FIG. 4.—Photograph taken on October 6 (after treatment), showing a remarkable regrowth of pubic hair. The dressing on the abdomen covers the D.C.A. implant.

A point worthy of note was the superiority of sublingual to swallowed testosterone; the patient was emphatic in her assurance that 25 mg. of sublingual testosterone was superior to a swallowed dose of 35 mg.

Discussion

In this case the history and clinical appearances were quite typical of Simmonds's disease arising from a subtotal pituitary necrosis produced by a post-partum haemorrhage. It would appear that the pituitary gland is peculiarly sensitive to the effects of haemorrhage at the moment of parturition; at other times it tends to escape destruction. Hobson and Fraser (1949) have, however, reported a case of Sim-

monds's disease following haematemeses due to a gastric ulcer.

A feature worthy of comment was the presence of well-marked erythema ab igne, which according to Sheehan and Summers (1949) "is almost always present on the legs of the female patients," the excessive sensitivity to cold causing these patients to sit huddled over a fire. The figures obtained for the blood-sugar and sugar-tolerance curve are similar to a set quoted by Farquharson (1950).

A noteworthy factor in the present case was the striking improvement in the wave pattern of the electrocardiogram after endocrine treatment, which did not include the use of extra salt. The abnormal cardiogram is not necessarily produced by the hypothyroid element in the disorder, but may arise from the secondary adrenal insufficiency. It is reported that cortisone has beneficial effects on the cardiogram in this type of case (Somerville, 1950).

Finally, it is interesting to speculate on the incidence of Simmonds's disease in the light of modern knowledge. In the past, spontaneous cures must have occurred as a result of the beneficial effects of subsequent pregnancies (Sheehan and Murdoch, 1938). In the future, Simmonds's disease due to post-partum haemorrhage may disappear following improvement in the blood transfusion and obstetric services.

Summary

A case of Simmonds's disease due to post-partum haemorrhage is described. The fact that the dominating symptoms were mental is stressed. An account, supported by biochemical data, is given of the beneficial effects of treatment with methyl testosterone, thyroid, and deoxycortone acetate.

My thanks are due to Dr. I. Atkin, physician-superintendent, for his encouragement and permission to record the case; and to Dr. J. Harkness for the steroid estimations. I am indebted to Dr. H. S. le Marquand for his practical assistance and advice. I am also grateful to those nurses and technicians of Rookdown House and Park Prewett Hospital who helped with the work involved.

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PLASMA PENTOSE LEVELS IN PRE-ECLAMPSIA AND THEIR AETIOLOGICAL SIGNIFICANCE

BY

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One fact on which all agree is that overstretching of the wall of the pregnant uterus, from whatever cause, plays a decisive initiating part in the pre-eclamptic state. Since we (Green, 1943; Green and Stoner, 1950a, 1950b) have studied extensively the local and general effects of muscle ischaemia it was natural to wonder whether this overstretching resulted in a functional ischaemia of the pregnant uterus. If this were so it would then seem highly likely that a metabolite(s) from ischaemic muscle or placenta was the exciting cause of the pre-eclamptic and eclamptic state. As we shall see, this proved to be no new hypothesis, but all the evidence in its favour was circumstantial.

We were able to tackle the problem somewhat more directly when we had shown that after large-scale ischaemia of voluntary muscle adenine nucleotides and their breakdown products were increased in the blood (see Green and Stoner, 1950a). As these are pentose compounds, the most useful method of estimation when haemolysis can be avoided is the chemical determination of the total pentose and phosphorylated pentose contents of the plasma. The figures thus obtained give no precise information about the nature of these pentose compounds, but when significantly increased they appear to indicate that a mass of tissue with an inadequate blood supply exists, or recently existed, in the body (see Green *et al.*, 1949a). For these reasons the methods were applied to the study of pre-eclamptic patients solely for the purpose of providing practical evidence for or against the hypothesis that utero-placental ischaemia is the basic pathological state underlying all the features of the syndrome. Seven years ago, with Dr. M. Bielschowsky's help, a few observations were made and the results were such that further work seemed desirable. We are now able to report on more recent findings in a series of normal and pre-eclamptic pregnant women, together with a few cases of frank eclampsia.

Chemical Methods

The blood, after collection in waxed 15-ml. centrifuge tubes containing 1 mg. of heparin, is centrifuged. The plasma, after precipitation with an equal volume of 10% trichloroacetic acid, is shaken, stood for one hour, and then centrifuged. The supernatant fluid is removed.

Total Pentose.—This is a modification of the method of Mejbaum (1939): 0.5 ml. of the supernatant fluid is diluted with water to 2 ml., and 2 ml. of orcinol reagent (1% recrystallized orcinol in concentrated HCl containing 2 vols. 10% $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in 100 ml. of acid) is added. The mixture is shaken and then heated for 20 minutes in a boiling water-bath. It is then cooled, filtered (Whatman 42) if turbid, and compared with standard ribose solutions on the Hilger absorptiometer.

Phosphorylated Pentose.—Supernatant fluid, 0.5 ml., is added to 10 ml. of water in a 15-ml. centrifuge tube followed by the addition of 1 ml. of 1.5% pure cadmium chloride solution and 2 ml. of 5% NaOH solution. The mixture is well shaken, allowed to stand for two hours, and then centrifuged. The supernatant fluid is poured off and the inverted tube allowed to drain for five minutes. Orcinol reagent, 2 ml., is added to the cadmium precipitate, and the volume is made up to 4 ml. with water. The pentose estimations are then made as described for total pentose (Bielschowsky, 1947).

Clinical Assessment

The precise degree of severity of the pre-eclamptic state is difficult to assess. It is a labile condition, varying almost from hour to hour. A woman admitted as a severe case may, when the blood sample is taken a few hours later, be actually recovering rapidly. The three gradings we have attempted—of severe (+++), moderate (++) and mild (+)—are based on the clinical findings at the time of admission to hospital. In the severe grade were included cases of frank eclampsia and those with pronounced hypertension (systolic B.P. 180+), and both severe oedema and albuminuria. The other cases were graded relatively to these. The borderline cases, particularly evident between moderate and mild, were included in one of the two grades alternately. Attempts at a more precise grading on a blood-pressure basis were made and abandoned. When available, normal pregnant women were bled in the week of pregnancy corresponding to that of a recent pre-eclamptic case.

Results

Whilst it was soon obvious that the plasma pentose content often rose steeply in severe pre-eclampsia it was just as obvious that some cases in which the diagnosis was not in doubt were providing figures within the normal range. Interest therefore centred on the statistical analysis of the group figures. Such an analysis (Table I) leaves little doubt that in this series of 59

TABLE I.—Comparison between Mean Plasma Pentose Values (mg./100 ml.) in Normal Pregnancies and in Toxaemic Pregnancies of Differing Grades of Severity

	No. in Group	Mean Total Pentose	Mean Phosphorylated Pentose
Controls	37	3.71 (3.46, 3.97)	1.91 (1.73, 2.09)
+	24	4.23 (3.74, 4.72)	2.19 (2.02, 2.36)
++	23	4.55 (4.09, 5.02)	2.45 (2.07, 2.84)
+++	12	7.02 (5.24, 8.81)	3.87 (2.57, 5.17)

An overall F. test on the differences between the groups shows that in both the case of total pentose and that of phosphorylated pentose the differences can be regarded as significant, with $P < 0.01$. The variances of the groups cannot be regarded as equal, and accordingly the 95% fiducial limits (as given in parentheses) for the various means have been calculated from the t-distribution as represented by the observations within the particular group.

toxaemic and 37 normal pregnancies there is a significant rise in both the total and the phosphorylated pentose in the toxaemic group as a whole. Moreover, the

extent of the rise increases with the severity of the group. It reaches its peak in frank eclampsia, two of such cases (see Table II) giving extremely high figures, equalled

TABLE II.—Individual Plasma Pentose Values (mg./100 ml.) in Eclampsia

Case	Before Treatment		During or After Treatment		Remarks
	Total Pentose	Phosphorylated Pentose	Total Pentose	Phosphorylated Pentose	
1	12.0	6.9	5.8	3.3	10 hours post partum
2	10.6	6.8	7.0	6.5	19 hours after Stroganoff treatment
3	5.3	2.0	—	—	Post-partum eclampsia
4	—	—	4.7	2.2	During Stroganoff treatment. Died
5	—	—	4.7	3.4	Recovering during treatment. Systolic B.P. 145
6	—	—	3.2	2.1	After treatment and delivery. Systolic B.P. 100

only by one other, a case of severe pre-eclampsia, in the whole series. A detailed analysis of the individual figures is unnecessary here, for it is obvious at a glance that a biochemical diagnosis could not be made with any certainty in the one instance, the borderline case, where it might have practical value.

It will be obvious that most of the cases showing very high values for both total and phosphorylated pentose belong to the severe group. In fact, only one of the twelve cases gave figures within the normal range, and in this instance the blood sample was a post-partum specimen. Two cases of accidental haemorrhage complicating severe pre-eclampsia gave the high figures of 6.4 and 2.5 and 7.6 and 2.9 for total and phosphorylated pentose. In the latter case (not included in the present series) death occurred after bilateral cortical necrosis.

The six cases of frank eclampsia (Table II) provided data which at first sight look rather anomalous, for in two cases the values are tremendously high and in the rest are much lower or normal. In only three (Cases 1 to 3) were blood samples obtained before active treatment was started, and in the one (Case 3) giving a comparatively low value the diagnosis was somewhat doubtful. The lower values were otherwise all in cases which were under treatment or, as in Case 6, had recovered after treatment. We have not yet enough follow-up figures in toxaemic cases, but so far as they go they suggest that high pentose values rapidly fall with clinical improvement, and Cases 1 and 2 illustrate this tendency. In eclampsia MgSO_4 treatment may, possibly by dilating the uterine vessels and/or relaxing the uterine muscles, relieve the uterine ischaemia and thus cause a rapid fall in the plasma pentose. Evacuation of the uterus would of course have the same effect. Incidentally, the fact that death occurred in Case 4 suggests that the pentose values have no prognostic significance.

Discussion

We have seen that there is a statistically significant increase in the content of total and phosphorylated pentose in the blood plasma of pre-eclamptic and eclamptic patients. In individual cases the figures may reach the relatively enormous values of three or more times the normal. The main importance of these findings is in their possible bearing on the aetiology of the pre-eclamptic state. There is good evidence for the assumption that this rise in the plasma pentose is the direct

consequence of a state of large-scale tissue ischaemia in or recently in existence. The findings of Stoner and Green (1944, 1945), that in experimental limb ischaemia, both in animals and in man, there is a raised adenosine equivalent in the whole blood, fall into line with the plasma pentose observations previously mentioned. There are also the large-scale observations on battle casualties (Green *et al.*, 1949b) which revealed a significant rise in the plasma pentose fractions, believed to be the result of ischaemia in the injured tissues. Incidentally, it is noteworthy that the average control value (3.7 mg. per 100 ml.) for total pentose in this series of pregnant women is exactly that of 164 healthy young soldiers.

The precise degree of ischaemia necessary to produce a rise is, not known, but it seems likely that a degree which diminishes the oxidative breakdown of carbohydrate even slightly is associated with this release of pentose compounds from the tissue.

Here the most important question is what tissues are involved. There is no evidence of any reduction, but rather of an increase, in blood flow to those tissues (for example, brain, kidney, liver, limbs, skin) which have been studied in pre-eclampsia (see Kellar, 1950), but nothing definite is known about uterine blood flow even in normal pregnancy. In view of the overwhelming importance of uterine overstretching in causation, it would seem that these plasma pentose values are *prima facie* evidence for the existence of a reduced blood flow, relative to requirements, in the uterus and placental site of the pre-eclamptic patient. Even if peripheral vasoconstriction exists, for which there is no evidence, it is not a likely cause of the raised pentose values, for they show no precise correlation with the degree of hypertension. Moreover, none of five hypertensive women in the control group showed pentose values outside the normal limits.

Of course, if the very high values had been confined to cases of eclampsia alone it might have been argued that the convulsive spasms could temporarily produce relatively ischaemic muscle masses and thus cause the rise in plasma pentose. Though such an effect would probably be of short duration it might have contributed to the great rise observed in the untreated cases of eclampsia. It could not be responsible for the whole, for apart from the fact that big rises were observed in pre-eclampsia, relatively high values were found in eclampsia many hours after the last convulsion.

There is no need here to review again the whole vexed question of the aetiology of this syndrome. Browne (1944) has provided a fairly recent critical review and there is still more recently the Ciba Foundation Symposium (1950). We came to the view that utero-placental ischaemia was a likely cause of the disease because of (1) its relation to overstretching of the uterus; (2) its association with the erect posture; and (3) the profound antidiuretic effect of tissue ischaemia. According to Eastman (1950) the hypothesis was first advanced in clean-cut fashion by J. Young in 1914, but Page (1939, 1948) has been foremost in reasoned advocacy for the hypothesis. He suggests that there exists a relative maternal ischaemia of the placenta. This leads to premature degeneration of the trophoblast with the liberation of toxic proteins. He lists possible causes of relative ischaemia as follows: increased hydrostatic pressure within the uterus—hydramnios, twins, triplets, increased intra-abdominal pressure; lack of stretching—primiparity (particularly early and late), obesity, short

stature; diffuse mechanical compression—labour; vasoconstriction of spiral arterioles—emotional strain, shock; systemic arterial disease—pre-existing hypertension, nephritis, diabetes; and severe maternal anaemia—hookworm, sickle-cell. The evidence for the hypothesis is mainly circumstantial—for example, the foetus often dies and its rate of growth is reduced.

Attempts have been made to find experimental support for the idea, and Page, with others (Ogden *et al.*, 1940) described a delayed rise in blood pressure after acute uterine ischaemia in pregnant dogs, and Bastiaanse and Mastboom (1950) have provided similar though not very convincing evidence. Page holds that toxic proteins from an ischaemic placenta could account for post-partum eclampsia, and in general puts forward a convincing argument for the hypothesis. He agrees that proof is lacking, for efforts to produce chronic ischaemia in the uterus of rabbits without death of the foetus were unsuccessful. Eastman (1950) also marshals well the arguments in favour of utero-placental ischaemia. He mentions the factor of erect posture, which has always seemed to one of us (H. N. G.) of paramount importance, for pre-eclampsia is a peculiarly human disease, and its importance is probably indicated by the simple fact that the most successful therapy in early cases is rest in bed.

Baker (1948) has pointed out that the main branches of the uterine artery come off at a hairpin bend after it enters the cervix and, moreover, in the upright posture are working against gravity. All this is most suggestive, but, as Eastman writes, "although the theory of uterine ischaemia has much in its favour . . . it has not yet been proved. No placental pressor substance has yet been demonstrated." Since then Thompson and Tickner (1949) have demonstrated *in vitro* the presence of a highly active mono-amino-oxidase in placental tissue capable of inactivating vasoconstrictor amines. The activity of this oxidase falls very strikingly with falling oxygen tension. Although no claim is made, this finding might account for the hypertension following placental ischaemia.

Here direct rather than circumstantial evidence in favour of the hypothesis is presented. The weak point is that complete individual correlation in our findings is lacking. This discrepancy, also noted in many other types of blood and urine assays, is, in our opinion, probably due to the great lability of the condition. Once the patient is recumbent the presumed utero-placental ischaemia could diminish or disappear rapidly, and so could the presumed biochemical indicator of its presence, for pentose compounds when injected disappear very rapidly from the circulation (see Green and Stoner, 1950a).

The chemical nature of the pentose compounds released from ischaemic muscle has been discussed before (Green and Stoner, 1950a, 1950b, 1951). Whether they play any part in the clinical picture of pre-eclampsia is at present pure guesswork. They could hypothetically be concerned in pre-eclamptic oedema, as the adenine nucleotides have a strong antidiuretic action (Green and Stoner, 1950a). It should be mentioned also that the adenine nucleotides, particularly A.T.P., strongly stimulate contractions in the pregnant uterus (Whiteley and Green, 1951). As excessive discharge of placental thromboplastin has been claimed to be an important factor in the pathogenesis of eclampsia (Schneider, 1950), it may be of some relevance that the thromboplastic activity of muscle rises steeply during and

following ischaemia (Stoner and Green, 1947, 1948, 1951), and that the toxic effects of these pentose compounds are strongly potentiated by thromboplastin (Green and Stoner, 1947). We have, however, no direct evidence at all that pentose compounds, thromboplastin, or both are concerned in the mechanism.

Indeed, the pentose compounds are likely to be vaso-depressor and most certainly do not provide the hypertensive agent, the nature of which remains the crux of the problem. The formation of this agent is probably an adaptive mechanism to preserve an adequate blood supply to the placental site. By exclusion the placenta seems to be its most likely source of origin, for ischaemic muscle does not release pressor substances, and the common occurrence of pre-eclampsia when a hydatidiform mole is present excludes the foetus as a source.

Finally, we present some new arguments for the ischaemic theory, arising directly from findings of the Sheffield Traumatic Shock Team. Muscle ischaemia may lead to a profound general interference with carbohydrate utilization. Any superadded disturbance in carbohydrate metabolism strongly increases the harmful effects of the post-ischaemic state. In regions where pellagra and beriberi are endemic the incidence of pre-eclampsia rises steeply, and diabetics are known to be more prone. All these diseases are manifestations of faulty carbohydrate utilization. In striking contrast general undernutrition, as distinct from specific vitamin deficiencies, reduces susceptibility, possibly by diminishing the growth rate of the foetus.

Of the many environmental factors affecting the bodily response to tissue ischaemia, the air temperature is perhaps the most important. A fall of a degree or two may convert a mild into a severe, even fatal, reaction. Though not proved, there is a strong impression that pre-eclampsia occurs most commonly when there is a sudden change to cooler weather.

The direct evidence presented here, supported by such a weight of indirect evidence, strongly favours the ischaemic utero-placental hypothesis. With H. J. Whiteley, experimental work directly testing the hypothesis is in progress, and when this is reported fresh data and points merely mentioned here will be elaborated.

Summary

There was a statistically significant rise in the average pentose and phosphorylated pentose content of the blood plasma in a group of women with pre-eclampsia.

The degree of the rise showed a correlation with the severity of the clinical condition, reaching a peak in frank eclampsia. It had no individual but only a group significance.

It is shown that this rise is probably due to relative utero-placental ischaemia in the pregnant uterus. The hypothesis that this is the proximate cause of pre-eclampsia is now supported by direct evidence. Other facts, some new, are presented which give strong indirect support to this hypothesis.

The nature of the substances which might be released from an ischaemic placenta and/or uterus is briefly considered. The important hypertensive agent, probably derived from ischaemic placenta, has still to be identified.

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HYPOGLYCAEMIA IN TREATMENT OF RHEUMATOID ARTHRITIS

BY

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Insulin has been used in three ways in an attempt to improve rheumatoid arthritis: in small dosage to improve metabolism and increase appetite (Copeman, 1931); in conjunction with cortisone in order to attempt to spare protein and to make carbohydrate available at the cell face (Henderson *et al.*, 1951); and to stimulate the pituitary-adrenal complex (Kersley *et al.*, 1950) by means of hypoglycaemia.

In October, 1950, we published a report on the treatment of a pilot series of 40 cases of rheumatoid arthritis with hypoglycaemia. Since this communication 32 further cases have received similar treatment, making a total of 72. All these cases have been followed up for at least two months, and some in which improvement has continued or been maintained, have been followed up for 12 months. Some of the patients who improved at the end of treatment and then relapsed were given a second course of hypoglycaemia. Some of the patients who did not respond