of hormone levels with pregnancy may explain the telangiectasia of the face and chest, reversible after parturition.

Disease of the liver, with disturbance of its ability to regulate oestrogen and androgen blood levels, has been known to be associated with telangiectasia of the face and palms, and occasionally with enlargement of the male breasts.

A myositis may be an early sign of thyrotoxicosis.

At some stage in their course malignant tumours of the genital organs—for example, the ovaries—may themselves produce steroids capable of affecting vessels and connective tissue.

Acanthosis nigricans in which there is hypertrophy and pigmentation of the skin, in adults, is in most cases associated with malignancy. The maximum incidence of the benign cases is at puberty, and in one case quoted there was additional evidence of endocrine disturbance (acromegaly and virilism).

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EFFECTS ON FOETAL WEIGHT OF GROWTH-HORMONE-CONTAINING ANTERIOR PITUITARY EXTRACTS GIVEN TO PREGNANT RATS

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It has long been recognized that pregnancy in women suffering from diabetes mellitus is associated with a high foetal mortality rate and the tendency to foetal gigantism. It is now well known that pregnancy in women who subsequently develop diabetes mellitus is also associated with these features, but in lesser degree (Miller *et al.*, 1944; Miller, 1945; Henley, 1947; Barns and Morgans, 1948; Gilbert and Dunlop, 1949; Gilbert, 1949). This pre-diabetic phase is probably of some fifteen years' duration (Barns and Morgans, 1948).

It has been suggested that excessive production of the diabetogenic-growth hormone by the maternal anterior pituitary gland may be responsible for the large foetuses in pre-diabetic and diabetic pregnancies and also for the subsequent development of the diabetic syndrome in the pre-diabetic woman (Barns and Morgans, 1948; Gilbert, 1949). Further, the overactivity of the maternal anterior pituitary gland may be responsible for the high foetal mortality rate (Barns and Morgans, 1948). Experimental studies in rats suggested the possibility that excess of the diabetogenic-growth complex itself may be the factor responsible for the foetal deaths (Barns *et al.*, 1950).

The present investigation has been undertaken to see whether there is any experimental support for the suggestion that an excess of the diabetogenic-growth factor causes foetal gigantism. In it we have studied the effects on the foetal weights of injecting pregnant rats with anterior pituitary extracts containing the diabetogenic-growth complex. The rat in such circumstances might reasonably be regarded as being in the "pre-diabetic state," although it must be pointed out that it is not possible to induce diabetes in this species by such injections (Young, 1938).

Experimental

Virgin adult female rats of mixed strains weighing 120–210 g. were used for the experiments recorded. They were put with bucks, and the finding of the "placental sign" (vaginal bleeding at about the 14th day of pregnancy) was adopted as a sign of conception. Subcutaneous injections were begun on the day of finding the placental sign and were given daily until the 20th day of pregnancy, when the animal was killed and the live foetuses were weighed. In each series of experiments control animals were treated similarly but were not injected. The fractionated anterior pituitary extract (fractionated A.P.E.) used was a "saline supernatant" fraction prepared by isoelectric precipitation from crude A.P.E. obtained from fresh ox anterior pituitary glands (Reid and Young, 1948; Reid, 1949). Two-thirds of the protein in this preparation consists of growth hormone, and it is possible that traces of other hormones present in the fraction are a constituent part of the diabetogenic-growth complex. The fractionated A.P.E. was unlikely to contain gonadotrophins in appreciable amounts, and tests carried out by three methods of assay failed to reveal their presence (Barns *et al.*, 1950).

Growth hormone (Armour and Co., J-21609R) was kindly supplied by the makers. Experiments were performed with this preparation to verify its activity, and the results clearly demonstrated its growth-promoting properties (Barns and Swyer, 1951). All the rats were weighed daily from the time of finding the placental sign. They were kept at 72° F. (22.2° C.), and were fed a vitamin-enriched cube diet *ad lib.*

Results

Controls.—Previous experiments (Barns *et al.*, 1950) had shown that saline injections and injections of liver extract had no effect on pregnancy in the rat; therefore no injections were given to the control animals. There were 35 pregnancies in the control group; seven of these were excluded from the series either because of early delivery or because of abnormality of the pregnancy such as uterine bleeding. Of the remaining 28 pregnant rats, 19 were killed on the 20th day of the pregnancy (corresponding with the fractionated A.P.E. experiment) and 9 on the 21st day of the pregnancy (corresponding with the growth-hormone experiment). From the former group of 19 controls there were 161 live foetuses and from the latter group 91. Further statistical details are shown in the table.

Fractionated A.P.E.—Eleven pregnant rats were injected with fractionated A.P.E. (0.5 ml. daily, corresponding in diabetogenic potency to 0.4 ml. of crude A.P.E. and to 1.2–2 mg. approximately of growth hormone); five of these rats were excluded from the series because some dead foetuses were found *in utero* when the animals were killed on the 20th day. The remaining six pregnancies produced 47 live foetuses. A further nine pregnant rats were injected with 0.3 ml. daily; two of these were excluded, one on account of early delivery and the other because of intrauterine death. The remaining seven pregnancies produced 36 live foetuses. Because the total numbers were small it

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was felt justified to combine the figures for the two groups, and we thus obtained 13 pregnancies which produced 83 live foetuses (see Table).

Effects of Injections of Fractionated A.P.E. and of Growth Hormone on Litter Size and Foetal Weight

Group		No. of Litters	Mean Litter Size and Standard Error	Mean Foetal Weight (g.) and Standard Error	Correlation of Foetal Weight and Litter Size
A.P.E. (killed on 20th day)	Control	19	8·474±0·421	2·984±0·249	−0·605
	Treated	13	6·385±0·813	4·117±0·267	−0·670
Growth hormone (killed on 21st day)	Control	9	10·111±0·807	4·138±0·206	+0·481
	Treated	7	8·714±0·944	4·877±0·198	−0·461

Growth Hormone.—Ten pregnant rats were given a daily dose of 1 mg. of growth hormone; three were discarded from the series owing to early delivery or intrauterine death. The remaining seven pregnant rats were killed on the 21st day of pregnancy and produced 61 live foetuses (see Table).

The table gives the mean litter size and mean foetal weight (together with their respective standard errors) for the various groups mentioned above. From these figures it may be concluded that the mean foetal weight of the rats treated with fractionated A.P.E. (the pregnancy being terminated on the 20th day) is significantly greater than those of corresponding controls ($t=3.034$, $n=30$, $P=0.005$). It also appears that the mean litter size of these rats is significantly less than that of the corresponding controls ($t=2.444$, $n=44$, $P=0.019$). However, since there is a significant correlation between foetal weight and litter size it is possible that the difference in the mean foetal weights could be due to the difference in the litter sizes. If we correct the foetal weights of both controls and treated groups for the difference in the litter size (using the mean value of the correlation for 20 days) it is found that the difference between the corrected mean foetal weights in the two groups ceases to be significant ($t=1.884$, $n=29$, $P=0.067$). It will be noticed, however, that this difference is only just short of significance at the 95% probability level.

In the case of the rats treated with growth hormone and killed on the 21st day of pregnancy, the mean foetal weight is again significantly greater than that of the corresponding controls ($t=2.530$, $n=14$, $P=0.024$). In this experiment, however, there is no significant difference in the mean litter size of the two groups ($t=1.167$, $n=44$, $P=0.256$). Furthermore no clear correlation between foetal weight and litter size exists either for the controls or for the treated animals. The explanation for this unexpected finding is not forthcoming. It is possible, though doubtful, that seasonal variation could account for this, because the experiment with fractionated A.P.E. and its corresponding controls was carried out at a different time of the year from that with growth hormone and its corresponding controls. It will be noticed that in both experiments the controls have a smaller mean foetal weight and a larger mean litter size than the corresponding treated animals. If it were thought justifiable to use the correlation obtained for the 20-day group in order to correct for the differences in litter sizes rather than the doubtful correlation values obtained for the 21-day group, then it would be found that the corrected mean foetal weight for the animals treated with growth hormone is not significantly different from that of the corresponding controls.

Discussion

Prolongation of the pregnancy in rats has been shown to produce enlargement of the foetus. This post-maturity has been produced by injecting the mother rat with alkaline extracts of anterior pituitary lobe (Teel, 1926; Hain, 1932). Sontag and Munson (1934) obtained large foetuses in rats, using growth hormone of the anterior pituitary gland ("antuitrin G"). In this case the enlargement was also thought to be due to prolongation of the pregnancy. In each of these investigations a number of stillbirths was obtained. Watts (1935) injected pregnant rats with preparations of growth hormone of the anterior pituitary gland and obtained large offspring without post-maturity. With some preparations, however, she also obtained prolongation of the pregnancy and usually stillbirths. She noted a significant increase in the maternal weight of the injected rats.

We have also obtained an increase in the weight of the mother animal treated with anterior pituitary extracts during pregnancy (Barns *et al.*, 1949). It is not possible to make the rat diabetic or to produce glycosuria by injections of the diabetogenic-growth complex; while receiving such treatment the rat reacts similarly to puppies in that an increase in weight is the principal effect (Young, 1945). It would therefore seem justifiable to assume that part of the injected diabetogenic-growth factor is utilized to cause this increase in growth rate of the mother animal, and that correspondingly less would be available for increasing the growth of the foetus. Clearly our results do not provide unequivocal evidence of increase of foetal weight under the influence of growth-hormone treatment; for in the case of A.P.E. significant reduction of litter size could itself have accounted for the larger foetus; while when growth hormone was used, the litters, though not significantly smaller, were certainly not as large as those of the controls. Our previous experiments with A.P.E. (Barns *et al.*, 1950) had already indicated its lethal effect on the foetus, and in the present experiments it will be recalled that when macerated foetuses were found *in utero* the litter was excluded. In addition to these late intrauterine deaths it would seem that earlier foetal death with complete resorption must have occurred in some of the injected animals, and so account for the observed smaller litters.

It is unfortunate that the number of experimental animals has been too small to enable us to obtain a definite answer to the question of whether an excess of the diabetogenic growth hormone could account for foetal gigantism. Limitation of the supply of hormone preparations at our disposal made this inevitable. It might be that had this experiment been carried out on a larger scale a more clear-cut result would have been obtained.

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A health insurance scheme for all was proposed to the President's Commission on the Health Needs of the Nation at its hearing in Washington on October 7 (*New York Times*). As outlined by a director of the Chicago Commission on Financing of Hospital Care, wage-earners would "prepay" medical care from diagnosis to the end of treatment. The rest of the population would be handled by categories—for instance, for the unemployed, hospital and medical care prepayments might be tied to unemployment insurance. The hearing was marked by a controversy revolving around Frank G. Dickinson, an economist of the American Medical Association. Mr. Dickinson's leading charge was that the "fact book" issued by the group was devoted more to cost than to the quantity and quality of medical care.