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PROGESTERONE IN PRE-ECLAMPTIC TOXAEMIA

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Recent work on the physiology of pregnancy has produced evidence which strongly suggests that the luteal hormone progesterone is necessary for the maintenance of gestation and for the nutrition of the developing uterine contents. In some species the hormone is produced essentially by the corpus luteum, and the removal of the ovaries or of the corpus luteum leads to an interruption of the gestation. In other species, including the human, removal of the ovaries is consistent with continuation of a normal gestation, and it is presumed that in these species the luteal hormone is produced by the placenta, from which organ it has, indeed, been recovered.

Experimental Work on Animals

In experiments performed some time ago (Robson, 1934) it was desired to determine the possible effect of the placental activity on the uterus following removal of the foetuses. For this purpose the technique described by Weymeersch (1912) and by Hammond (1917) was used; the embryos were removed under aseptic precautions in pregnant rabbits through small incisions in the uterine wall. When the operation was performed at about the mid-stage of pregnancy or shortly afterwards it was found, as had been previously described, that the placentae might be retained for varying periods within the uterine lumen and were then expelled. When, however, the embryos were removed at a later stage of pregnancy the course of events was quite different. The animals very rapidly developed symptoms of acute intoxication and died, sometimes within twenty-four hours of the operation. On post-mortem examination an acute toxic condition was found, and it appeared likely that the source of the intoxication was within the uterus.

In further experiments precautions, including strict asepsis, were used, but the results were nevertheless the same. It appeared possible that the removal of the embryos was followed by acute changes within the remaining uterine contents which resulted in an intoxication of the animal. As the uterus was unable to expel these contents death of the animal rapidly followed. Since removal of the embryos is followed by a cessation of the luteal secretion (Hammond, 1917), it was concluded that the condition within the uterus might be due to a failure of the nutrition of the placenta following the removal of the luteal secretion.

More recent experiments on the function of the corpus luteum during pregnancy have also yielded some interesting and suggestive results. In the rabbit the removal of

the pituitary during pregnancy is followed by a degeneration of the corpus luteum and by an interruption of the gestation; when the operation is performed after about the middle of pregnancy the uterine contents are expelled within twenty-four to forty-eight hours. By the administration of small doses of gonadotropic hormone it is possible to maintain the activity of the corpus luteum after the removal of the pituitary, and when gonadotropic hormones are administered to animals hypophysectomized during pregnancy it is possible to maintain the gestation (Robson, 1936). In some such experiments the maintenance of the luteal function was only very partial; as a result the gestation was not maintained and death of the embryos ensued, but the uterine contents were not expelled. Under such conditions toxic symptoms occasionally supervened rapidly, leading to the death of the animal.

Details of One Experiment

In one such experiment a histological examination of the tissues was made. This animal was hypophysectomized on the seventeenth day of pregnancy, and then was given small doses of gonadotropic hormone twice daily. Careful palpation, together with the examination of the weight curve, showed that after a few days the pregnancy was not progressing normally. On the morning of the sixth day after the removal of the pituitary the animal went into convulsions. It was obviously very ill, and was killed in order that a subsequent post-mortem examination might be as satisfactory as possible.

Post-mortem examination showed an acute toxic condition; the uterine contents were in a state of partial reabsorption. The pituitary had been completely removed. The corpora lutea showed considerable small-cell infiltration.

Professor Drennan very kindly carried out a microscopical examination of the liver, kidneys, and spleen, and reported as follows.

Spleen.—The only feature in this is marked engorgement of the pulp sinuses.

Kidney.—This organ shows acute and subacute lesions. The latter take the form of surface depressions due to disappearance of tubules, with bunching together of the surviving glomeruli and fibrous overgrowth. It is not possible to give the age of this with absolute accuracy, but it may be regarded as from a week or ten days at least. In places this loss of tubules and interstitial fibrosis extends inwards as far as the pelvis. The glomeruli and vessels do not appear appreciably altered in these areas.

The acute lesions, which have the same general lineal distribution from pelvis to cortex, consist of dense cellular infiltrations. The cells vary in proportion in different patches, but there are many polymorphs, together with various mononuclear types (such as lymphocytes and histiocytes). This infiltration is in the interstitial tissues, causing separation of the tubules, many of which are also disintegrated; above are dilated tubules. No organisms could be demonstrated in these acute lesions, though the appearance and characters of the lesions suggest a bacterial or toxic origin. The kidney otherwise shows minor changes; the convoluted tubules generally are swollen, but the glomeruli show no specific change.

Liver.—The liver cells in the central two-thirds of the lobules show loss of distinct outline, their cytoplasm is vacuolated and contains small yellow granules (? bile); the nuclei, with few exceptions, stain quite well. The cells of the outer third stain more uniformly and darkly—a more normal appearance. Scattered irregularly in lobules and in portal tracts are small groups of blood cells (polymorphs and myelocytes) and some swollen endothelial cells. These groups are within the sinusoids of the lobules or in the tissue of the portal tract. There is no fibrosis; the bile ducts and portal vessels show no abnormality.

It was not possible to test for fat in the material available, and so no statement can be made as to the cause of the central vacuolation of cells above noted. The general appearance suggests an acute toxic damage and some stimulation of haemopoietic tissue.

These experiments showed that toxic conditions may be produced in the pregnant rabbit when pregnancy is interrupted without a complete expulsion of the uterine contents, and that such conditions are associated with a failure in the secretion of the luteal hormone. They suggested the possibility that toxic states observed during pregnancy in women might also be associated with an insufficiency in the luteal secretion, and that treatment with the luteal hormone (progesterone) might have beneficial effects. It was therefore decided to determine the effect of treatment with corpus luteum hormone in a series of pre-eclamptic cases. Messrs. Schering Ltd. very kindly put a generous supply of proluton at our disposal: 1 c.cm. of the preparation used contains 5 mg. of synthetic progesterone. This was administered intramuscularly in all cases.

Clinical Experiments

So far only twelve cases have been treated. The results have on the whole been encouraging, but the data are necessarily limited, since the number of severe cases suitable for experimental treatment passing through one hospital is small. This preliminary report has therefore been communicated in the hope of encouraging other investigators to use a similar treatment, and thus lead to a more rapid collection of information.

The following criteria were used in the choice of cases.

- (1) The blood pressure was high, the systolic being 160 or over and the diastolic 90 or over.
- (2) Oedema was present in all cases, and marked in most of them.
- (3) Albumin was present in the urine, often in large quantities.
- (4) The urea concentration was normal, and the blood urea was within normal limits (20 to 40 mg. per cent.).
- (5) The general clinical impression and the symptoms (such as headache, visual disturbances, and vomiting) were such as to suggest that eclampsia might be imminent.

In ten out of twelve cases conservative treatment had been tried at home under the supervision of the hospital ante-natal clinics or under the patient's own medical attendant. The period of treatment before admission extended over one to four weeks, and the treatment included rest in bed on a low protein diet. The patients were admitted to hospital only when they failed to show

improvement or became worse under conservative measures. Two of the cases were admitted as emergencies without any previous treatment.

In all cases treatment was restricted essentially to the administration of progesterone, but the following basic precautions were taken. (1) A balanced diet of approximately 1,650 calories was given, not salt-free and not protein-free, though the protein intake excluded red meat. (2) In every case where oedema was a marked feature fluid intake was restricted to less than 40 ounces until the fluid output was greater than the intake, and the oedema showed signs of disappearing or had disappeared. (3) Where headache was severe luminal was given in half-grain doses twice or three times a day. In one case (No. 4), where epigastric pain, acute headache, and sudden rise in blood pressure developed when only one dose of progesterone had been given, resort was had to venesection and the use of morphine. Progesterone was given in 5 mg. doses daily for the first three or four days, and thereafter, depending on the response, at longer intervals. The results are presented in Table I, the symptoms being graded + to ++++ according to the presence and intensity of headache, eye symptoms, vomiting, and oedema.

Several features of the response to treatment are worthy of note. In the first place, none of the patients developed fits, and all recovered. Secondly, every patient showed a gradual improvement as judged by the signs and symptoms. Blood pressure fell (though it is difficult to estimate what significance can be attached to such a comparatively inaccurate standard), while albuminuria, as estimated by Esbach's method, showed a gradual diminution in most cases. In the third place, the final result to the mother was complete recovery of kidney function eventually in all cases except one. In this case (No. 2) the patient was left with a mild nephritis. Lastly, although foetal mortality was high (six out of twelve cases), all these deaths were by no means attributable to the toxæmic condition.

The cause of the foetal deaths requires additional consideration. The first foetal death (No. 1) occurred *in utero* before the woman came into the hospital. She was admitted as an emergency, and the foetal heart was never heard. The second foetal death (No. 2) was definitely due to prematurity. The third foetus was born in a deformed condition, and the labour, which was prolonged and difficult, showed abnormality of uterine action (non-polarity of the uterus). Special interest may possibly be attached to the fifth foetal death (No. 7). The mother's response to treatment was rapid and satisfactory, so that the dosage was reduced to 5 mg. every fourth day. It was on the fourth day after her last injection (five weeks after the beginning of treatment) that the mother complained of feeling worse and showed a rise in the blood pressure. On examination the foetal heart, which had been heard on the previous day, was no longer audible. Surgical induction was performed, and the child was stillborn. It is possible that his death might not have occurred if more frequent doses had been given.

In one case (No. 4) it was observed that treatment with corpus luteum hormone appeared to cause a delay in the onset of labour. Because of failure to improve beyond a certain point the membranes in this case were ruptured artificially at twenty-nine weeks, and the treatment with progesterone was continued. The patient did not go into labour for five days, and then only after the temporary cessation of treatment. Because of this, and because of the high foetal mortality in the earlier cases, induction of labour at or near term when the condition of the mother

TABLE I

Case	Gestation (Weeks) at the Beginning of Treatment	Day	Symptoms	B.P.	Urine Albumin (grammes per litre)	Total Dose of Progesterone	Fate of Foetus	Remarks
1 (B600)	26	Ad. 2nd 3rd 4th 5th 7th 4th (p.p.)	++++ +++ +++ +++ ++ + +	200/150 190 140 190 140 180 130 180 130 155/125 140/100	5.5 5.5 5.0 5.5 2.5 2.0 trace	30	28 wks; still-born	Emergency; cleared up entirely in the end
2 (B782)	24	Ad. 2nd 3rd 4th 6th 3rd (p.p.)	++++ ++ ++ ++ ++ ++	190/120 160/110 185/120 170/120 140/110 185/130	5.0 4.0 3.25 3.25 1.75 1.0	50	26 wks; S. B. (pre-maturity)	Accouchement forcé; blood urea rising; left with mild nephritis (swinging thereafter)
3 (B701)	36	Ad. 2nd 3rd 4th 6th 5 wks. (p.p.)	+++ ++ ++ ++ ++ ++	165 120 140 100 155 100 150 110 140/110 135/85	1.75 1.0 0.5 0.5 1.75 clear	25	Term; S. B. (deformed)	Non-polarity of uterus; cervix incised; forceps
4 (B732)	28	Ad. 2nd 3rd 4th 5th 11th 2nd (p.p.)	++++ ++++ ++++ ++++ ++++ ++++ ++	160 96 195 120 (venesection) 150 80 170 100 170 100 175 100 120/80	6.0 6.0 3.0 11.0 12.0 2.25 trace	35	30 wks; S. B.	Induction of labour; clinically a very severe case
5 (B761)	32	Ad. 2nd 3rd 4th 8th 11th 3rd (p.p.)	+++ +++ +++ ++ + + +	160/100 160/100 160/100 145 100 160 120 130/100 130/100	12.0 7.0 8.0 3.5 1.25 0.25 1.0	45	35 wks; born alive, did well	Induction because mother and child in good condition
6 (B950)	30	Ad. 2nd 3rd 4th 10th 3rd (p.p.)	++++ +++ ++ ++ ++ ++	190/120 150/120 148/100 145 100 118/88 100/65	8.0 4.0 clear clear clear	30	33 wks; alive	Spontaneous labour
7 (B985)	31	Ad. 2nd 3rd 4th 6th 8th 1st (p.p.)	++++ +++ +++ +++ ++ + +	198/132 170 120 178/120 192 118 152 92 154/105 135/90	12.0 12.0 12.0 12.0 1.5 2.0 0.75	50	36 wks; S. B.	Foetal heart not heard for 24 hours before induction
8 (B1153)	38	Ad. 2nd 3rd 4th 6th 8th 16th (p.p.)	+++ ++ ++ ++ ++ ++ ++	168/110 144/104 138 98 140/102 132 94 144 96 106/70	1.5 1.0 1.5 0.5 clear	25	Term; alive and well	Induction because mother and child in good condition
9 (B1155)	38	Ad. 2nd 3rd 4th 8th 13th 4th (p.p.)	++ ++ ++ ++ ++ ++ ++	160 90 148 96 144/98 136 94 152 96 116 76 116/76	2.0 1.25 1.25 1.5 0.5 clear clear	25	Term; alive and well	Induction because mother and child in good condition

Case	Gestation (Weeks) at the Beginning of Treatment	Day	Symptoms	B.P.	Urine Albumin (grammes per litre)	Total Dose of Progesterone	Fate of Foetus	Remarks
10 (B1252)	39	Ad. 2nd 3rd 4th 2nd	++++ +++ +++ ++ +	184 94 146 114 160 114 146 104 148/106	7.5 4.0 3.75 1.0	25	Term; alive and well	Born spontaneously. Recurrence of symptoms 2nd day p.p.; cleared up with further treatment
11 (B1273)	34	Ad. 2nd 3rd 4th 5th 10th 11th (p.p.)	+++ ++ ++ ++ ++ ++ ++	162 114 154 110 148 108 166 114 166/114 160/112 124/96	10.0 4.0 1.75 2.0 1.0 1.5 1.0	35	Alive and well	Born spontaneously
12 (B952)	32	Ad. (p.p.) 2nd 3rd 6th 8th	++++ ++++ ++++ +++ ++ +	190/110 170/100 205/110 146 108 134/104	8.0 0.25 1.3	20	32 wks; S. B.	Labour occurred on the 2nd day, B.P. rising on 2nd day p.p.; progesterone continued

had reached a satisfactory but stationary point was resorted to in most of the later cases. This measure was attended with marked success.

Discussion

In presenting the results in these cases we fully realize the difficulties of assessing adequately the part played by the treatment with progesterone. It is possible that rest in bed under hospital conditions might account for the undoubted amelioration in the symptoms, and that the same series of cases treated conservatively in hospital would have shown the same ultimate results. In view of the difficulties of devising a true control experiment, we decided that it might be of value to study the figures for the previous year. We therefore surveyed the records of all pre-eclamptic cases which were admitted to hospital between the dates of our experiment (May 1 to October 31, 1936), and compared these with the records of all

TABLE II

	1935	1936
Total cases admitted with pre-eclampsia ...	21	31
Mild and moderate ...	11	18
Severe ...	10	13

TABLE III.—Comparing the Result of Conservative Treatment and Treatment with Progesterone in Severe Cases

	1935	1936
No. of cases ...	10	13
No. of cases conservatively treated ...	10	1
No. of cases developing fits ...	4	1
No. of deaths ...	2	1
No. of cases treated with progesterone ...	0	12
No. of cases developing fits ...	—	0
No. of deaths ...	—	0

such cases admitted between May 1 and October 31, 1935. Similar periods were chosen in order to exclude the possibility that seasonal variations might affect the incidence and severity of the condition.

The results are given in Tables II and III. Out of ten severe cases admitted in 1935 and treated conservatively, four developed fits, and two patients died; while out of twelve severe cases treated in 1936 with corpus luteum hormone none developed fits and none died. The results therefore appear to be suggestive and encouraging.

In an investigation of the possible value of progesterone in the treatment of certain toxæmias of pregnancy it was obviously desirable to select severe cases, since the significance of results obtained could then be more easily estimated. At the same time it is well realized that if the treatment was definitely shown to be effective it would be advisable to apply it at an earlier stage, and to determine whether under such conditions it might not be of prophylactic value.

Summary

1. Certain experiments, in which toxic conditions leading to death were produced in pregnant rabbits, are described; these conditions were associated with a failure in the secretion of the luteal hormone.

2. The results obtained following the administration of progesterone in twelve cases suffering from severe pre-eclamptic symptoms are given. Clinical improvement appears to have been produced in these cases.

3. It is evident that the numbers are too small to establish formal proof of the efficacy of the treatment, and the results are published at this stage because it would take many years to collect adequate data in a single hospital. The results appear to be sufficiently encouraging to deserve testing on a wider scale without delay.

We should like to express our gratitude to the honorary staff of the Elsie Inglis Memorial Hospital for permission to use some of their cases, and to the Medical Research Council for defraying the expenses of the experimental part of this investigation.

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C. Kroetz (*Med. Klinik*, November 6, 1936, p. 1521) points out that carbon monoxide poisoning is a danger which may arise in garages, streets, factories, tunnels, and domestic houses. It may produce in the heart muscle haemorrhages and necrotic patches especially close to the papillary muscles of the mitral valve. Entering the upper respiratory passages it affects the vagus, causing spasm of the coronary blood vessels. Later, arteriosclerotic changes occur in the vessel walls. The electrocardiogram often gives evidence of these pathological changes. Clinically, a heart with necrotic foci following carbon monoxide poisoning reacts more quickly with attacks of angina pectoris. Kroetz, acting as referee in a compensation case, showed that symptoms of cardiac stenosis must be carefully looked for in cases of CO poisoning. In 1915 an engine driver of 38 had an attack of angina pectoris after working in a tunnel with a known high CO content. Two other well-authenticated attacks occurred in the same manner in 1922 and 1928. Previous to 1915 the patient had had no heart trouble. Although he was off work for 285 days between 1915 and 1922, his symptoms were put down to neurosis. He was pensioned off in 1933. In 1936, upon re-examination, his condition had not deteriorated. Syphilis and senile arteriosclerosis had been excluded in 1915.

THE RELATION BETWEEN THE HYPOCHROMIC ANAEMIAS AND IRON DEFICIENCY

BY

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There has been much speculation as to the mode of action of iron in the hypochromic anaemias, and especially as to the reason why it requires to be given in large doses. The successful treatment of the hypochromic anaemias with large doses of iron has been one of the most encouraging chapters in medicine during the last decade, and iron can now be regarded as a specific remedy.

Schulten (1930) has emphasized the importance of large doses in the case of ferrum redactum. He showed that in some cases this preparation could be given for four weeks in doses of 2 grammes (30 grains) daily without any response, but when the dose was raised to 6 grammes (90 grains) there was an immediate rise of reticulocytes and return of the blood picture to normal. In this country and in the U.S.A. the preparations of iron most in vogue until recently have been iron and ammonium citrate in doses of from 60 to 90 grains daily, and pil. ferri carb. (Blaud's pill) in doses of from 45 to 90 grains daily. Although it has been recognized that some patients respond to considerably smaller doses (Witts, 1933), the necessity for the large doses mentioned as average optimum doses has been very clearly established in clinical experience (Dameshek, 1934; Heath, 1933; Schulten, 1930; Witts, 1933). And there is no question that the specificity of iron therapy has only been generally accepted since these preparations have been used in large doses as originally suggested by Blaud (1832).

Definition of Hypochromic Anaemia

A hypochromic type of blood picture may be found in association with almost any disease picture, and may respond to a greater or less degree to iron therapy. The term "hypochromic anaemia" is, however, used in this paper to signify a certain group of cases. The blood picture is characterized by a low colour index, hypochromia and microcytosis in the stained film, and a low mean corpuscular haemoglobin concentration. The number of white blood corpuscles is at or below the normal level. In the absence of treatment the course of the anaemia is chronic or torpid; the reticulocytes are within normal limits, and there is no spontaneous recovery. In the absence of complications such as fever, sepsis, cancer, nephritis, or pronounced arteriosclerosis, iron therapy causes the blood picture to return to normal provided it is adequate and, if necessary, prolonged. In one of its purest forms hypochromic anaemia is found in women of the child-bearing epoch, and is commonly associated with achlorhydria or hypochlorhydria. This syndrome has been very fully described in the literature as idiopathic hypochromic anaemia or chronic microcytic anaemia (Faber, 1913; Witts, 1930; Waugh, 1931; Minot, 1932; Dameshek, 1933). Quite frequently chronic blood loss or dietetic inadequacy are believed to be aetiological factors. Heath (1933) found that of eighty-four cases responding to iron 93 per cent. were idiopathic in association with reduced gastric acidity, or were associated with chronic haemorrhage or dietary deficiency. It is this group of cases in an uncomplicated state which is used for the study of the relation of hypochromic anaemia to iron deficiency.