PRE-ECLAMPSIA IN THE LIGHT OF CURRENT RESEARCH*

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Research work in the United States and elsewhere on diabetes in pregnancy has already given some indication as to what form the future treatment of pre-eclampsia may take. It is the aim of this article to correlate the results of these researches with contemporary views on the aetiology of pre-eclampsia and other allied conditions encountered in pregnancy.

It is necessary to mention only some of the salient features of diabetes in pregnancy. For as much as five years prior to the development of frank diabetes there is a prediabetic phase during which the birth weights of infants is greater than normal and the foetal mortality is raised (Allen, 1939). When frank diabetes appears these become more pronounced and there is a fairly constant picture of hydramnios, large babies and high foetal and neonatal death rates in untreated cases. The explanation offered for these are mechanical difficulties due to the 'giant' baby and to the age of the mother, but there are other causes which are imperfectly understood. Toxaemia, which is frequently associated with the diabetes, is apparently an important factor (Barns and Morgans, 1948, 1949). These writers point out that the remarkable variation in estimates given by different observers of the increased liability to toxaemia in diabetes (which range from three to fifty times normal) depends chiefly on the severity of the standard chosen for toxaemia. No doubt there are other factors, but it would appear that foetal hypoglycaemia, at one time thought to be an important cause of neonatal death, is not in fact a common one (Sisson, 1940; Barns and Morgans, 1948, 1949).

Smith and Smith (1938, 1940, 1948) have demonstrated that in these cases there is a profound hormonal imbalance, chiefly in the form of low oestrogens and progesterone levels in the blood. They describe a reciprocal relationship between the vascular supply of the placenta and the circulating level of steroid hormones, adequate vascularity being essential for the normal pro-

duction and metabolism of oestrogens and progesterone and vascular development of the pregnant uterus. They suggested the administration of stilboestrol to combat the deficiency and this work has been carried on and elaborated by Priscilla White (1940) using also progesterone. White and her co-workers recommended increasing doses of stilboestrol and 'pregnolinine' (or progesterone) until the enormous dosage of 120 mgm. daily of the former was reached at the 34th week.

Of present concern is the fact that the incidence of toxaemia, which was 75 per cent. in White's 'hormonally abnormal and uncorrected group', fell to nil in the treated group where there was also a foetal survival rate of 90 per cent. It has also been suggested that the gigantism found in diabetic babies was due to an over-production of growth hormones and that these large doses of oestrogens might act as an anterior pituitary depressant (Barns and Morgans, 1948, 1949). Doubt has, however, been cast as to whether the foetal skeleton is larger than normal (Sisson, 1940). Certainly the diabetic baby is abnormally fat and presumably shares in the general hormonal disturbance.

Let us now turn our attention to another aspect of pre-eclampsia and review the work of Beker (1949) and other Dutch observers. Briefly stated, Beker's thesis is that pre-eclampsia should be regarded as a circulatory maladjustment in response to pregnancy rather than due to some toxin. He reminds us that this elusive toxin may never be found, hinting thereby that it does not exist.

He argues that the outstanding feature of pre-eclampsia, namely the hypertension, is explicable in terms of a vaso-dynamic disturbance due to pregnancy. He reminds us that the circulatory demands made reflexly by an actively functioning organ involve considerable vaso-motor readjustment by the body as a whole to meet them. The demands of the gravid uterus, hormonally mediated, become increasingly heavy in order to ensure an adequate blood flow to the placenta as pregnancy proceeds, and may tax the vaso-motor system to its utmost, even to the point of producing hypertension. Certainly we are all aware of

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circulatory changes in pregnancy whether it be an increase in blood volume, alteration of blood flow in the nail bed capillaries or the simple fainting of early pregnancy. The crux of the problem is whether hypertension is an exaggeration of this circulatory or vaso-motor reflex.

Beker believes that uterine hypertonia, due to varied causes such as imperfect vascularisation of the muscle or over-distension of the organ, produces such resistance to the blood flow in the walls of the uterus that hypertension results in an attempt to maintain an adequate blood flow to the placenta. Imperfect vascularization, or 'sub-arterialization' as he calls it, is characteristic of the primiparous uterus, a fact which he demonstrates by injection methods. Increased resistance to the blood flow by distension and over-stretching of the muscle he offers as an explanation of the toxæmia associated with twins and hydramnios. The fact that hypertension makes its appearance after the fourth month he attributes to the onset of rhythmic contractions about this time. We might add the slight rise of blood pressure sometimes seen at the onset of labour.

Other Dutch observers, Maastboom (1949) and Van Bouwdijk Bastiaanse (1949), have shown that constriction of the uterine artery gives rise to hypertension in pregnant, but not in non-pregnant, dogs. We are reminded of the 'Goldblatt kidney' (1938) and Trueta's (1947) observations on ligature of the femoral artery.

Hypertension in pregnancy becomes intelligible in the light of these observations in terms which, if not wholly proven, are at least intellectually satisfying. Above all it offers a most acceptable explanation of the response to rest. This we can readily picture as a circulatory readjustment so that blood is not needlessly diverted to somatic structures (muscles, etc.); thus the necessity for hypertension abates. Certainly it has been difficult in the past to explain the astonishing instability of the blood pressure in pre-eclampsia, and even more so the response to rest in terms of any 'toxin,' presumably placental in origin. The occurrence of post-partum eclampsia is more difficult to explain in terms of these 'vaso-dynamic' theories but this has indeed been the Achillean heel of many theories.

One can see that in both the Smiths' and in Beker's outlook on the causation of pre-eclampsia there is the idea of imbalance, on the one hand a hormonal one and on the other a vaso-motor one dependent on the tonus of the uterine muscle. Both writers stress the importance of the vascularization of the uterus, though for different reasons. The Smiths believe that imperfect vascularization impairs the metabolism and production of hormones with consequent imbalance,

though the relation is a reciprocal one. Beker believes that an attempt to overcome this imperfect vascularization, whether congenital or due to increased tonus of the muscle, is the origin of hypertension. Having regard to the physiological action of oestrogens in promoting hypertrophy and vascularization of the uterus the beneficial effect of oestrogens in the prevention of pre-eclampsia becomes intelligible in terms of either theory.

Naturally in discussing pre-eclampsia against a background of diabetes it may be argued that one is pleading a special case. Smith and Smith (1948) have shown, however, that oestrogens given prophylactically in cases of anticipated complications in pregnancy including cases of repeated abortion, stillbirth or pre-eclampsia not associated with diabetes, diminish the incidence of toxæmia to a degree comparable with diabetic cases. Equally one must exercise caution in discarding the 'toxin' theories of eclampsia, as Beker implies. The degenerative changes in the kidney can be envisaged in terms of ischaemia, more especially cortical necrosis in the light of Trueta's (1947) work, but how are we to account for the massive changes found in the liver in fatal cases of eclampsia?

In the past a variety of conditions including hyperemesis, water and salt retention and hypertension have, for convenience, been grouped together as 'toxæmia of pregnancy.' This is a convenient term but it disguises the fact that they may have little in common other than the pregnancy. It may also have been responsible for over-zealous attempts to unify their causation. It seems not unlikely that our knowledge of water and salt retention may be enriched by the important research work in progress in the United States on the adrenal steroids such as cortisone (compound E) and adrenocorticotrophic hormones.

Many of us must have been struck by the similarity between the striking, though temporary amelioration of rheumatoid arthritis as a result of pregnancy and the dramatic, though also temporary, response to the administration of these hormones. Two of the chief drawbacks of treatment with cortisone or ACTH are a disturbance of electrolyte balance and hypertension. Here are clues at least suggestive that some imbalance of adrenal steroids may form part of the picture in pre-eclamptic toxæmia. Further research may strengthen our conviction that the type of hormonal imbalance and degree to which each hormone is concerned may account for the varied picture of pregnancy toxæmia.

The ultimate problem is to integrate these varied types of research and evolve from them a satisfactory form of therapy not only for established pre-eclampsia but for its prophylaxis.

Though hormonal treatment offers prospects of preventing pre-eclampsia it is by no means clear what value treatment with massive doses of oestrogens and progesterone has in the established case. Smith and Smith (1940) have shown that in severe or fulminating cases the imbalance cannot be corrected sufficiently rapidly and, in any event, oestrogen and progesterone destruction is so rapid that it is impossible to replace them. Another serious drawback is the enormous cost of treatment. To ensure that such a costly treatment is properly applied it is especially desirable to single out suitable cases at the earliest possible stage. In diabetic cases this is relatively easy owing to the high incidence of toxæmia and hormonal assays should reveal the cases likely to benefit from treatment.

The problem is much more difficult to solve when applied to ordinary antenatal clinics. Manifestly, routine hormonal assays are impracticable and we need simpler means of detecting the potential pre-eclamptic. It would

seem that we must rely on the well-known vaso-motor instability latent in such cases. Tests for this purpose have been devised such as the injection of vaso-pressor drugs to see if they will elicit an exaggerated rise of blood pressure. They are not entirely satisfactory.

All that can be said is that a patient whose blood pressure was above 130/70 when first seen but which falls when she has been lying quiet, betrays the vaso-motor instability we are striving to detect. This is the 'early warning rise' of blood pressure which Browne (1933) has emphasized as being of such prognostic significance. Such a patient is often regarded as 'nervous.' She may be nervous, but she should be regarded as a potential pre-eclamptic. In the absence of other tests more suitable for routine use we have to rely on simple clinical methods such as these in the selection of cases.

There remains the formidable problem of expense.

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