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We have previously shown that corticoids probably play an important part in the aetiology of toxaemia (Parviainen, Soiva & Ehrnroot, 1949, 1950 a, b, c, d). Our investigations into urinary corticosteroid excretion, which were carried out by the method of Heard and Sobel (Parviainen, Soiva & Vartiainen, 1950), support this opinion. Further evidence is also given by the more extensive hormone determinations of Devis & Devis-van den Eeckhoudt (1949). As we were unable to carry out accurate corticoid determinations, we have studied the adreno-cortical function in cases of toxaemia by the so-called indirect methods (cf. Parviainen & Pärnänen, 1950). The oral glucose tolerance test was chosen as our attempts to obtain ACTH were unsuccessful.

Pincus et al. (1946) found that the glucose tolerance test caused changes in the white blood count similar to those found in normal
human subjects exposed to stress (e.g. raised temperature and psychomotor stress). The changes resemble those produced by Forsham et al. (1948) with ACTH, and Recant et al. (1948) with adrenaline. According to Forsham et al. (1948) these changes are not found in Addison’s disease or they may be less marked or even opposite in type; hence the changes in the white blood count may be considered as related to an increased adrenocortical secretion. According to Jailer et al. (1948) this cannot be fully proved, as they showed that intravenous administration of glucose to a patient with Addison’s disease as well as to one with Simmonds’ disease caused a fall in lymphocytes equal to that observed in normal subjects. These authors also reported more marked changes in diabetics and in one patient with Cushing’s syndrome than in normal subjects. According to Pincus & Elmadjian (1946), the changes in psychotic subjects were opposite to those seen in normal subjects.

Another reason for choosing glucose was that it has often been used in the treatment of toxaemia. It should be mentioned that Johnson & Bonsnes (1948) found that, in pregnant women particularly, the glucose tolerance varied according to the method of administration. Pregnant women often show a diminished tolerance to glucose given orally, whilst they tolerate intravenous glucose better than non-pregnant women. In spite of this we chose the oral glucose tolerance test as being the more common method.

Our aim was to determine whether the activity of the adrenal cortex could be intensified by the administration of glucose to healthy pregnant women as well as to toxaemic patients whether they respond in the same way as patients with Addison’s disease. By this means we hoped to gain information about the adrenocortical reserve of toxaemic patients.

As has been previously mentioned (Parviainen, Soiva & Ehrnrooth, 1949) adrenocortical hormones act by regulating the activity of different enzymes (cf. e.g. Verzár, 1948). For this reason it was desirable to study what effect, if any, the oral glucose tolerance test has on the activity of the serum cholinesterase.

The reasons for selecting cholinesterase were as follows: Davis et al. (1948) observed remarkably low cholinesterase values in the sera of 2 cases of uteroplacental apoplexy. Hofbauer and
Woodbury et al. found increased serum cholinesterase levels in toxaemia and regarded this increase as a possible contributory factor to preeclampsia. Hofbauer moreover showed that the acetylcholine content of the placenta was low in cases of preeclampsia and eclampsia. Chang, Guggisberg, etc., observed that acetylcholine had a marked action on the uterus. According to Ammon (1945) this substance stimulates the uterine muscle through the parasympathetic nervous system. Selye considers it to be one of the substances responsible for shock. Cismigiu (1948), too, regards it as an important contributory factor to obstetric shock. Acetylcholine is believed to regulate the circulation of blood in certain organs, as is shown by the prostigmine test of pregnancy.

Ezes (1948) emphasized the fact that in eclamptics the predominant hormones are those which have a sympathetic effect, whilst a decrease occurs in the secretion of hormones with a vagotonic effect. He suggested that eclampsia is primarily a disturbance in the function of the diencephalon, and that one of the main problems is whether the diencephalon is affected directly or indirectly by a chemical mediator (histamine or acetylcholine?).

In some cases we have also investigated what effect the glucose tolerance test has on the sodium-potassium ratio in the plasma and in the erythrocytes.

In a previous paper (Parviainen, Soiva & Ehrnrooth, 1950 b) we pointed out that a patient suffering from severe toxaemia showed changes in the sodium-potassium ratio of certain tissues. If the changes in the sodium and potassium levels of erythrocytes were similar to the changes in other cells, the results could be used in treatment. As the changes in sodium and potassium levels, however, will be discussed in a separate paper (Parviainen, Soiva & Ehrnrooth, 1950 d), they are only briefly mentioned here.

Sayers et al. (1949) observed that ACTH lowered the plasma potassium, increased the urinary excretion of potassium, and produced retention of sodium and chloride in the tissues, while the plasma sodium and chloride levels remained practically unchanged. Conn & Louis (1950) emphasized that the electrolyte composition of the urine is a poor indicator of the activity of salt-active corticoids because of the well-known renal rebound phenomenon. They obtained interesting results from their investigations into the effect of a prolonged ACTH treatment on (1) the sodium and chloride contents of the sweat and urine; (2) the urine potassium, glucose, 17-ketosteroid, nitrogen, and uric acid levels, and (3) the changes in eosinophils.
For the sake of comparison we included in our study a few cases in which we observed the changes which could be produced by androgens, since they produce effects rather similar to those of cortisone (glucocorticoids), and by mineralocorticoids.

Our chief aim was to determine whether investigations of this kind are desirable in cases of toxaemia of late pregnancy.

MATERIAL AND METHODS

After fasting for at least 12 hours, each patient was given 100 gm. of glucose in 300 ml. of water orally. The specimens were taken half an hour and 1 hour later. Control specimens were taken immediately before the administration of glucose.

The white blood count was determined in capillary blood in the usual way, so that the margin of error is considerable, particularly with regard to eosinophils. The non-specific cholinesterase of the serum was determined by the direct titration method with the modifications of Davis et al. (1948). In order to prevent the continual destruction of acetylcholine during titration, we modified the method further by using physostigmine salicylate as enzyme inhibitor. Before titration, 0.1 ml. of the solution containing 163 mg. of physostigmine salicylate in 100 ml. of absolute alcohol was added to each test specimen. Sodium and potassium determinations were carried out with a lithium internal standard flame photometer according to Hallman de Leppänen (1949) in the laboratory of the Children's Hospital. The results were calculated in m. Eq. per litre.

The specimens were taken from patients treated in the Women's Clinic. Oral glucose tolerance tests were performed on 6 non-pregnant patients, 4 of whom suffered from chronic salpingitis, on 7 normal pregnant women, and on 12 toxaemic patients. Mineral analyses could not be carried out in all cases.

Androgens (Testosterone »Medica« or Neohombreol »Organon«) were administered by intramuscular injection of 150 mg. to 1 patient treated for uninfected abortion, to 1 normal pregnant woman, and to 2 toxaemic patients. One normal pregnant and 1 toxaemic patient were each given 10 mg. of desoxycorticosterone acetate (Percorten »Ciba«).

In order to make the comparison easier, we have expressed the values obtained for the test specimens, in percentages of the controls. The calculations were made according to the method of Jailer et al.
which we have used in a previous investigation (Parviainen & Pärnänen, 1950). The findings are shown in Fig. 1, which gives the averages of the greatest variations. These averages were calculated from the per cent changes described below. In each case the greater of the two percentages was taken into account, whether positive or negative, but if both positive and negative percentages occurred in the same case, both were used.

The curves of Fig. 2 and Fig. 3 give the percentages of the changes in each case. The first point, 0 per cent, gives the control value, the second point indicates to what extent in per cent the value obtained in the test specimen half an hour later, was higher (or lower) than the control value, and the third point indicates the corresponding percentage for the specimen taken 1 hour later.

Only a few examples of the glucose tolerance test are given (Fig. 2, case 1 non-pregnant, case 2 normal pregnant, and cases 3—7 toxæmic patients), but the results of all the tests with androgens and Percorten are shown (Fig. 3 and Table 1).

We regret that our material is limited and that the determinations are often inexact. We have to admit that the cause of the changes is in many cases uncertain or obscure, and that opinion of them varies, as is also the case for the changes in eosinophils. The dependence of the lymphocyte count on adrenocortical activity is, however, recognized. As it is impossible to repeat these reservations in each case, we shall only refer to shock symptoms when dealing with a rise in eosinophils and lymphocytes.

**RESULTS**

**White Blood Count.**

*All leucocytes.* — Leucocytosis, which is characteristic of the glucose tolerance test in normal subjects, was hardly observed in the non-pregnant women in our material. In 2 cases of chronic salpingitis, the leucocyte count appeared to decrease. In normal pregnant women and toxæmic patients the leucocytosis was even less marked, and a slight decrease in leucocytes more common. In 8 of the 12 cases of toxaemia, the leucocytes showed a fall, which was followed by a subsequent rise above the control level in 4 cases.

*Lymphocytes.* — At least one determination showed a decreased lymphocyte count in all non-pregnant women, though
the decrease was slight and of short duration in 2 patients with salpingitis. In non-toxaemic pregnant women too, the lymphocyte count fell, except in 1 case of pyelitis and 1 case of prolonged pregnancy, both of which had a considerable increase in lymphocytes. In another case of prolonged pregnancy the lymphocyte count showed a slight initial rise. A fall in lymphocytes was observed in 8 of the 12 toxaemic patients, but in 1 of them only in the first test determination. In the remaining 4 cases the lymphocyte count showed an increase in the first, and a decrease in the second (3 cases), of the test determinations. In most of these cases the increase was greater than that found in non-pregnant women.

Eosinophils. — In the groups of non-pregnant women, 2 patients with salpingitis showed an increase in eosinophils instead of the usual fall. In 5 cases of normal pregnancy, eosinophils showed an initial rise far above the non-pregnant level, generally followed by a decrease below the control level. A continuous fall was seen in 2 cases only. The changes were much greater in toxaemic patients, 5 of whom showed a continuous fall in the eosinophil count. The typical effects of the glucose tolerance test in normal subjects are leucocytosis and decreased lymphocyte and eosinophil count, but these reactions were not always seen in our material. On the contrary, 2 cases of salpingitis showed slight leucopenia accompanied by an increase in lymphocytes and eosinophils. The changes were more marked in pregnant than in non-pregnant women, and they attained their peak in some toxaemic cases. The variations were particularly great in the eosinophil count. This is seen in Fig. 1, which gives the averages of the greatest increases and decreases in leucocytes. But as Fig. 2 shows, the changes in total leucocytes and in lymphocytes and eosinophils are not always parallel. This may be due partly to the technical errors and also to differences in the speed at which the changes take place in the several types of white blood cells.

Our material includes 5 cases of severe toxaemia. In the most severe case (Fig. 2, case 6), the changes in the white
Fig. 1.
Mean Percentages of the Highest Positive and/or Negative Changes in the White Blood Count, Serum Cholinesterase Activity, and the Sodium-Potassium Ratio in Blood Plasma and Erythrocytes after Oral Administration of 100 gm. of Glucose.
blood count showed no abnormality other than an almost total absence of leucocytosis. There was a marked decrease in lymphocytes and eosinophils. This implies that the patient's adrenocortical reserve was practically normal. In contrast to most of the other cases, the cholinesterase activity increased, though no symptoms of shock were seen in the white blood count. The sodium-potassium ratio in the plasma dropped at first, but was soon raised by an increase in sodium. The sodium-potassium ratio also fell in the erythrocytes because of a sudden decrease in sodium and a transitory increase in potassium, but subsequently it showed a tendency to rise. The other severe cases had very marked symptoms of shock (Fig. 2, cases 3, 5, and 7), as far as can be judged from the white blood count.

Cholinesterase. — In 14 out of the total 24 cases the cholinesterase values were 10 per cent higher than the control values, but only 3 cases showed a decrease of 10 per cent following the administration of glucose. In 8 cases the increase was seen in both test specimens taken half an hour and 1 hour after the intake of glucose. The increase in the activity was often considerable, viz. in 8 cases over 20, and in 3 over 40, per cent above the control values.

The changes in the cholinesterase activity were, in general, more marked in patients with salpingitis than in healthy non-pregnant women, greater in pregnant women than in the above groups, and greatest in toxaemic patients (Fig. 1). In 3 cases of severe toxaemia the cholinesterase activity increased, but it remained unchanged in a slightly less severe case. In 1 of the 5 severe cases it was not determined. An increase of 42 per cent was observed in a primigravida aged 44 who had mild toxaemia. Judging from the remarkable increase in lymphocytes and particularly in eosinophils, she had very marked symptoms of shock. It would appear that the adrenocortical reserve decreases with advancing age. The cholinesterase values generally seem to rise together with the increase in eosinophil count, that is, in connection with (or following?) shock.
Fig. 2.

Changes in the White Blood Count, Serum Cholinesterase Activity, and the Sodium-Potassium Ratio in Blood Plasma and Erythrocytes after Oral Administration of 100 gm. of Glucose.
In 6 non-pregnant women the average cholinesterase level was 2.93 (ranging from 2.58 to 3.36), in 13 normal pregnant women it was 2.37 (0.92—3.39), and in 21 toxaemic patients 2.60 (1.48—5.08).

According to Végh & Stangl (1950), Piccolo & Longo (1948), the level of serum cholinesterase is lower in pregnant than in non-pregnant women. Overbeek (1949) was unable to demonstrate any difference in the cholinesterase activity of normal and adrenal-ectomized rats. Stefanelli & Petronio found that histamine raised, and pituitrin lowered, the cholinesterase activity, while oestrogen had no effect.

**Sodium-Potassium Ratio.**

*Plasma.* — After the administration of glucose the sodium-potassium ratio in the plasma generally rose, particularly in toxaemic patients and, to a lesser degree, in pregnant women (Fig. 1).

*Erythrocytes.* — The sodium-potassium ratio in the erythrocytes varied more in normal pregnant women than in non-pregnant women, but the variations were greatest in toxaemic patients. The ratio appeared to fall in the cases in which the lymphocyte count decreased, showing an increased secretion of glucocorticoids. The rise in the ratio seemed to accompany an increase in eosinophils, which is an indication of shock symptoms.

The variations in the ratio depend on changes in both sodium and potassium. No clear correlation could be detected between these changes. Some of them were no greater than could be attributed to possible error in the estimations. In the *erythrocytes* the potassium content decreased in most non-pregnant women, while it nearly always increased in pregnant women, particularly in toxaemic cases. The increased ratio seen in toxaemic cases may be due to the fact that the erythrocyte potassium was very low in most of these patients. In non-pregnant women the sodium content of the erythrocytes generally fell together with the potassium content, and rose with the potassium, as was often also the case in pregnant women. In toxaemic cases the sodium content usually fell, at least in the first determination after the test meal.

The potassium content of the *plasma* decreased in most non-pregnant, and in all pregnant women. It usually increased in toxaemic patients. The sodium content varied less regularly, but the increases were more marked than were the decreases.
In the cases in which the lymphocyte count fell very markedly, the potassium content of the erythrocytes generally increased and the sodium content decreased, while the potassium content of the plasma generally decreased and the sodium content increased, at least in the first test specimens. Changes of this kind appear to reflect the effect of glucocorticoids.

In the most severe cases of shock, i.e., in those showing an increase in eosinophils (and lymphocytes), the potassium content of the erythrocytes often fell and the sodium content rose, while the plasma sodium frequently decreased, at least in the first test specimen, whilst the plasma potassium varied in an unpredictable manner. These changes seem to reflect the effect of mineralocorticoids.

Androgens.

The changes in the white blood count produced by androgenic hormones (Neohombreol or Testosterone) were similar to those brought about by the glucose tolerance test, but symptoms of shock were very slight. Neohombreol (Fig. 3, case 2 and 3) appeared to raise the cholinesterase activity, although the eosinophil count fell. The sodium-potassium ratio in the plasma rose in all patients. In the erythrocytes the ratio fell slightly in normal pregnant women, but considerably in 1 case of abortion. In both toxaemic cases, however, the ratio rose to an unusually high level. The rise of the sodium-potassium ratio in the erythrocytes was chiefly due to retention of sodium in the cells, as is seen in Table 1. The potassium content of the erythrocytes tended to fall.

Mineralocorticoids.

The changes seen in the white blood count after the administration of Percorten were more unpredictable than those due to androgens. There was evidence of shock. The cholinesterase activity decreased when the eosinophil count rose, and increased when the eosinophil count fell. The sodium-potassium ratio in the plasma rose in normal pregnancy and fell in the toxaemic case. The changes in the erythrocytes were opposite in type. (Fig. 3, Table 1).
Fig. 3.

Changes in the White Blood Count, Serum Cholinesterase Activity, and the Sodium-Potassium Ratio in Blood Plasma and Erythrocytes after Single Injection of 150 mg. of Androgens or 10 mg. of Mineralocorticoids.
Table 1.
Effect of Androgens and Mineralocorticoids on the Sodium and Potassium Content (in m. Eq. per Litre) of Blood Plasma and Erythrocytes.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Testosterone or Neohombreol</th>
<th>Percorten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>Erythrocytes</td>
</tr>
<tr>
<td></td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>Abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>144.5</td>
<td>5.00</td>
</tr>
<tr>
<td>after ½ hour</td>
<td>149.5</td>
<td>5.00</td>
</tr>
<tr>
<td>after 1 hour</td>
<td>153.5</td>
<td>5.25</td>
</tr>
<tr>
<td>Normal Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>141.5</td>
<td>4.55</td>
</tr>
<tr>
<td>after ½ hour</td>
<td>150.0</td>
<td>4.35</td>
</tr>
<tr>
<td>after 1 hour</td>
<td>146.0</td>
<td>5.10</td>
</tr>
<tr>
<td>Mild Toxaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>143.0</td>
<td>4.90</td>
</tr>
<tr>
<td>after ½ hour</td>
<td>149.5</td>
<td>4.85</td>
</tr>
<tr>
<td>after 1 hour</td>
<td>141.5</td>
<td>4.90</td>
</tr>
<tr>
<td>Severe Toxaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>143.5</td>
<td>4.35</td>
</tr>
<tr>
<td>after ½ hour</td>
<td>149.0</td>
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<tr>
<td>after 1 hour</td>
<td>143.5</td>
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</table>
As our material is limited and the methods are not free from possible technical errors, our data require critical examination. These considerations prevent us from drawing detailed conclusions. It is, however, evident that the glucose tolerance test may cause a reaction resembling shock, with leucopenia, lymphocytosis, and/or eosinophilia, even in non-pregnant women. Shock symptoms seem to be more marked and appear more readily in pregnant women, but they are particularly severe in toxaemic patients. Shock is usually transitory. It is followed by a counterreaction, Selye's countershock, which is most marked in toxaemic cases. This suggests that the adrenocortical reserve is not completely absent in toxaemia. The presence of the reserve is also indicated by the marked reaction in the white blood count which showed increased adrenocortical activity in one of our severe cases of toxaemia.

Our tests seem to indicate that the adrenocortical activity of toxaemic patients is more labile than is usually the case. At the present stage of our investigations we are unable to state whether the lability of the adrenocortical activity is constitutional in these patients. Our tests, however, support our clinical observation of the extreme susceptibility to shock of toxaemic patients. They also account for the fatal consequences which may follow a sudden and excessive administration of glucose in toxaemia, and sometimes even in normal pregnancy.

The increase in cholinesterase activity which seems to accompany symptoms of shock supports the assumption that certain corticoids may have an inhibitory effect on the cholinesterase activity. During pregnancy, when the secretion of corticoids remains at a high level, the cholinesterase activity is often lower than in non-pregnant women. It is somewhat higher in toxaemic than in normal pregnancy. But toxaemia is believed, e.g. by Sauramo (1949) to be a secondary shock, which according to Selye, is characterized by the hypersecretion of mineralocorticoids. Selye also believes that glucocorticoids may be of value in treating shock. We found that percorten seemed to raise the cholinesterase activity in the toxaemic case. If
these observations are correct, they suggest that susceptibility to shock in toxaemia may be due to an excessive secretion of mineralocorticoids accompanied by an insufficient and unbalanced activity of the adrenal cortex in other directions. Moreover, in toxaemic patients, Percorten causes a decrease in the plasma sodium and a retention of sodium in the erythrocytes, and possibly also in other cells as it is known to bring about a decrease in the urinary excretion of sodium. Thus Percorten does not seem suitable for the treatment of toxaemia.

Neohombreol appears to increase the cholinesterase activity, although its effect on the white blood count is similar to that of the glucocorticoids. Androgens also increase the sodium content of the plasma. A simultaneous decrease in the sodium content of the erythrocytes is seen in normal subjects, but a considerable increase occurs in toxaemic patients. This increase in the sodium content of both the plasma and the erythrocytes is the more remarkable as toxaemic patients are kept on a diet poor in sodium. It is true that in our material percorten increased the sodium content of the erythrocytes, but the plasma sodium decreased. It is possible that the large doses of androgens caused excretion of potassium and a compensatory retention of sodium more readily in toxaemic cases than in the others. This effect of the androgens is similar to that of the mineralocorticoids and may be due to them. It would thus appear that androgens, like percorten, are unsuitable for the treatment of toxaemia. These points need to be checked by further investigations, which we have not yet been able to undertake.

SUMMARY

1) The total leucocyte, lymphocyte, and eosinophil counts in capillary blood, the serum cholinesterase activity, and the blood plasma and erythrocyte sodium and potassium were determined in non-pregnant, normal pregnant, and toxaemic women before, and half an hour and 1 hour after, the oral administration of 100 gm. of glucose.

2) Leucocytosis and a decrease in lymphocytes and eosino-
phils, which are usually found after the ingestion of glucose, were not usually found in our material, but variations in the opposite direction occurred in several cases.

3) A considerable rise in cholinesterase activity after the glucose test meal was usually found.

4) Changes in the sodium-potassium ratio in the plasma and red cells were observed after the ingestion of glucose. In the plasma a rise in the sodium-potassium ratio was usually obtained. In the erythrocytes the variations in the ratio were not so consistent.

5) There seemed to be some correlation between the variations in the plasma and red cell electrolyte content and the changes in the cholinesterase activity and lymphocyte and eosinophil counts. The material was, however, too limited and the possibility of technical errors too great to allow of any definite conclusions.

6) The changes in the total leucocyte, lymphocyte, and eosinophil counts, the cholinesterase activity, and the sodium-potassium ratio in the plasma and erythrocytes observed after the intake of glucose were smallest in non-pregnant women, somewhat larger in normal pregnant women, and largest in toxaemic patients.

7) The changes produced by androgens and mineralocorticoids, which were studied in some cases, were compared with the results of the glucose test.

The above findings are discussed, and the authors suggest that the findings which appear to be related to the adrenocortical mechanism indicate the existence of considerable changes in the reaction mechanism of the adrenal cortex during pregnancy, and especially in toxaemia of late pregnancy. The authors emphasize that considerable adrenocortical reserve is still present in the most severe case of toxaemia.
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