than with the various copper reduction methods. He proved that this was due to the superiority of zinc hydroxide precipitation of non-sugar reducing substances. He then described zinc, copper and iron methods of precipitating protein.

Even better protein precipitation was claimed by Fujita and Iwatake (1931) using cadmium hydroxide. The filtrates yielded almost identical sugar results when examined by a ferricyanide method and by filtration. The method was examined by Miller and Van Slyke (1936) who found no more than 1.5 mg.% of residual reducing substance after fermentation of fresh normal human blood with yeast and subsequent precipitation of the proteins by the cadmium hydroxide method.

Whereas /
Whereas previous ferricyanide methods had depended upon the iodometric titration of the excess ferric salt after reduction had taken place, a new method which was described by Miller and Van Slyke (1936) depended upon the direct titration of ferrocyanide with standard ceric sulphate in the presence of an oxidation-reduction indicator. These authors modified the cadmium precipitation of Fujita and Iwatake by adding excess of barium carbonate to the precipitated mixture of blood and cadmium hydroxide in order to rid the filtrate of traces of dissolved cadmium. When they compared ten samples of normal blood with their method and that of Hagedorn and Jensen they found that the latter yielded results in nine cases which were an average 7 mg.% higher. The cerimetric determination of blood glucose was again used successfully by Nimmo-Smith (1946).

The colorimetric determination of ferrocyanide with \( L\)-dipryidyl is used in the determination of serum iron levels. The ferrocyanide produced from the reduction of ferricyanide by glucose was caused by Ramsay (1950) to react with \( L\)-dipryidyl to form a red ferrous-dipryidyl complex. The colour could then be read in a colorimeter and compared with that produced by a number of standard glucose solutions. Protein precipitation is carried out with cadmium hydroxide. The filtrate obtained from 0.1 ml. of blood is analysed in duplicate, but the method is sufficiently sensitive to allow a single estimation to be made from 0.02 ml.
THE METHOD

Reagents.
(i) Cadmium sulphate crystals 4.33 g/l in H$_2$SO$_4$ 0.02N.
(ii) Sodium hydroxide 0.045 N.
(iii) Barium carbonate (solid).
(iv) Potassium ferricyanide 0.005M in sodium carbonate 0.2M.
(v) $\text{L-dipyridyl}$ 0.25% in acetic acid 50%.

All chemicals must be of AR quality.

Technique.
(i) Into a clean dry test-tube pipette 1 ml. distilled water - this will form the blank. For test solutions pipette 0.9 ml. water into a dry test-tube and add 0.1 ml. of blood. Mix thoroughly.
(ii) To each tube add 2 ml. CdSO$_4$ solution.
(iii) To each tube add 2 ml. NaOH.
(iv) Mix thoroughly and heat in a boiling water bath for 3 minutes.
(v) Remove and add 0.1 - 0.2 g. BaCO$_3$ (A.R.). Cool.
(vi) When cold, filter through a dry 7 cm. No. 42 filter paper into a dry test-tube. This gives a protein free Cd (OH)$_2$ filtrate.
(vii) Into a number of dry test-tubes graduated at 25 ml., pipette from each Cd(OH)$_2$ filtrate two separate 1 ml. portions (deliver into lower part of tube).
(viii) To each tube add 3 ml. of water and 1 ml. alkaline ferricyanide solution.
(ix) Mix and heat all tubes simultaneously in a briskly boiling /
boiling water-bath for exactly 10 minutes.

(x) Into each tube pipette 1 ml. dipyridyl while the tubes are still in the bath.

(xi) After a further 10 minutes remove the tubes, fill up with distilled water nearly to the mark and mix thoroughly.

(xii) Allow the tubes to cool, adjust carefully to the mark and mix again.

Following this the pink ferrous-dipyridyl complex is read in a colorimeter fitted with a 624 Ilford narrow green filter. The blanks are read against distilled water. The value of the blood sugar level may then be read from a previously determined calibration graph.

Cleanliness of apparatus.

In addition to the normal cleaning process all glass-ware must be cleaned with hydrochloric acid. Test-tubes and filter funnels are immersed in hot 50% hydrochloric acid before being washed with distilled water from an all-glass still. Pipettes, volumetric flasks, etc., are filled with and immersed in 50% hydrochloric acid overnight before being washed. The acid is changed frequently.

EXPERIENCE OF RAMSAY'S METHOD

The first trial of Ramsay's method was a complete success. Three sets of twelve readings (six duplicate analyses) at various known concentrations of glucose were made. The results showed little scatter even at 25 mg. glucose per 100 ml. The highest scatter in any set of 12 readings gave a standard deviation of only 1.8 per cent of the /
the mean. This was a quite different experience from the disappointments encountered with the copper method.

The method was practised further and a number of minor difficulties and potential sources of error were found. These can be overcome very simply.

**Blood samples.**

Oxalated venous blood sometimes yielded turbid cadmium filtrates. The turbidity persisted throughout the reduction and colour production stages, and it eventually interfered with photo-electric colorimetry. It was found to result from an excess of oxalate in samples of venous blood received from the hospital wards. Similar interference with protein precipitation was noted by Folin and Malmros (1929).

**Alkaline ferricyanide reagent.**

Fresh alkaline ferricyanide reagent was made about twice monthly. Each batch was stored in a dark cupboard in a number of small brown bottles. The other reagents were perfectly stable and were made up in large volumes. The water for all reagents was obtained from an all-glass still.

**Cleanliness of apparatus.**

The cleaning of a great deal of glass-ware with hot 50% hydrochloric acid almost excludes Ramsay's method from the routine laboratory. The cleaning had to be done carefully and personally. When the task was delegated to a technician the blank analyses commonly rose and the duplicates showed unacceptable variability.

The glass-ware for the first trial was taken from the oven just beforehand. Following upon this success, however,
the test-tube baskets were lined with grease-proof paper to protect the tubes from oven dust during drying. The dry tubes were then wrapped up in paper parcels and stored in cardboard boxes. Accuracy was lost with the introduction of this "safe-guard". The paper was found to give a red colour when treated with \( \mathcal{L} \)-dipyridyl, and clearly contained a contaminant. The glass-ware was dried thereafter in unlined baskets and stored in clean tinned biscuit boxes.

**Exposure to light.**

The red ferrocyanide-dipyridyl complex is stable in intensity for 24 hours or more if the tubes are protected from daylight. If they are exposed on a bench, however, and particularly if they are in sunlight, then the red colour deepens. The photo-electric reading of the blank increased from 30 to 100 in 2\( \frac{1}{2} \) hours one sunny afternoon. \( \mathcal{L} \)-dipyridyl did not alter colour in sunlight, but when potassium ferricyanide reagent was added and the tubes were left exposed to the light then a deep red colour developed over a two-hour period. Other tubes containing \( \mathcal{L} \)-dipyridyl and potassium ferricyanide were kept in a dark cupboard overnight and the mixture of reagents remained yellow. On exposure to sunlight potassium ferricyanide is slowly reduced to ferrocyanide, so that a red colour develops in the presence of \( \mathcal{L} \)-dipyridyl. Following upon this observation the window blinds were drawn before the ferricyanide reagent was added to the tubes, and if colorimetry was delayed then the tubes were kept in a dark cupboard.

When the method was firmly established it was compared with /
### TABLE 47

**COMPARISON OF IMMEDIATELY SUCCESSIVE BLOOD SAMPLES ANALYSED BY THE METHODS OF RAMSAY AND HAGEDORN-JENSEN**

<table>
<thead>
<tr>
<th>BABY</th>
<th>BLOOD SUGAR mgm.%</th>
<th>BABY</th>
<th>BLOOD SUGAR mgm.%</th>
</tr>
</thead>
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<tr>
<td></td>
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<td><strong>H-J</strong></td>
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</tr>
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<tr>
<td>16</td>
<td>105, 101</td>
<td>101</td>
<td>32</td>
</tr>
</tbody>
</table>
Comparison of the methods of Ramsay and of Hagedorn and Jensen.

The blood sugar level of 32 normal infants was determined personally (Ramsay's method) and by a technician in the routine Biochemistry Laboratory of the Royal Infirmary (Hagedorn and Jensen method).

Each infant's heel was stabbed with a triangular skin cutting needle. 0.1 ml. of blood was taken from it and delivered into a tube containing fresh cadmium hydroxide solution. A further 0.1 ml. of blood was taken immediately afterward and delivered into another tube containing fresh zinc hydroxide solution. The blood was measured personally. Duplicate analyses of the cadmium hydroxide filtrate and a single analysis of the zinc hydroxide filtrate were made. The results are compared in Table 47. They agreed well, and, as was expected, the cadmium hydroxide precipitates yielded rather lower results.

Conclusion.

The Ramsay method is accurate and the results can be compared favourably with those obtained by the Hagedorn and Jensen method. Duplicate analyses may be made on the filtrate obtained from 0.1 ml.

The method was used continuously thereafter for a year and sporadically for another year. The same standard of accuracy was maintained, and various glucose standard solutions were analysed in duplicate with each blood sample or group of samples.
APPENDIX IV

METHODS OF COUNTING EOSINOPHILS IN BLOOD
The eosinophil leucocytes may be enumerated in blood by the differential counting of stained smears and knowledge of the total white cell count. This method is both slow and inaccurate, especially when the number of eosinophils is small (Rud, 1947; Speirs and Meyer, 1949). They may also be enumerated in counting-chambers by using diluted samples of capillary or venous blood. One part of blood is usually mixed with twenty parts of diluting fluid in a white cell pipette. The error in counting cells is generally proportionate to the square root of the number of eosinophils counted, so that error will decrease as the number of eosinophils increases. For this reason, a large counting-chamber (Fuchs-Rosenthal) is generally employed. The various diluents are based upon the specific staining properties of the eosinophilic granules and the relatively increased resistance to lysis of eosinophil cells over other white and red blood cells.

The Acetone Diluents.

The first direct counting-chamber method was described by Mayett (1888), but the original acetone diluent was introduced by Dunger (1910). It has been modified by Rud (1947), Thorn et al (1948) and Speirs (1952).

1. Dunger's diluent.
   
   **Aqueous eosin** = 0.1 g.
   **Acetone** = 10.0 ml.
   **Distilled water** = 100.0 ml.

2. /
2. **Rud's modification.**
   - Magdala red (or phloxine) - 0.02 g.
   - Acetone - 12.0 ml.
   - Sodium carbonate 10% - 1.0 - 2.0 ml.
   - Distilled water - 90.0 ml.

3. **Thorn's modification.**
   - Aqueous eosin - 0.1 g.
   - Acetone - 5.0 ml.
   - Distilled water - 95.0 ml.

4. **Speirs's modification.**
   - Phloxine B - 0.02 g.
   - Acetone - 15.0 ml.
   - Distilled water - 85.0 ml.
   - Detergent (Alconox) - 0.02 g.

All of these diluents contain an acid dye with which to stain the eosinophil granules, and water with which to rupture the blood cell membranes (eosinophils are more resistant to lysis than other blood cells). All contain acetone which has an inhibitory effect upon the lytic action of water proportionate to the concentration used, e.g. at 0 - 10% all the red cells and most white cells will have lysed and the eosinophils will also rupture on standing, whereas at 10 - 20% the eosinophils will be preserved, and at 50% all the cells will remain intact. The addition of an alkali by Rud was believed to increase the lytic action of water on the red cells and the neutrophil polymorphs, and to increase the speed with which the eosinophil granules take up the dye. The detergent added by Speirs was believed to facilitate the mixing of blood and diluent and to increase the rate of eosinophil staining.

An effective acetone diluent should produce rapid lysis of red cells and rupture or a ghost-appearance of white cells other than eosinophils. The latter should be seen easily because /
because of their red granules. In practice, however, the acetone diluents may be unsatisfactory. The eosinophils may break if there is too little acetone (Speirs, 1952); they may disintegrate on standing or during shaking (Swanson et al, 1952), or, if the reagent is insufficiently alkaline, the lysis of red cells is incomplete. The counting-chambers must be filled within 5 minutes of mixing the pipette (Henne-man et al, 1949), for if the pipette is allowed to wait longer, then many of the eosinophils will fragment on reshaking. Furthermore, the relatively rapid evaporation of the fluid means that there can be no delay in performing counts. These factors introduce practical difficulties when several samples must be taken from infants at various points in a hospital within a short space of time. In Smart's experience (1950) the stipulated mixing period of 30 seconds is probably too short to permit adequate mixing, but if this period is exceeded then the eosinophils may break and disappear.

If an acetone-diluent is to be used, then the stages should be carefully timed, and four counting-chambers should be filled rather than one as recommended by Rud.

The Propylene Glycol Diluents.

These diluents depend upon the isotonicity of a solution of equal parts of propylene glycol and water, and the invisibility of the erythrocytes when one part of blood is mixed with twenty parts of the diluent.

1. /
1. **Randolph's diluent.**

This diluent consists of two solutions, equal parts of which are mixed immediately before use. One contains eosin and propylene glycol, and the other is an aqueous solution of methylene blue. When blood is mixed with the diluent the eosinophils are stained pink and the nuclei are blue. The erythrocytes cannot be seen. The stains are inclined to crystallise, however, and the diluent has been modified considerably.

2. **Pilot's diluent.**

50 ml. propylene glycol.  
40 ml. distilled water  
10 ml. 1% phloxine in water.  
1 ml. 10% sodium carbonate in water.

The sodium carbonate in this diluent weakens the cell membrane of other leucocytes. Pilot believes that no significant change in the count occurs when the diluted blood specimen is examined within three hours, but that an average reduction of 35% takes place should the specimen be left for 24 hours. Greater and quicker changes in the cell count, ascribed to cell clumping, have been described by Macfarlane and Cecil (1951) using this diluent. They could not disperse the clumps by further shaking, and they believed that it resulted from the partial denaturation of the blood proteins by the higher pH of Pilot’s fluid and the consequent partial precipitation of fibrin.

3. **Macfarlane and Cecil's modification of Pilot's diluent.**

These authors believed that the precipitation of fibrin by Pilot's diluent could be overcome by adding to it one unit of heparin per millilitre. Their results, however, were subjected /
subjected to sharp statistical criticism by Manners (1951) who maintained that they were too even to have arisen by chance, and that they implied "some error in the technique of counting".

4. **Smart's diluent.**

50 ml. propylene glycol.
50 ml. 0.05% phloxine in water.

With this simple diluent and the correct use of microscope condenser and diaphragm, even dispersal and good visibility of the eosinophils are effectively achieved.

**The Urea Diluent.**

Both the eosin-acetone and the propylene glycol diluents have been criticised by Manners (1951). He criticised the former for the reasons already given, and he objected to the high viscosity of the latter because it hinders rapid mixing, and to all the leucocytes being visible because this complicates counting. He proposed the use of a urea diluent.

- **Urea** - 50 g.
- **Trisodium citrate** - 0.6 g.
- **Distilled water** to 100 ml.
- **Aqueous phloxine 2%** - 5 ml.

The high concentration of urea is said to retard evaporation but to raise the viscosity so little that mixing of cells takes place easily and quickly. Other leucocytes are lysed so that eosinophils are easily enumerated.

**EXPERIENCE OF RANDOLPH'S AND MANNERS' DILUENTS**

Because several blood samples were to be taken in an hour and then left aside, after dilution, until the protein precipitation /
precipitation stage of simultaneous blood sugar samples had been carried through, Dunger's method and the modifications of it were excluded.

1. **Randolph's Diluent.**

   This method was being used in 1951 in the Department of Child Health, University of Aberdeen, by Dr. Joan Burrell. A visit to that laboratory, however, showed that the stains tended to crystallise in the pipette or the counting-chamber if left standing for about half-an-hour. Fresh solutions prepared in the Simpson Memorial Maternity Pavilion laboratory were found to behave similarly, and because delay of an hour or more was inevitable during part of the present study the method was abandoned.

2. **Manners' Diluent.**

   A trial of this method revealed two possible disadvantages. During mixing of blood in the white cell pipettes sedimentation of cells into the pipette stem from the bulb was repeatedly observed. Proper mixing was then impossible. This difficulty was never noticed with propylene glycol diluents.

   The urea tended to crystallise in the heat of the microscope lamp and obscured the cells.

   From the following examples a tendency for lower counts when the urea stain was used may be observed. This may be the result of losing cells from the bulb to the stem of the pipette. (Table 48).

   The method was not used during the present studies for these reasons and because Smart's method was found to be perfectly satisfactory.
EXPERIENCE OF SMART'S DILUENT

Preparation.

The mixture of equal parts of 0.05% phloxine in water and propylene glycol is well shaken and then centrifuged for 15 minutes at 4000 revolutions / minute in order to precipitate any particles to which eosinophils might adhere. The fluid is carefully removed from the centrifuge tubes by pipette and stored in small, clean, dust-proof bottles.

Pipettes.

The white blood cell pipettes were not thought to be completely comparable. They were therefore numbered, and the same pipette was used for the same baby throughout. They were cleaned regularly.

Counting-chambers.

Two double-sided Fuchs-Rosenthal counting-chambers were filled for each count so that the absolute eosinophil count was obtained by multiplying the aggregate of four separate counts by a factor. In order to minimise error, the chambers were also numbered, and the same two were used for the same baby throughout. The chambers and cover-slips were kept very clean.

Technique.

The heel of the infant was cleaned with ether, and when dry it was stabbed with a straight triangular skin-cutting needle. The first drop of blood was removed, and blood from the second was taken carefully to the 0.5 mark. The outside of the pipette was cleaned and then, while rotating the pipette gently in alternate directions, diluent was taken up carefully /
### TABLE 48

**COMPARISON OF IMMEDIATELY SUCCESSIVE BLOOD SAMPLES BY THE PROPYLENE GLYCOL AND UREA METHODS**

<table>
<thead>
<tr>
<th>CASE</th>
<th>Smart's diluent</th>
<th>Urea diluent</th>
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</thead>
<tbody>
<tr>
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<td>119, 124</td>
</tr>
<tr>
<td></td>
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<td>450</td>
</tr>
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</table>
carefully to the 11 mark. The pipette was then carefully shaken for half to one minute and then sealed by stretching a wide rubber band from end to end of it. The charged pipettes were placed in a closed Petri dish with a small pad of damp filter paper. Under such conditions the count is said to remain unchanged for 48 hours, but in practice the pipettes were kept beyond 3 hours only on rare occasions.

In order to mix the cells thoroughly the pipette was shaken along the line of its axis for 5 minutes while being continuously rotated in the fingers. This was followed by gentle rocking and rotation for 3 minutes and a final shake for one minute. This routine was followed invariably and was timed with a stop-clock. The first four drops were discarded and the fluid was then introduced most carefully into the counting-chambers. The latter were then left in a closed, humid Petri dish for 15 minutes so that the cells might settle. The cells were clearly visible with the low-power objective of the microscope. The eosinophils were stained pink. The cell membrane, which had to be intact, was clearly visible, and the cytoplasm was stippled. When the nature of a cell was in doubt, it was studied under a higher power and with different intensity of light.

A possible source of error.

During a practice period, and before commencing the proper study, cells were observed in the counting-chambers which were pink in colour but which were considerably smaller than eosinophils. Their cytoplasm was not stippled or granular, however, but had a ground-glass appearance. They appeared /
appeared in variable numbers, they were probably commoner in the first few days of life, and they were not apparent in adult blood. More detailed study of these cells under higher power showed them to have the morphological characteristics of red cells. They tended to disappear on standing and so the error of including them as eosinophils would be more likely if the count were carried out soon after dilution. The reason for the visibility of these few erythrocytes when so many were rendered invisible by the refractive index of the diluent is not apparent.
APPENDIX V

STATISTICAL EXAMINATION OF SIMULTANEOUS BLOOD SUGAR AND EOSINOPHIL LEVELS
APPENDIX V

STATISTICAL EXAMINATION OF SIMULTANEOUS
BLOOD SUGAR AND EOSINOPHIL LEVELS

The statistical examination was guided by Dr. Lilli Stein, then of the Department of Social Medicine at the University of Edinburgh, and although the calculations were carried out personally, she is responsible for this report.

The analyses of the serial observations of blood sugars and eosinophils were directed first to the description of the levels found in these newborn infants in order to establish a standard with which other infants might be compared, and secondly to the examination of the hypothesis that in the newborn infant the change in blood sugar is synchronous with, but in the opposite direction to, the change in circulating eosinophils. Descriptions consisted of means, standard deviations from means, coefficients of variation and sampling errors of means, for males and females separately as well as for the group as a whole. In addition, correlation coefficients between blood sugar and eosinophil levels in the same infant were calculated for each age, and also for the day-to-day changes from the first day to the tenth and for the change between levels in the interval sixth to tenth day.

GROUP DESCRIPTIONS AT EACH AGE.

Blood Sugar Levels at Each Age. The variability of the readings around the mean was considerable at each age, and there was little regularity either for males or for females; even at the later ages, the range of normality was from 30 per cent /
cent to 50 per cent higher or lower than the mean (Table 49).

There was no significant difference between the sexes; the slightly higher blood sugar means for females than for males were well within the range of chance occurrence. The sampling errors of the means were too high to define the mean as a reliable index for the group. The results indicated that the means could not be taken as definite standards either for the purpose of defining normal children or for the purpose of comparison with other groups of infants. It appeared that blood sugar in the individual infant was too variable a character to constitute a satisfactory index of adrenal function during the first ten days of life.

**Circulating Eosinophils at Each Age.** The impression of a falling trend in the group mean was not confirmed by the trends of the male and female means separately; for males alone the means tended to rise in the later days. However, standard deviations and sampling errors of means were so great (Table 50) that no precise trend in eosinophil levels in the individual could be deduced, and the normal range on any day could have been from zero to more than double the mean. The differences between male and female means were not significant. The tremendous fluctuations in daily eosinophil levels in each child indicate that this character cannot be used as an index of the infant's functional response in the first ten days of life, and that the group means cannot be taken as definite standards for purposes of comparison.

**Day-to-Day Changes.** It has already been noted that, although after the third day the group means of blood sugar and /
THE RELATIONSHIP BETWEEN BLOOD SUGAR AND EOSINOPHIL CHANGES
BETWEEN THE 6th AND 10th DAYS OF LIFE IN 25 NORMAL FULL TERM INFANTS

Figure 100

BLOOD SUGAR & EOSINOPHIL CHANGES BETWEEN 6TH AND 10TH DAY OF LIFE
IN 25 NORMAL FULL TERM INFANTS.

MALES (13) *
Correlation $r = +0.286$

FEMALES (12) ○
Correlation $r = -0.293$

Both Sexes
Correlation $r = +0.151$

CHANGE in Blood Sugar mg.%

-300 -200 -100 0 10 20 30 40 +ve

CHANGE in Eosinophils, c. mm.

-300 -200 -100 0 100 200 +ve

* CHANGE in Blood Sugar *

* CHANGE in Eosinophils, c. mm.
and eosinophil levels appeared to move steadily, the means for males and females separately did not show any consistent day-to-day trend. The explanation of this apparent inconsistency can be found in the standard deviations of the individual increments, which were so great that during each time-interval large decreases in blood sugars were just as much within the range of normality as large increases (Table 51). The scatter of the day-to-day increments was even greater for eosinophils than for blood sugar (Table 52).

This variability in changes from one day to the next might be thought to conceal a steady trend which would emerge if a longer interval were studied. However, for the four-day period from the sixth to the tenth day the variability was just as apparent (Figure 100); both for blood sugar and for eosinophils large decreases and increases fell within the normal range. These results indicate that the means of day-to-day changes cannot be taken as definite standards for the purpose of defining normal children or for the prediction of expectation in the trend of blood sugar or eosinophil levels.

GROUP COMPONENTS: CORRELATION BETWEEN BLOOD SUGAR AND EOSINOPHILS.

It is often assumed that the time-trend of a group mean can be taken as representing also the time-trend in the individual. That this is not justified when the character is very widely scattered in the population has already been illustrated above; for the purpose of treating an infant and for prediction for the individual it is necessary to know the extent of correlation between the two characters in the individual /
individual child. In the present series of newborn infants, the correlations between blood sugar and eosinophil levels (Tables 53 and 54) were not significant, being most extremely small. Moreover, most of the coefficients were positive — whereas, if there had been an inverse relationship of high blood sugar to low eosinophil levels, one would expect to get negative correlations fairly consistently. The few negative correlations which occurred in one sex were on days when for the other sex the correlation was positive. The conclusions must be that there was no consistent relationship between the levels of blood sugar and eosinophils in the individual infant on any day up to the tenth.

It might be thought that, nevertheless, the direction of change in blood sugars was inversely related to the direction of eosinophil change. From the correlation coefficients between blood sugar and eosinophil day-to-day changes, it was evident that there was in fact no relationship whatever. Many of the correlations were positive though not significant, and the negative correlations which did occur were quite insignificant. Over the four-day period, when trends in individual infants might have become more stable, the correlation between blood sugar increases and eosinophil increases was actually positive for the group taken as a whole, though it was negative for the females taken alone. This can be seen in Figure 100, in which is illustrated the individual infant's blood sugar change against his or her eosinophil change. During this four-day interval, four males and seven females had an increase in blood sugar accompanied by a decrease in eosinophils,
eosinophils, and one male and one female had a decrease in blood sugar accompanied by an increase in eosinophils. On the other hand, five males and three females had an increase in both characters, whilst three males and one female had a decrease in both. Thus it appears that, even over a longer period than one day, no relationship could be found between blood sugar and eosinophil trends during the first ten days of life.

CONCLUSION.

The very detailed analyses of the serial readings of blood sugars and eosinophils, both for daily levels and for day-to-day changes, were undertaken in order to scrutinize most closely the hypothesis that in a newborn baby (after the first few hours) there would be a rise in blood sugar and a fall in eosinophils. No such relationship was found. This failure may well be due to the unreliable index represented by the circulating eosinophils, whose day-to-day fluctuations have been shown to be so great that their mean values have little meaning. These statistical findings do not prove that the hypothesis is mistaken but that no evidence has been found to support it.
<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Observations</th>
<th>Arithmetic Mean</th>
<th>Range</th>
<th>Standard Deviation</th>
<th>Coefficient of Variation</th>
<th>Standard Error of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
</tr>
<tr>
<td>Birth</td>
<td>14 16 30</td>
<td>69.61 80.70 75.53</td>
<td>43.0-102.25</td>
<td>58.5-104.75 43.0-104.75</td>
<td>14.70 11.95 14.41</td>
<td>21.1% 14.8% 19.1%</td>
</tr>
<tr>
<td>2 days</td>
<td>14 18 32</td>
<td>64.73 66.29 65.61</td>
<td>47.0-80.5 42.75-102.0 42.75-102.0</td>
<td>8.52 14.08 12.00</td>
<td>13.2% 21.2% 18.3%</td>
<td>2.36 3.41 2.15</td>
</tr>
<tr>
<td>3 days</td>
<td>14 18 32</td>
<td>63.20 66.13 64.84</td>
<td>48.75-90.75 45.5-83.5 45.5-90.75</td>
<td>11.62 10.36 11.02</td>
<td>18.4% 15.7% 17.0%</td>
<td>3.22 2.51 1.98</td>
</tr>
<tr>
<td>4 days</td>
<td>14 18 32</td>
<td>68.09 69.85 69.08</td>
<td>42.0-86.5 54.0-89.25 42.0-98.25</td>
<td>12.76 9.03 10.86</td>
<td>18.7% 12.9% 15.7%</td>
<td>3.54 2.19 1.95</td>
</tr>
<tr>
<td>5 days</td>
<td>14 18 32</td>
<td>70.48 75.46 73.28</td>
<td>49.25-95.5 53.25-94.0 49.25-95.5</td>
<td>12.79 9.84 11.49</td>
<td>18.1% 13.0% 15.7%</td>
<td>3.55 2.39 2.06</td>
</tr>
<tr>
<td>6 days</td>
<td>14 18 32</td>
<td>72.86 75.39 74.28</td>
<td>51.25-94.25 53.0-88.0 51.25-94.25</td>
<td>10.67 9.68 10.20</td>
<td>14.6% 12.8% 13.7%</td>
<td>2.96 2.35 2.06</td>
</tr>
<tr>
<td>7 days</td>
<td>14 17 31</td>
<td>72.79 81.40 77.51</td>
<td>55.0-82.75 65.5-104.75 55.0-104.75</td>
<td>8.14 9.79 10.04</td>
<td>11.2% 12.0% 13.0%</td>
<td>2.26 2.45 1.83</td>
</tr>
<tr>
<td>8 days</td>
<td>14 17 31</td>
<td>77.14 80.02 78.72</td>
<td>61.75-100.25 54.0-114.25 54.0-114.25</td>
<td>10.40 15.22 13.34</td>
<td>13.5% 19.0% 16.9%</td>
<td>2.88 3.80 2.43</td>
</tr>
<tr>
<td>9 days</td>
<td>14 16 30</td>
<td>83.16 82.33 82.72</td>
<td>66.75-104.75 60.75-111.0 60.75-111.0</td>
<td>11.38 12.97 12.26</td>
<td>13.7% 15.8% 14.8%</td>
<td>3.16 3.35 2.28</td>
</tr>
<tr>
<td>10 days</td>
<td>14 14 28</td>
<td>79.48 83.07 81.28</td>
<td>60.75-98.0 69.25-96.0 60.75-98.0</td>
<td>10.19 8.07 9.37</td>
<td>12.8% 9.7% 11.5%</td>
<td>2.83 2.24 1.80</td>
</tr>
</tbody>
</table>
**TABLE 50**

PARALLEL BLOOD SUGAR AND EOSINOPHIL LEVELS
SERIAL READINGS IN NORMAL FULL-TERM NEWBORN INFANTS

Eosinophil Cells c./mm.

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Observations</th>
<th>Arithmetic Mean</th>
<th>Range</th>
<th>Standard Deviation</th>
<th>Coefficient of Variation</th>
<th>Standard Error of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M. F. Both M. F. Both</td>
<td>M. F. Both M. F. Both</td>
<td>M. F. Both M. F. Both</td>
<td>M. F. Both M. F. Both</td>
<td>M. F. Both M. F. Both</td>
</tr>
<tr>
<td>Birth</td>
<td>14 18 32</td>
<td>538 383 451</td>
<td>164-1011 70-1153 70-1153</td>
<td>292.3 264.6 287.6</td>
<td>54.3% 69.1% 63.8%</td>
<td>81.1 64.2 51.7</td>
</tr>
<tr>
<td>2 days</td>
<td>14 18 32</td>
<td>381 352 365</td>
<td>47-820 144-966 47-966</td>
<td>204.8 194.3 199.5</td>
<td>53.8% 55.2% 54.7%</td>
<td>56.8 47.1 35.8</td>
</tr>
<tr>
<td>3 days</td>
<td>13 18 31</td>
<td>425 364 390</td>
<td>116-882 156-708 116-882</td>
<td>192.5 166.2 180.2</td>
<td>45.2% 45.6% 46.2%</td>
<td>55.6 40.3 32.9</td>
</tr>
<tr>
<td>4 days</td>
<td>14 18 32</td>
<td>337 251 289</td>
<td>130-1076 18-488 18-1076</td>
<td>235.3 119.5 184.6</td>
<td>69.8% 47.6% 64.0%</td>
<td>65.3 29.0 33.2</td>
</tr>
<tr>
<td>5 days</td>
<td>14 18 32</td>
<td>296 236 262</td>
<td>31-719 30-608 30-719</td>
<td>177.4 145.3 162.9</td>
<td>60.0% 61.6% 62.2%</td>
<td>49.1 34.2 29.3</td>
</tr>
<tr>
<td>6 days</td>
<td>14 18 32</td>
<td>292 258 273</td>
<td>114-705 36-608 36-705</td>
<td>154.6 149.2 152.6</td>
<td>52.9% 57.8% 55.8%</td>
<td>42.9 36.2 27.4</td>
</tr>
<tr>
<td>7 days</td>
<td>14 18 32</td>
<td>274 273 273</td>
<td>120-434 78-561 78-561</td>
<td>92.0 121.0 109.3</td>
<td>33.6% 44.4% 40.0%</td>
<td>25.5 29.3 19.6</td>
</tr>
<tr>
<td>8 days</td>
<td>14 17 31</td>
<td>292 261 275</td>
<td>83-467 95-550 83-550</td>
<td>122.7 129.9 127.6</td>
<td>42.0% 49.8% 46.4%</td>
<td>34.0 32.5 23.3</td>
</tr>
<tr>
<td>9 days</td>
<td>14 16 30</td>
<td>291 252 271</td>
<td>136-570 53-519 53-570</td>
<td>124.0 122.6 124.8</td>
<td>42.6% 48.6% 46.1%</td>
<td>34.4 31.7 23.2</td>
</tr>
<tr>
<td>10 days</td>
<td>13 16 29</td>
<td>288 235 259</td>
<td>144-494 116-461 116-494</td>
<td>107.4 97.7 105.5</td>
<td>37.3% 41.6% 40.8%</td>
<td>31.0 25.2 19.9</td>
</tr>
</tbody>
</table>
## Table 51

### Parallel Day-to-Day Blood Sugar and Eosinophil Changes

In Normal Full-Term Newborn Infants

**Blood Sugar Increments**

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Observations</th>
<th>Arithmetic Mean</th>
<th>Range</th>
<th>Standard Deviation</th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
</tr>
<tr>
<td>0-2 days</td>
<td>14 16 30</td>
<td>-4.88 -12.03 -8.69</td>
<td>-22.75 to +23.0 -41.75 to +20.25 -41.75 to +23.0</td>
<td>13.15 16.58 15.49</td>
<td>270% 138% 178%</td>
</tr>
<tr>
<td>2-3 days</td>
<td>13 18 31</td>
<td>-1.02 0.17 -0.52</td>
<td>-17.25 to +15.0 -36.00 to +17.75 -36.00 to +17.75</td>
<td>9.50 12.18 11.14</td>
<td>932% 7.612% 2.125%</td>
</tr>
<tr>
<td>3-4 days</td>
<td>13 18 31</td>
<td>+4.69 +3.72 +4.13</td>
<td>-24.00 to +26.5 -10.25 to +22.5 -24.00 to +26.5</td>
<td>11.94 9.24 10.46</td>
<td>254% 248% 253%</td>
</tr>
<tr>
<td>4-5 days</td>
<td>14 18 32</td>
<td>+2.39 +5.61 +4.20</td>
<td>-15.50 to +14.75 -8.75 to +21.75 -15.50 to +21.75</td>
<td>9.91 7.16 8.62</td>
<td>14% 128% 205%</td>
</tr>
<tr>
<td>5-6 days</td>
<td>14 18 32</td>
<td>+2.38 -0.07 +1.0</td>
<td>-5.50 to +18.25 -15.50 to +12.75 -15.50 to +18.25</td>
<td>6.20 8.02 7.38</td>
<td>261% 11.548% 738%</td>
</tr>
<tr>
<td>6-7 days</td>
<td>14 17 31</td>
<td>-0.07 +6.19 +3.36</td>
<td>-15.75 to +12.5 -8.75 to +29.25 -15.75 to +29.25</td>
<td>9.09 9.56 9.85</td>
<td>12.719% 154% 293%</td>
</tr>
<tr>
<td>7-8 days</td>
<td>14 16 30</td>
<td>+4.36 -1.42 +1.28</td>
<td>-13.00 to +21.0 -28.25 to +19.75 -28.25 to +21.0</td>
<td>8.72 11.24 10.55</td>
<td>200% 791% 827%</td>
</tr>
<tr>
<td>8-9 days</td>
<td>14 15 29</td>
<td>+6.02 +2.60 +4.25</td>
<td>-12.75 to +22.5 -33.50 to +21.0 -33.50 to +22.5</td>
<td>8.44 13.05 11.20</td>
<td>140% 502% 263%</td>
</tr>
<tr>
<td>9-10 days</td>
<td>13 13 26</td>
<td>+3.44 -1.40 -2.42</td>
<td>-28.25 to +10.0 -19.50 to +9.0 -28.25 to +10.0</td>
<td>11.49 8.64 10.22</td>
<td>334% 615% 422%</td>
</tr>
<tr>
<td>6-10 days</td>
<td>13 12 25</td>
<td>+6.85 +6.42 +6.64</td>
<td>-23.00 to +40.0 -6.0 to +17.0 -23.00 to +40.0</td>
<td>16.16 6.61 12.52</td>
<td>236% 103% 189%</td>
</tr>
</tbody>
</table>
# Table 52

**Parallel Day-to-Day Blood Sugar and Eosinophil Changes in Normal Full-Term Newborn Infants**

**Eosinophil Increments**

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Obs.</th>
<th>Arithmetic Mean</th>
<th>Range</th>
<th>Standard Deviation</th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
<td>M. F. Both</td>
</tr>
<tr>
<td>0-2 days</td>
<td>14 16 30</td>
<td>-161 -31 -92</td>
<td>-636 to +185 -377 to +166 -636 to +185</td>
<td>200.1 130.7 178.8</td>
<td>124% 418% 195%</td>
</tr>
<tr>
<td>2-3 days</td>
<td>13 18 31</td>
<td>+27 +12 +18</td>
<td>-172 to +258 -294 to +176 -294 to +258</td>
<td>127.6 115.0 120.6</td>
<td>471% 954% 657%</td>
</tr>
<tr>
<td>3-4 days</td>
<td>13 18 31</td>
<td>-75 -113 -97</td>
<td>-295 to +194 -430 to +111 -430 to +194</td>
<td>125.6 153.8 143.9</td>
<td>167% 136% 148%</td>
</tr>
<tr>
<td>4-5 days</td>
<td>14 18 32</td>
<td>-41 -15 -27</td>
<td>-357 to +77 -303 to +327 -357 to +327</td>
<td>99.9 137.4 123.1</td>
<td>242% 913% 464%</td>
</tr>
<tr>
<td>5-6 days</td>
<td>14 18 32</td>
<td>-3 +22 +11</td>
<td>-186 to +99 -308 to +294 -308 to +294</td>
<td>75.7 120.1 103.9</td>
<td>2.356% 534% 923%</td>
</tr>
<tr>
<td>6-7 days</td>
<td>14 17 31</td>
<td>-18 +13 -1</td>
<td>-271 to +139 -160 to +216 -271 to +216</td>
<td>98.0 78.5 89.2</td>
<td>536% 621% 6.744%</td>
</tr>
<tr>
<td>7-8 days</td>
<td>14 16 30</td>
<td>+18 -12 +2</td>
<td>-186 to +188 -89 to +109 -186 to +188</td>
<td>81.5 50.8 68.6</td>
<td>449% 11% 3.548%</td>
</tr>
<tr>
<td>8-9 days</td>
<td>14 15 29</td>
<td>-0.9 -10 -5</td>
<td>-130 to +126 -142 to +207 -142 to +207</td>
<td>66.5 98.0 84.4</td>
<td>7.763% 1.013% 1.559%</td>
</tr>
<tr>
<td>9-10 days</td>
<td>13 13 26</td>
<td>+10 -21 -6</td>
<td>-143 to +121 -161 to +63 -161 to +121</td>
<td>63.0 56.4 61.7</td>
<td>6.45% 27% 1.107%</td>
</tr>
<tr>
<td>6-10 days</td>
<td>13 12 25</td>
<td>+12 -51 -18</td>
<td>-211 to +213 -267 to +58 -267 to +213</td>
<td>119.8 90.8 111.3</td>
<td>1.03% 180% 661%</td>
</tr>
</tbody>
</table>
### TABLE 53

<table>
<thead>
<tr>
<th>AGE</th>
<th>MALES</th>
<th></th>
<th>FEMALES</th>
<th></th>
<th>BOTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>14</td>
<td>+0.0034</td>
<td>0.2774</td>
<td>16</td>
<td>+0.2333</td>
</tr>
<tr>
<td>2 days</td>
<td>13</td>
<td>-0.2444</td>
<td>0.2774</td>
<td>18</td>
<td>+0.3431</td>
</tr>
<tr>
<td>3 days</td>
<td>14</td>
<td>+0.1133</td>
<td>0.2774</td>
<td>18</td>
<td>+0.1792</td>
</tr>
<tr>
<td>4 days</td>
<td>14</td>
<td>+0.5470</td>
<td>0.2774</td>
<td>18</td>
<td>+0.3736</td>
</tr>
<tr>
<td>5 days</td>
<td>13</td>
<td>+0.7079</td>
<td>0.2774</td>
<td>14</td>
<td>-0.1813</td>
</tr>
<tr>
<td>6 days</td>
<td>13</td>
<td>+0.5799</td>
<td>0.2774</td>
<td>14</td>
<td>+0.4034</td>
</tr>
<tr>
<td>7 days</td>
<td>14</td>
<td>+0.1632</td>
<td>0.2774</td>
<td>13</td>
<td>-0.0804</td>
</tr>
<tr>
<td>8 days</td>
<td>14</td>
<td>+0.3864</td>
<td>0.2774</td>
<td>13</td>
<td>-0.4708</td>
</tr>
<tr>
<td>9 days</td>
<td>14</td>
<td>+0.5508</td>
<td>0.2774</td>
<td>13</td>
<td>-0.5799</td>
</tr>
</tbody>
</table>

The range of chance of a correlation coefficient is at least twice its standard error. Hence the correlation coefficients in this series cannot be considered highly significant.
TABLE 54
CORRELATIONS BETWEEN BLOOD SUGAR CHANGE AND EOSINOPHIL CHANGE IN SUCCESSIVE TIME-INTERVALS IN NORMAL FULL-TERM NEWBORN INFANTS

<table>
<thead>
<tr>
<th>AGE</th>
<th>MALES</th>
<th></th>
<th></th>
<th>FEMALEs</th>
<th></th>
<th></th>
<th>BOTH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 days</td>
<td>14</td>
<td>+0.3093</td>
<td>0.2774</td>
<td>16</td>
<td>+0.1061</td>
<td>0.2582</td>
<td>30</td>
<td>+0.0979</td>
</tr>
<tr>
<td>2-3 days</td>
<td>13</td>
<td>-0.3408</td>
<td>0.2887</td>
<td>18</td>
<td>-0.1976</td>
<td>0.2425</td>
<td>31</td>
<td>-0.2507</td>
</tr>
<tr>
<td>3-4 days</td>
<td>13</td>
<td>-0.0590</td>
<td>0.2887</td>
<td>18</td>
<td>-0.0009</td>
<td>0.2425</td>
<td>31</td>
<td>-0.0191</td>
</tr>
<tr>
<td>4-5 days</td>
<td>14</td>
<td>+0.1551</td>
<td>0.2774</td>
<td>18</td>
<td>-0.1315</td>
<td>0.2425</td>
<td>32</td>
<td>-0.1122</td>
</tr>
<tr>
<td>5-6 days</td>
<td>14</td>
<td>+0.2969</td>
<td>0.2774</td>
<td>17</td>
<td>+0.0728</td>
<td>0.25</td>
<td>31</td>
<td>+0.2709</td>
</tr>
<tr>
<td>6-7 days</td>
<td>14</td>
<td>+0.3983</td>
<td>0.2774</td>
<td>16</td>
<td>-0.0023</td>
<td>0.2582</td>
<td>30</td>
<td>-0.0121</td>
</tr>
<tr>
<td>7-8 days</td>
<td>14</td>
<td>-0.1560</td>
<td>0.2774</td>
<td>15</td>
<td>-0.0123</td>
<td>0.2673</td>
<td>29</td>
<td>+0.0354</td>
</tr>
<tr>
<td>8-9 days</td>
<td>14</td>
<td>+0.1258</td>
<td>0.2774</td>
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*The range of chance of a correlation coefficient is at least twice its standard error. Hence, none of the correlation coefficients in this series is significant.*
APPENDIX VI

HEIGHTS AND WEIGHTS OF INFANTS OF DIABETIC WOMEN
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*No exactly matching control child could be found for this case.*
APPENDIX VII

REFERENCES
REFERENCES

Abel P. (1931) Arch. Gynaek., 147, 444.

Bastenie /


Bayer J. (1942) Virchows Arch., 308, 659.


Benirschke K. (1956b) Obstetrics and Gynecology, 8, 412.


Buoncore P. (1946) Pediatria, 54, 42.


Clatworthy /


Gobliner S. (1911) Z. Kinderheilk., 1, 207.


Cotes P.M., Reid E. and Young F.G. (1949) Nature (Lond.), 164, 209.


Daly J.J. (1956) Lancet, 2, 710.


De /
Dohan F.C. and Lukens F.D.W. (1948) Endocrinology, 42, 244.
Emery /
Farquhar J.W. and Lewis I.C. (1948) Lancet, 2, 244.
Fujita A. and Iwatake D. (1931) Biochem. Z., 212, 43.
Furuhjelm /

Gairdner D. (1958) at the 29th Annual General Meeting,
British Paediatric Association, Windermere.


Gotsky (1913) Z. Kinderheilk., 2, 44.


Grollman /


Haas F. (1931) Z. Kinderheilk., 51, 400.


Hills /
Hoet J.P. Personal communication.
Hoet P.L. (1953) J. Physiol. (Lond.), 120, 68P.
Jones /
Komrower G.M. (1957) Personal communication.
Lawrence /

Mackay /
Medical Research Council (1951) Lancet, 2, 585.
Medical Research Council (1955) Lancet, 2, 833.
Miller /
Nakamura N. (1924) Virchow's Arch., 253, 286.
Nysten E. (1921) Acta paediat. (Uppsala), 1, 79.
Osler M. (1958) 3rd Congress of the International Diabetes Federation, reported in Lancet, 2, 313.

Pack /
Pedersen J. (1952b) Acta endocr., Copenhagen, 2, 342.
Peel J.H. (1951) Practitioner, 166, 143.
Poursines /

Randolph T.G. (1944) J. Allergy, 15, 89.
Reardon H.S., Field S.H. and Baumann B.S. (1955) Combined Meeting of the American Pediatric Society, British Paediatric Society, the Society for Pediatric Research and the Canadian Paediatric Society, Quebec. P. 188.
Rott F. (1910) Z. Kinderheilk., 1, 43.
Salber /
Salber E. and Bradshaw E. (1954) Human Biology, 26, 156.
Smart G.A. (1950) Personal communication.
Smith /
Svensgaard E. (1931) Acta paediat. (Uppsala), 12, suppl. 4.
Synek /

Tähkä H. (1951) Acta paediat. (Uppsala), 40, suppl. 81.


Von Noorden C. (1917) Die Zuckerkrankheit. 4 Aufl.


Walker /
White P. (1957) Diabetes, 6, 523.
Wilkins /


Wolfe S.M. and Paschkis K.E. (1952) Metabolism, 1, 413.


Young F.G. (1936) Lancet, 2, 297.


Zweifel (1878) Centralbl. für Gynaek., No.1.