weakness so often present in thyrotoxic patients is the result of a myopathy and not part of the general asthenia.

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RESPONSE OF HUMAN FOETAL HEART AND MATERNAL CIRCULATION TO ADRENALINE AND NORADRENALINE

BY

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Auscultation of the foetal heart is one of the few methods available to obstetricians for assessing the condition of the foetus *in utero*. Interpretation of the information provided by this method has always been based on the tacit assumption that bradycardia is due to foetal hypoxia; but Hon (1959) and others have shown that the foetal heart is also affected by a number of other stimuli.

Adrenaline and noradrenaline are normally present in the adult circulation and may be capable of affecting the foetal circulation. It has been shown that both these substances are increased in adults by emotion or physical exertion (Elmadjian *et al.*, 1957). Dornhorst and Young (1952) and Martin and Young (1960), working with guinea-pigs, showed that single intravenous injections of adrenaline and noradrenaline constantly produced foetal bradycardia as a result of placental ischaemia. In this pilot study an attempt has been made to assess to what extent these results are obtainable in the human foetus and, in addition, to add to the limited knowledge of the physiology of the foetal circulation free from the stress of labour.

Materials and Methods

Twenty-one volunteer patients were admitted to hospital for an afternoon. An attempt was made to select the phlegmatic type of patient for the experiment, to avoid the effects of increased endogenous adrenaline and noradrenaline secretion produced by anxiety in emotionally labile individuals (Elmadjian *et al.*, 1957). The duration of pregnancy varied between 34 and 42 weeks.

Adrenaline or noradrenaline was given to the patients in the following manner: (1) by continuous intravenous infusion for one hour; (2) by a single rapid intravenous injection to achieve a transitory blood concentration of the drug; or (3) by combining these two methods. The solutions were made up in the following concentrations: adrenaline 4 mg./l. and noradrenaline 8 mg./l. in a 5% dextrose solution. A standard plastic transfusion set and a No. 1 hypodermic needle were used for the infusion.

Recordings of the foetal heart rate were taken by a single observer, using a foetal stethoscope and stopwatch, counting the foetal heart rate over one-minute intervals. It had previously been determined, with a second observer listening to the foetal heart at the same time, that a high degree of accuracy was achieved for rates up to 160 beats a minute. The volume of the foetal heart sounds was also noted and checked by a second observer independently, being recorded as "louder" or "softer." At all times the foetal stethoscope was lightly placed on the abdomen to avoid the disturbance of foetal heart rate which can result from abdominal pressure. All doubtful recordings, such as those associated with excessive movement of the foetus or the temporary disappearance of foetal heart sounds, were discarded. The maternal blood-pressure and pulse were taken at the same time as the foetal heart rate by the second observer. Basal recordings of the foetal heart rate, maternal blood-pressure, and pulse rate were taken during a 20-minute period prior to infusion.

Results in Controls

Four patients were infused and injected with 5% dextrose solution under experimental conditions. From the results the range of the normal foetal heart rate, maternal blood-pressure, and pulse rate were defined as follows: (1) severe bradycardia—a fall in foetal heart rate of at least 20 beats a minute below the lowest basal recording; (2) bradycardia—a fall of at least 10 beats a minute below the lowest basal recording; and (3) tachycardia—an increase in rate of at least 10 beats a minute above the highest basal recording sustained for longer than two minutes. Irregularities of foetal heart rate and rhythm were too variable to define accurately. No significance was attached to changes in maternal blood-pressure of less than 10 mm. Hg and pulse rate of less than 10 beats a minute.

Results with Noradrenaline

Seven patients were given between 0.1 and 0.34 µg./kg./minute by intravenous infusion. Four more patients were given between 0.2 and 0.34 µg./kg. by

intravenous injection alone. Three more patients were given intravenous injections of 0.2–0.28 $\mu\text{g./kg.}$ during an infusion of noradrenaline. The results are summarized in Tables I and II.

TABLE I.—Noradrenaline Infusion

Foetal Heart Rate	No. of Cases
No change	4
Tachycardia followed by bradycardia	2
Irregular	1

Infusion.—In one case the foetal heart rate was irregular throughout an infusion of 0.19 $\mu\text{g./kg./minute}$, varying between 128 and 156 beats a minute, and becoming regular only after the infusion was stopped. In a second case the foetal heart remained at a basal level of 128 beats a minute during infusion, which was gradually increased from 0.2 to 0.34 $\mu\text{g./kg./minute}$. When the infusion was discontinued the foetal heart rate rose to 160 beats, with an associated rise in maternal pulse rate from 56 to 130 beats. In a third case, during infusion a transitory rise in foetal heart rate to 154 beats a minute was followed by a fall to 126 beats a minute until the infusion was discontinued. In the remaining four cases no significant alteration from the basal foetal heart rate occurred during or after the infusion.

Injection.—In one case a fall in foetal heart rate from 130 to 110 beats a minute occurred within one minute of an injection of 0.2 $\mu\text{g./kg.}$; at the stage of maximal slowing the foetal heart became grossly irregular. Ten minutes later an injection of 0.26 $\mu\text{g./kg.}$ reproduced the foetal bradycardia with a fall from 128 to 78 beats a minute. In a second case an injection of 0.28 $\mu\text{g./kg.}$ produced a fall in foetal heart rate from 150 to 120, though on this occasion the heart rate remained regular. An identical injection given 10 minutes later failed to reproduce the bradycardia. In both these cases the foetal heart sounds were softer during the bradycardia. In the remaining two cases no significant change in foetal heart rate occurred with injections of 0.3 and 0.34 $\mu\text{g./kg.}$ respectively.

Injection with Infusion.—Fig. 1 illustrates a typical case; the episode of bradycardia closely corresponds in timing with that observed when noradrenaline was given by injection alone. The failure to reproduce the foetal bradycardia at a later stage is well demonstrated in this experiment. In a second case an initial foetal tachycardia of 160 beats a minute which appeared when an injection of 0.25 $\mu\text{g./kg.}$ was given at the start of an experiment fell to 138. When the infusion was increased from 0.25 to 0.34 $\mu\text{g./kg./minute}$ the foetal

heart became irregular, varying from 125 to 138. In a third patient an injection of 0.25 $\mu\text{g./kg.}$, combined with an infusion of 0.2 $\mu\text{g./kg./minute}$, produced profound foetal bradycardia from 140 to 78 beats a minute within one minute of giving the injection. The infusion was discontinued at this stage and restarted eight minutes later, when the basal heart rate had been resumed. Despite raising the infusion rate to 0.34 $\mu\text{g./kg./minute}$, no further change in foetal heart rate could be produced.

All changes of foetal bradycardia due to noradrenaline had certain features in common: bradycardia started within approximately one minute of injection; the period of maximal slowing lasted about 20 seconds; recovery was gradual, the basal level being resumed within five to nine minutes from the time of injection; the heart sounds became softer. Foetal bradycardia could not be reproduced by repeating the injection in four out of five cases. The maternal circulation always responded to intravenous noradrenaline by a rise in

FIG. 1.—Response to injection with infusion of noradrenaline.

TABLE II.—Results with Noradrenaline and Adrenaline

	No. of Cases	Gestation in Weeks	Method of Intravenous Administration	Average Change of Foetal Heart Rate Beats/Minute	Intensity of Foetal Heart Sounds	Average Duration of Change Minutes	Average Change of Maternal	
							Blood-pressure Systole/Diastole	Pulse Rate Beats/Minute
Noradrenaline								
Severe bradycardia ..	4	38, 41, 41, 34,	2 injection with infusion.	−39	Softer	6.5	+30/25	−22
Bradycardia	1	38	2 injection	−12	No effect	7	+30/30	−15
No effect	2	40, 40	Injection with infusion	—	„ „	—	+15/5	−8
Adrenaline								
Severe bradycardia ..	2	36, 39	2 injection with infusion	−57	Softer	7	+15/0	None
Tachycardia	4	41, 40, 40, 40	1 injection. 3 infusion	+18	Louder	1 persistent.	+25/15	+20
No effect	1	36	with injection	—	—	3 intermittent	+20/0	+34
			Infusion					

blood-pressure and fall in pulse rate. A relationship between the degree of maternal circulatory response and the severity of the foetal bradycardia does seem to exist (Table II).

Side-effects.—These were mild, consisting of a sensation of difficult inspiration, post-experimental fatigue, and occasional painless uterine contractions.

Results with Adrenaline

One patient was given $0.24 \mu\text{g./kg./minute}$ by infusion alone. A further patient was given $0.19 \mu\text{g./kg.}$ by a single intravenous injection. Five more patients were given intravenous injections from 0.15 to $0.29 \mu\text{g./kg.}$ during infusions ranging from 0.09 to $0.56 \mu\text{g./kg./minute}$. The results are summarized in Table II.

Infusion.—Apart from a transient episode of tachycardia from 134 to 145 beats a minute on starting the infusion, the foetal heart rate remained regular throughout.

Injection.—In this case, after an injection of $0.19 \mu\text{g./kg.}$, the foetal heart rate became irregular, varying from 134 to 150 beats a minute, for 15 minutes before resuming the basal rate of 140. The injection was not repeated.

Injection with Infusion.—Two cases of severe foetal bradycardia occurred in this group. In one of them an initial slowing from 140 to 125 beats a minute after an injection of $0.12 \mu\text{g./kg.}$, during an infusion of $0.12 \mu\text{g./kg./minute}$, was followed 10 minutes later by a fall from 138 to 80 one minute after an injection of $0.17 \mu\text{g./kg.}$ during an infusion of $0.17 \mu\text{g./kg./minute}$. The basal heart rate was resumed five minutes later. In the second case a slowing of 130 to 80 beats a minute occurred as soon as an infusion of $0.27 \mu\text{g./kg./minute}$ was started. The basal heart rate was resumed 11 minutes later, when the rate of infusion had been slowed. After this episode single injections of $0.25 \mu\text{g./kg.}$ did not affect the foetal heart rate. In both

these cases at the maximal rates of infusion of 0.33 and $0.56 \mu\text{g./kg./minute}$ and after the infusion was stopped, the foetal heart was grossly irregular. In the remaining three cases single intravenous injections during the infusion did not significantly alter the foetal heart rate. However, Fig. 2 demonstrates the gradual increase from 126 to 150 beats a minute which occurred as the infusion rate was raised from 0.1 to $0.32 \mu\text{g./kg./minute}$ in one of these. This was associated with an irregular foetal heart rate, extrasystoles, louder heart sounds, and increased movements of the foetus, which persisted for approximately 10 minutes after the infusion was stopped. In the other two cases similar alterations in the foetal heart rate were recorded, especially during the higher rates of infusion (0.34 and $0.42 \mu\text{g./kg./minute}$ respectively).

The response of the maternal circulation to adrenaline infusion or injection was a rise in systolic blood-pressure mainly, and tachycardia. The degree of response showed wide individual variation, but was more pronounced during the higher rates of infusion.

Side-effects.—An increased respiratory rate and peripheral vasodilatation were constant findings. The patients occasionally complained of vague abdominal discomfort.

Discussion

Broadly, there are two possible mechanisms which could account for these changes in foetal heart rate.

1. Foetal Hypoxia as a Result of Uterine Vasoconstriction by Adrenaline or Noradrenaline

This mode of action has been demonstrated by similar experiments in the guinea-pig, rabbit, and sheep (Dornhorst and Young, 1952; Dawes *et al.*, 1957; Martin and Young, 1960; Misrahy *et al.*, 1960; Adams *et al.*, 1961). It is difficult to know how much of this work is applicable to the human foetus, for not only is there variation in species response to these substances but the anatomical relationships of maternal and foetal placental circulations in these animals differ from those in man. The reduction in uterine blood flow, and foetal bradycardia after pregnant women have been exercised (Morris *et al.*, 1956; Hon and Wohlgenuth, 1961), lend indirect support to this concept.

2. Transplacental Passage of Adrenaline or Noradrenaline, with Direct Stimulation of the Foetal Circulation

A tentative interpretation of the results of this study has been made by comparing them with known actions of adrenaline and noradrenaline in adult man, the clinically observed effects of hypoxia on the foetus, and the results of parallel animal experiments.

Foetal Bradycardia.—The pattern of response of the foetal heart during the episodes of bradycardia in this study bears a marked resemblance to the hypoxic bradycardia described by Dornhorst and Young (1952) and Martin and Young (1960) in rabbits and guinea-pigs, and lends support to the concept of uterine vasoconstriction. The failure to reproduce foetal bradycardia after the initial episode is paradoxical. Drug tachyphylaxis could explain this phenomenon if we assume that mother and foetus react differently, for the maternal circulation always responded to adrenaline and noradrenaline.

Lever *et al.* (1961) have suggested that after about 10 minutes of noradrenaline infusion a vasodilator

FIG. 2.—Response to infusion and injection of adrenaline.

substance is produced in the skeletal muscle which overcomes the initial noradrenaline vasoconstriction. If smooth muscle responds in the same manner the uterine vasculature would become less sensitive—or even insensitive—to larger doses of noradrenaline given at a later stage of the infusion. Table II shows that bradycardia occurred more commonly after a single injection of noradrenaline than after a similar injection of adrenaline. Why this should happen is not certain, but it may possibly be due to the more constant general peripheral vasoconstricting effect of noradrenaline as compared with adrenaline.

It is not possible altogether to exclude the direct action of maternal adrenaline and noradrenaline in the foetal circulation. In adult man a single intravenous injection of noradrenaline, and less commonly adrenaline, briefly slows the heart rate (Goodman and Gilman, 1955). This is a reflex response following the effect of a rise in peripheral arterial pressure acting on carotid sinus baroreceptors. There is no absolute evidence as yet that the foetus possesses this reflex. However, Dornhorst and Young (1952) and Adams *et al.* (1961) showed that the guinea-pigs and sheep foetal circulations do respond to noradrenaline, although they are relatively insensitive in comparison with the adult.

Foetal Tachycardia.—Infusion of adrenaline, especially at the higher rates, commonly produced foetal tachycardia, extrasystoles, and cardiac irregularities. These changes are similar to those found in the adult circulation during infusion (Goodman and Gilman, 1955). It is not possible to determine, however, whether the adrenaline acting on the foetal circulation originates from the infusion or from endogenous foetal production as a response to placental ischaemia. Reynolds (1960) has suggested from animal studies that while sudden severe foetal hypoxia produces bradycardia, mild but prolonged hypoxia may result in a mass foetal sympathetic response with secretion of endogenous adrenaline, and foetal tachycardia.

The findings of this study are broadly in agreement with those described by Dornhorst and Young (1952) and Martin and Young (1960). Until such time as an accurate method is available for measuring simultaneously in humans the changes in uterine blood flow, maternal and foetal blood oxygen tensions, no firm conclusions can be reached. The possibility of the transplacental passage of noradrenaline is being investigated at the moment.

Summary and Conclusions

After a single intravenous injection of noradrenaline to the mother, transient bradycardia was commonly observed in the foetus. Bradycardia was less common when a single injection of adrenaline was given. It is suggested that the foetal bradycardia is a result of uterine vasoconstriction with subsequent foetal hypoxia.

Infusion of the mother with adrenaline produced foetal tachycardia, cardiac irregularities, extrasystoles, and louder heart sounds. It is suggested that this is caused by the direct action of either infused or foetal adrenaline on the foetal circulation.

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STANDARDS FOR SUBCUTANEOUS FAT IN BRITISH CHILDREN

PERCENTILES FOR THICKNESS OF SKINFOLDS OVER TRICEPS AND BELOW SCAPULA

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Though standards for height and weight are certainly useful in following the growth progress of individual children and in assessing the health and nutrition of different populations and social groups, they are not sufficient by themselves to answer many important questions. They do not tell us with any degree of assurance, for example, how fat or thin a child is, relative to his fellows or relative to his state at a previous age. A child who is above average weight for his height may be a fat child, or he may be a muscular child, or he may even be a child with heavy bones. Conversely, a child who is underweight for his height may be simply lean or may be lacking in muscle or in bone mineralization. Even a gain in weight, in children, cannot be taken as evidence that fat has been put on, as it usually can in adults.

The amount of subcutaneous fat can be measured directly, with very fair accuracy, by pinching up a fold of skin and subcutaneous tissue and measuring its thickness with a special calliper. The correlation between these measurements and direct measurements of fat-width by x-ray is high, being 0.85 to 0.90. Such skinfold measurements have been increasingly used over the past 10 years in assessing obesity and subnutrition in children and adults. Consequently we have thought it useful to provide standards for skinfold measurements for British children similar to those we have published for height and weight (Tanner, 1958; Tanner and Whitehouse, 1959).

The recent survey of the body measurements of London County Council children (Scott, 1961) incorporated, at our suggestion, two measurements of