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SOME CARDIOVASCULAR RESPONSES IN FOETAL, NEW-BORN AND ADULT RABBITS

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In 1939 Bauer (1939) observed that a 14-day-old rabbit showed only a trivial rise of blood pressure during acute asphyxia, whereas adult rabbits respond with a substantial rise (Jarisch & Wastl, 1926). In new-born rabbits failure to respond to asphyxia with a rise of blood pressure might be due to lack of sensitivity of the cardiovascular system to pressor amines, to immaturity of the chemoreceptor and other vascular reflexes, or to special features of the neonatal circulation such as continued patency of the ductus arteriosus. This paper is mainly concerned with experiments designed to test the first of these possibilities.

In the rabbit and guinea-pig Dornhorst & Young (1952) described the foetus as some twenty times less sensitive to injected adrenaline than the mother. Young (1956) has therefore concluded that the circulation of the mature mammalian foetus is much less sensitive, weight for weight, to the injection of sympathetic amines than is that of the adult. However, this generalization does not hold for the mature foetal lamb (Dawes, Mott & Rennick, 1956) and we have therefore been led to repeat Dornhorst & Young's experiments upon the rabbit. According to our criteria the circulation of the mature foetal rabbit is as sensitive to injected adrenaline or noradrenaline as that of the adult. A preliminary account of these observations has been given (Dawes, Handler & Mott, 1957).

METHODS

Nineteen adult rabbits (1·6–3·5 kg body weight) were used. The majority were anaesthetized with sodium pentobarbitone (Nembutal, Abbott Laboratories, 30 mg/kg) given intravenously. Two received urethane (1 g/kg), and one each chloralose (60 mg/kg), morphine (18 mg/kg) with chloralose (50 mg/kg), and morphine (9 mg/kg) with urethane (1 g/kg), respectively. These were supplemented as necessary with ether. The results of the experiments were not influenced by the choice of anaesthetic.

Observations were made on seventy-two foetal rabbits, delivered from does anaesthetized with 30–40 mg/kg sodium pentobarbitone given intravenously and supplemented as necessary with ether. The foetuses were manipulated as little as possible and were kept moist and warm. One of the difficulties encountered in working with foetal rabbits is that the placenta tends to separate because of uterine movements. Very often other foetuses are pushed out through the uterine incision. These troubles can be minimized by making two small transverse uterine incisions, one over the head and the other over the tail of the foetus selected for study. The forequarters and hind quarters are then delivered, leaving the uterus to encircle the abdomen like a cummerbund. Even with this procedure it was uncommon to succeed in making satisfactory observations on more than two or three foetuses in good condition out of any one litter. Sixteen new-born rabbits 7 min–28 days old were anaesthetized with sodium pentobarbitone 30 mg/kg intraperitoneally, supplemented by open ether. Injections were given into an external jugular vein. In a few foetuses injections were given into an umbilical vein.

Blood pressure was recorded by a condenser manometer from a carotid artery. The electrocardiogram was recorded from conscious rabbits on an Elema electrocardiograph or on a Cambridge three channel recorder. Heart rate was recorded as described by Wyatt (1956, 1957) using the pressure pulse or e.c.g. to drive the meter.

Gas mixtures were delivered through calibrated rotameters and adjusted as required for delivery to the maternal trachea or (in unanaesthetized new-born rabbits), to an inverted glass funnel beneath which they were placed.

Adrenaline HCl (British Drug Houses) and noradrenaline bitartrate (Levophed, Bayer Products) were used; all doses are expressed in terms of base.

RESULTS

Cardiovascular responses to asphyxia and anoxia

In the first place it seemed desirable to confirm Bauer's (1939) observations on the effect of asphyxia and anoxia on rabbits of different ages, using other methods and anaesthetics. In the adult rabbit asphyxia or anoxia, whether acute or slow in onset, causes a rise of blood pressure but comparatively small immediate changes in heart rate (Jarisch & Wastl, 1926; Bauer, 1939). Our observations agree with these conclusions. We always observed a fall of heart rate during asphyxia caused by rebreathing into a collapsible rubber bag, and never an increase.

New-born rabbits. In fourteen anaesthetized rabbits 7 min–6 days old, acute asphyxia was caused by occluding the trachea, and this procedure invariably led to a fall of heart rate. The arterial pressure was recorded in six of these new-born rabbits, but only one showed a transient rise of pressure before the inevitable and progressive fall ensued.

Asphyxia induced by tracheal occlusion (the method used by Bauer in new-born rabbits) is abrupt and leads to great changes in intrathoracic pressure. More gradual oxygen deprivation was brought about by giving low O_2 or low O_2–high CO_2 gas mixtures, or by rebreathing into a collapsible bag. With the low O_2 mixtures the heart rate and blood pressure remained steady for a while and then fell gradually in thirteen rabbits, 12 min–24 days old. There was sometimes a post-anoxic rise of blood pressure or heart rate. Ten of twenty rabbits, 0–24 days old, showed initially a slight rise of blood pressure suc-

ceeded by a fall, when made to rebreathe. During recovery a small rise of blood pressure above the resting level was usual, and the heart rate sometimes exceeded the resting level. Unanaesthetized new-born rabbits never showed any significant tachycardia on exposure to low O_2 mixtures.

Foetal rabbits. Acute asphyxia of the foetus produced by obstructing the umbilical cord or the maternal trachea invariably caused the well known response of a profound fall of heart rate and blood pressure. Administration of

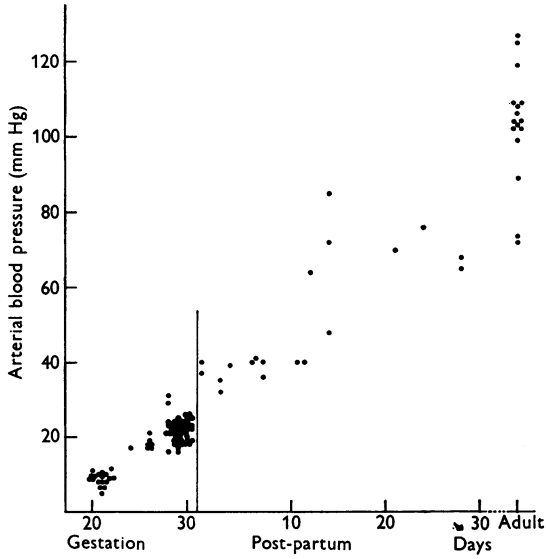

Fig. 1. Ordinate, mean arterial blood pressure; abscissa, age of rabbit. The blood pressure rises during the last third of gestation and continues to rise towards adult levels after birth. Each point represents one rabbit.

low O_2 mixtures to the doe, in some instances combined with 4–6% CO_2, rarely induced any immediate foetal response but caused a gradual fall of heart rate and blood pressure in twenty-two foetuses. The infrequent instances of tachycardia hardly exceeded in magnitude normal variations of heart rate.

The sensitivity of rabbits to adrenaline

The mean blood pressure of the anaesthetized rabbit increases from about 9 mm Hg at 20 days gestation age to some 105 mm Hg in the adult (Fig. 1). Small doses of adrenaline or noradrenaline (0·2–3·0 μg/kg body weight) injected intravenously caused an increase of blood pressure in all the animals investigated, the youngest of which was 24 days gestation age. Fig. 2 shows the rise in blood pressure in response to two doses of adrenaline in a rabbit foetus of 29 days gestation age, weighing 35 g. Injection of 0·01 μg adrenaline

(< 0·3 μg/kg) into a jugular vein caused a blood pressure rise of 16%, while 0·02 μg adrenaline (< 0·6 μg/kg) caused a rise of 29%, lasting considerably longer. The absolute increase of pressure was greater in older animals, whose resting blood pressure was higher, but the percentage increase of pressure for given doses (weight for weight) was approximately the same at all ages (Fig. 3).

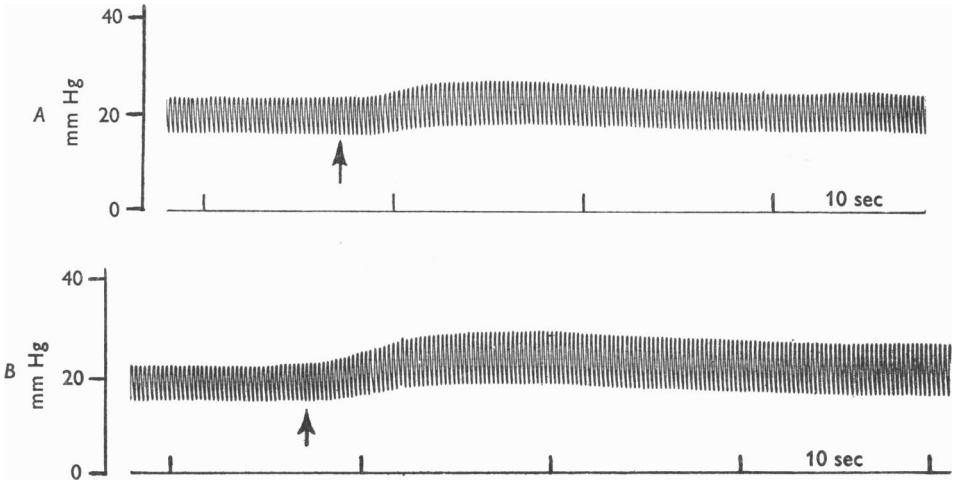

Fig. 2. Foetal rabbit, 35 g, 29 days gestation, pentobarbitone anaesthesia. Records of arterial blood pressure. Adrenaline was injected at the arrows: *A*, 0·01 μg; *B*, 0·02 μg. There was no significant change of heart rate.

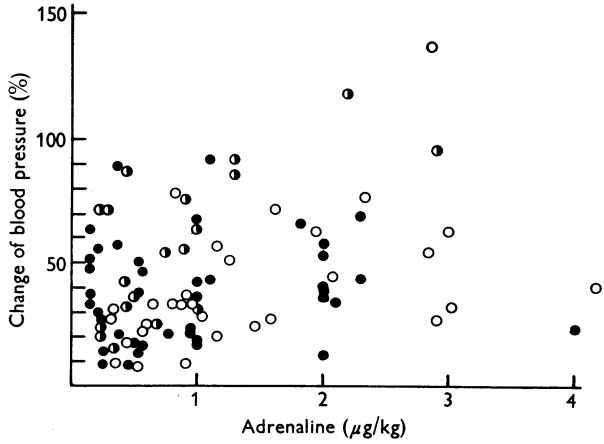

Fig. 3. The maximum percentage increase of mean blood pressure has been plotted against the dose of adrenaline/kg, given intravenously. The response of foetal (●) and new-born (◑) rabbits did not differ from that of adults (○).

The effect of adrenaline on heart rate

Adult rabbits. In adult rabbits the heart rate nearly always decreased as the blood pressure rose after the intravenous injection of 0·7–8·0μg/kg adrenaline (Fig. 4). The size of the decrease varied considerably from one rabbit to another, regardless of the dose of adrenaline or the depth of anaesthesia. Only two of nineteen intact rabbits responded with a *rise* of heart rate at some stage of the experiments; in one other the fall was preceded by a small rise. This occasional rise of heart rate did not seem dependent on a low resting heart rate or on the depth of anaesthesia. It should be mentioned, however, that

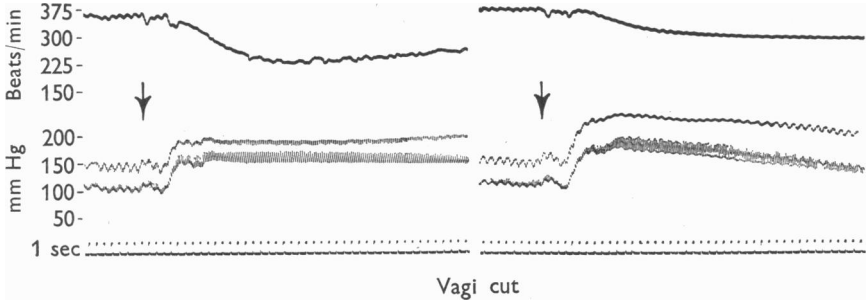

Fig. 4. Adult rabbit, 3·3 kg., pentobarbitone anaesthesia. Records of heart rate (above) and blood pressure (below). 10μg adrenaline was injected at each arrow. The vagi were cut between the two parts of record.

the resting heart rates of these anaesthetized rabbits (263–380 beats/min) were a little higher than those of six conscious rabbits (217–340 beats/min), whose e.c.g.'s were recorded while they sat quietly in their cages.

Since the slowing of the heart appeared to be related to the rise of blood pressure caused by adrenaline, it seemed probable that it was of vagal origin as a result of stimulation of carotid and aortic pressure receptors. Division of the cervical sympathetic nerves did not change the response. The initial heart rate was little altered by vagotomy, but the fall of heart rate caused by the injection of adrenaline was reduced from a range of 14–45% to 2–21% in seven rabbits (Fig. 4).

In three rabbits denervation of the carotid sinuses diminished the fall of heart rate on the injection of adrenaline from 8–16% to 1–7%. Denervation of the carotid sinuses and section of the depressor nerves reduced cardiac slowing on injection of adrenaline from 15–53% to 0–29% in four rabbits.

These observations show that some of the cardiac slowing caused by small doses of adrenaline in adult rabbits is due to vagal activity initiated by stimulation of afferent nerves. The fact that about half the bradycardia was present after vagotomy implies that this response must also be due to a reduction of sympathetic activity, either reflexly or as a result of a central

action of adrenaline. Five rabbits, in which the vagi and depressor nerves had been cut and the sinuses denervated, still gave 4–6% fall of heart rate on injection of the normal small dose of adrenaline, though in two of them an increase of heart rate was elicited by a very large dose (100μg) of adrenaline. The heart rate of one rabbit in which the thoracic sympathetic chains had been removed on both sides, and of one rabbit with the spinal cord cut in the neck, *increased* with small doses of adrenaline. Moreover, it is well known that the isolated rabbit heart accelerates on administration of adrenaline. The bradycardia observed in the intact rabbit therefore occurs in spite of the direct accelerating action of adrenaline upon the heart muscle.

New-born rabbits (<28 *days old*). When adrenaline or noradrenaline was injected into new-born rabbits, the heart rate always fell if the animal was

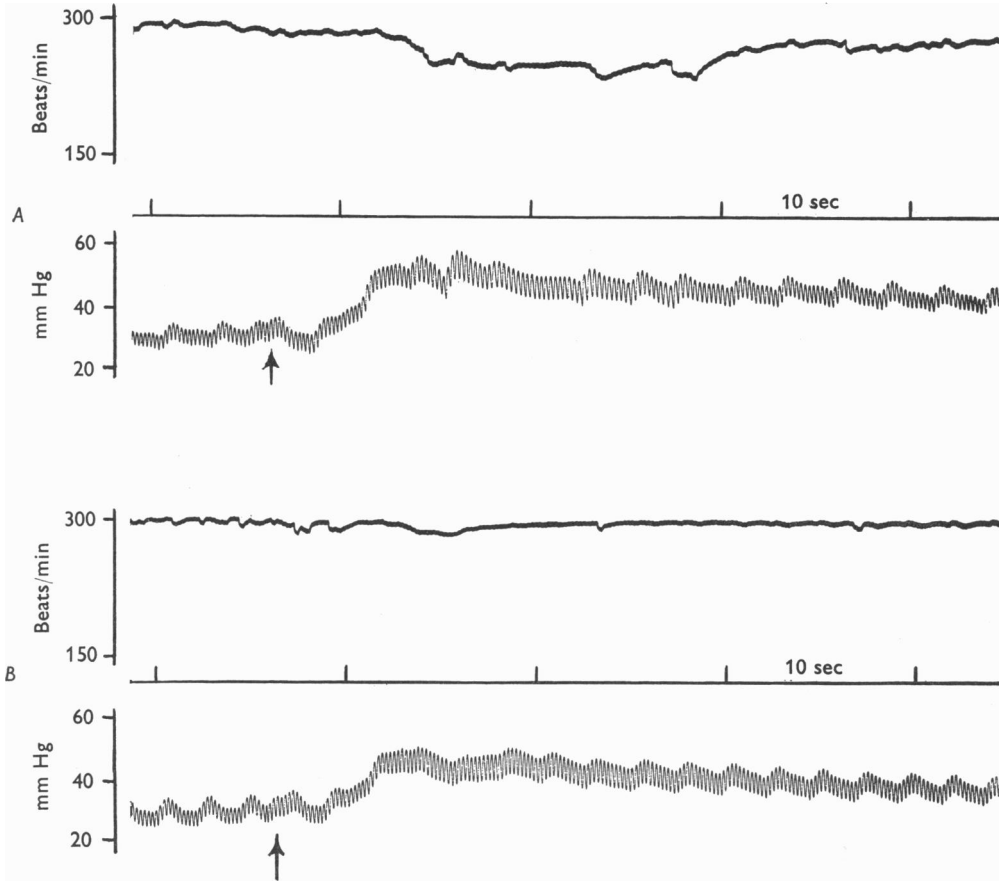

Fig. 5. New-born rabbit, 43 g, less than 1 day old, pentobarbitone anaesthesia. Records of heart rate (above) and arterial blood pressure (below). 0·01μg adrenaline was injected at the arrows, *A* before and *B* after cutting both vagi.

more than 1 day old. In seven younger rabbits there was sometimes a rise of heart rate and sometimes a fall. The heart rate usually increased in nine young rabbits when the vagi were cut. Vagotomy always reduced or abolished bradycardia caused by injection of adrenaline (Fig. 5). In two other rabbits there was actually a small tachycardia in response to adrenaline after vagotomy. Cutting the spinal cord of one rabbit and crushing the neck of two others also changed the response to adrenaline from no change or a fall of heart rate to an increase of heart rate.

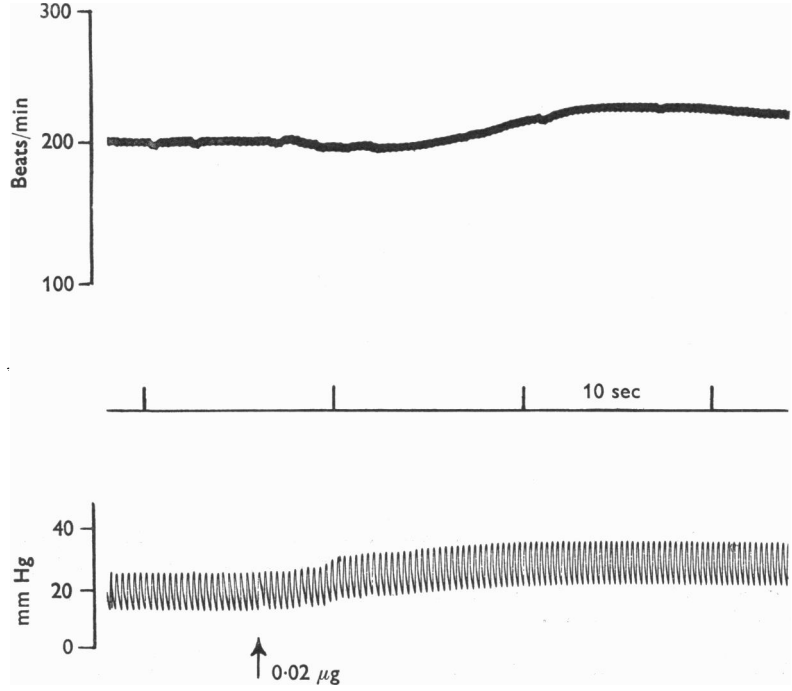

Fig. 6. Foetal rabbit, 10 g, 26 days gestation, pentobarbitone anaesthesia. Records of heart rate (above) and blood pressure (below). Adrenaline 0·02 μg was injected at the arrow.

Foetal rabbits. Foetal rabbits of 24 days gestation age onwards normally responded to the injection of adrenaline or noradrenaline by an increase of heart rate (Fig. 6), though in two instances there was a decrease and in four no change. In two foetal rabbits vagotomy caused a small increase of heart rate, but did not significantly alter the response to adrenaline.

The relation between heart rate and blood pressure

Fig. 7 shows the relationship between the percentage change of heart rate and the maximum mean blood pressure caused by the injection of adrenaline or noradrenaline. Foetal, new-born and adult animals are distinguished by different symbols. When the maximum mean blood pressure exceeded

80 mm Hg, the heart (with the transitory exceptions mentioned above) always responded by slowing. Conversely, rabbits in which the maximum mean blood pressure achieved was less than 40 mm Hg normally responded with tachycardia. All but two of the rabbits represented in this part of the graph were in the foetal condition. A blood pressure rise to between 40 and 80 mm Hg occurred in the majority of new-born rabbits and in a few foetuses. Half of these animals, including one foetus, exhibited slowing of the heart and the remainder an increase of heart rate.

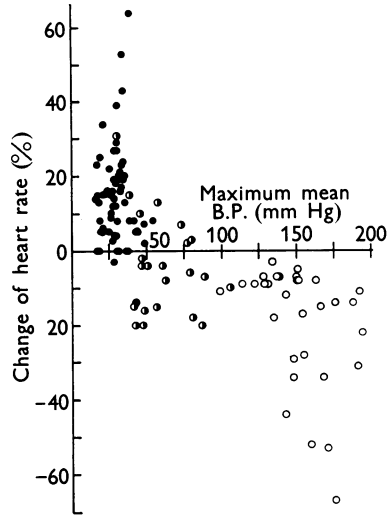

Fig. 7. This diagram shows the relation between the percentage change of heart rate and the maximum mean blood pressure on injection of adrenaline, in nineteen foetal (●), eleven new-born (◑) and sixteen adult (○) rabbits. The higher the maximum blood pressure, the greater the fall of heart rate.

Fig. 7 demonstrates that there is a general relationship between the maximum mean blood pressure induced by the injection of adrenaline and the behaviour of the heart rate. If the pressure is high enough, the heart slows. Thus in adult rabbits bradycardia is normal, and in new-born rabbits frequent, but in foetuses tachycardia is the rule. The adult bradycardia has been shown to be largely reflex. The absence of this response in most foetuses and some new-borns is not due to insensitivity to adrenaline. Most of them showed tachycardia and the blood pressure rose, but perhaps not to a sufficiently high absolute level to cause reflex slowing of the heart. Electrical stimulation of the vagus of three new-born rabbits 0–3 days old caused a profound fall of blood pressure and heart rate (Fig. 8). The efferent mechanism is therefore present and functional at birth, and there remain the further possibilities that either the afferent mechanisms or their central counterpart are insufficiently developed.

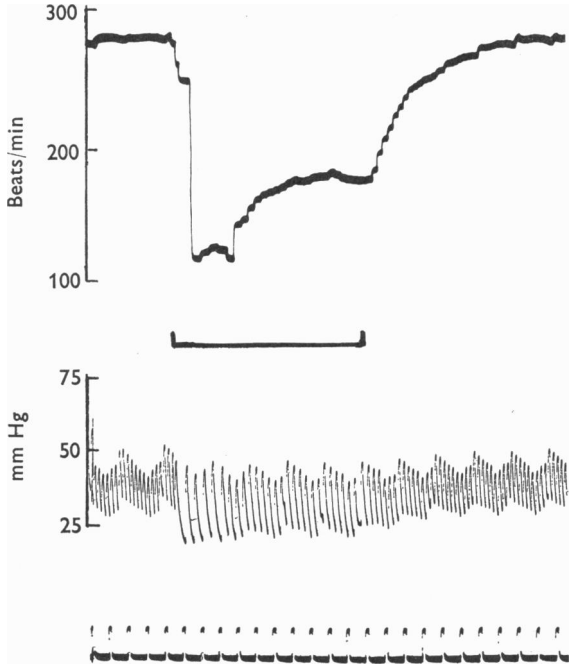

Fig. 8. New-born rabbit, 49 g, less than 1 day old, pentobarbitone anaesthesia. Above, heart rate; below, arterial blood pressure. Stimulation of peripheral cut end of left vagus nerve during signal mark.

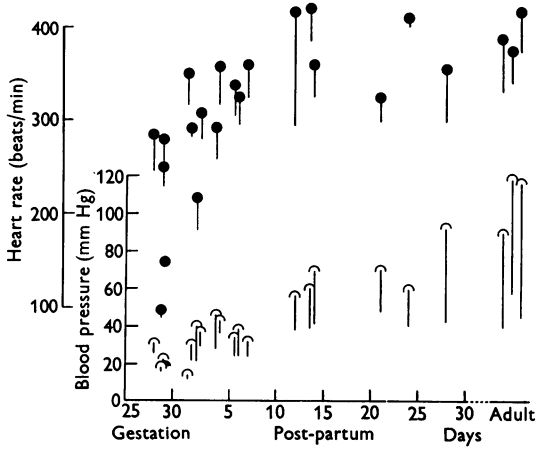

Fig. 9. The immediate effect of the intravenous injection of 1·7-10·9 mg/kg hexamethonium is to cause a fall of heart rate and blood pressure in rabbits of different ages. The initial heart rate is represented by the closed circle and the initial blood pressure by the open half circle. The vertical line from each point represents the fall of heart rate or blood pressure.

The effect of hexamethonium

In so far as the behaviour of the circulation depends on the activity of the sympathetic nervous system, it would be expected that the injection of hexamethonium would lower the blood pressure and heart rate and modify some of the circulatory responses to certain stimuli.

All new-born and adult rabbits showed a substantial fall of heart rate and blood pressure on injection of 1·7 to 10·9 mg/kg hexamethonium (Fig. 9). The responses were of rather short duration at all ages. Four of five foetuses of 28–29 days gestation age also showed a fall of heart rate and blood pressure. In a few new-born rabbits which had shown a rise of blood pressure on asphyxia, this rise was no longer observed after administration of hexamethonium.

DISCUSSION

Asphyxia and anoxia

Bauer (1938) showed that when acute asphyxia was caused by clamping the umbilical cord of a foetal rabbit there was a progressive fall of heart rate. When the trachea of a new-born rabbit was occluded, there was also a fall of heart rate (Bauer, 1939). At 14 days of age acute asphyxia caused only an insignificant rise of blood pressure. We have confirmed these observations and have also shown that even when asphyxia was induced more slowly, a fall of blood pressure and heart rate was the usual response in foetal and new-born rabbits. Only very rarely did blood pressure or heart rate increase above the initial levels, even during the recovery period. This is quite different from the changes observed in foetal and new-born lambs, in which gradual asphyxia or anoxia always induces a rise of blood pressure and, initially, of heart rate, even two-thirds of the way through gestation, at an age when independent existence is not yet possible (Born, Dawes & Mott, 1955). In the new-born puppy, foal and calf we have also observed a rise of blood pressure during asphyxia or anoxia which was accompanied, at first, by an increase of heart rate. The reactions of the new-born rabbit to asphyxia or anoxia are therefore different from the new-born of several other species. It is worth mentioning, at this point, that the rabbit is less mature at birth, by most external criteria, than are members of the other species which were considered. Yet even in the adult rabbit asphyxia, anoxia or injection of adrenaline normally causes a fall of heart rate, although the blood pressure rises. This may possibly be related to the fact that, in the rabbit, the resting heart rate is normally high.

Sensitivity of the foetal circulation to adrenaline

There are various reasons why the blood pressure of the foetal or new-born rabbit should not increase during oxygen lack. One of the possibilities, suggested by the work of Dornhorst & Young (1952), was that the circulation

of the foetal rabbit was less sensitive to the action of sympathetic amines than that of the adult. However, we found the foetus as sensitive as the adult, provided that the basis of comparison was the percentage rise of blood pressure, rather than the absolute rise. Dornhorst & Young (1952) did not define their criteria of cardiovascular sensitivity towards adrenaline. It is true that the absolute rise of blood pressure caused by the injection of adrenaline in the foetal rabbit is small compared with that in the adult. The resting blood pressure of the foetal rabbit is however also small (Fig. 1), and since the aspect of physiological importance is rate of blood flow, it is the proportionate change of pressure which is likely to be of most significance.

There are a few technical differences between our procedure and that of Dornhorst & Young (1952) which had better be enumerated for the sake of clarity. Thus we used barbiturate anaesthesia; they used urethane. We delivered the foetus through small transverse uterine incisions and supported it on the mother's abdomen; they made a longitudinal incision and delivered the foetus into a saline bath. We regularly observed a rise of blood pressure on injection of 0·01μg adrenaline; the smallest dose of adrenaline mentioned in their paper was 0·25μg. They also mention that Clark (1932) in the cat, and Burlingame, Long & Ogden (1942) in the rat, had observed a relative insensitivity of the foetal response to adrenaline. Yet reference to Clark's (1932) paper shows a record of an increase of blood pressure from about 17·5 to 26·5 mm Hg (over 50%) in response to an injection of 0·2μg adrenaline, with a duration which Clark himself remarks as relatively longer than that seen in the adult. Burlingame *et al.* (1942) only injected adrenaline into one foetal rat, and that injection was made into an umbilical artery; this is clearly not comparable with an intravenous injection. Neither of these observations supports the conclusion that the mature foetus is less sensitive to adrenaline than the adult.

There are two other minor points which cannot be omitted from this discussion. First, the course of the foetal circulation is such that adrenaline, injected into a jugular vein, is much diluted before it reaches the heart (Dawes *et al.* 1956). It would therefore have been desirable, but was found technically impracticable, to inject into a femoral vein. Secondly, the placenta is a low-resistance vascular circuit in parallel with the foetus, and this may possibly limit the absolute value of the blood-pressure rise on injection of adrenaline. A direct comparison of the cardiovascular reactions of the foetus and the adult is thus less simple than might at first sight appear.

Heart-rate changes in the adult rabbit

The response of the heart rate of the rabbit towards adrenaline is complex in the adult. The final result is almost invariably a bradycardia of considerable magnitude. A substantial proportion of the slowing is due to the stimulation,

by the rise of blood pressure, of the aortic and carotid sinus pressure receptors, and this component may be abolished by section of the depressor nerves and denervation of the carotid sinuses. Since vagotomy does not completely abolish the bradycardia, and never allows a tachycardia to develop in response to the injection of adrenaline, some other efferent path for the response must exist. Bardier (1898) published an illustration of the effect of 'extrait capsulaire' on the rabbit's circulation which clearly shows a bradycardia similar to that of our rabbits. Verworn (1903) also noted that this bradycardia caused by the injection of adrenaline into rabbits was not abolished by vagotomy. And Allen (1935) found that the slowing of the heart caused by stimulation of the depressor nerves persisted after vagotomy, but that cordotomy at C7 prevented all bradycardia. He therefore concluded that depressor stimulation inhibited sympathetic tone, and this would explain some of our observations. There must be another afferent mechanism involved besides the carotid and aortic pressure receptors, since vagotomy and denervation of the carotid sinuses did not entirely abolish the bradycardia, and since the direct effect of adrenaline is to increase heart rate. von Euler (1938) searching for an explanation for the secondary fall in blood pressure after administration of adrenaline to rabbits, a fall which persists after denervation of the carotid sinuses and cutting the depressor nerves, concluded that the effect could be explained by stimulation of the vasodilator and cardio-inhibitory centres, due to restriction of medullary blood supply by vasoconstriction. This could explain our findings. There is also the possibility that not all the afferent nerve fibres from the pressure receptors distributed up and down the great vessels were in fact interrupted by vagotomy and carotid sinus denervation.

Autonomic control of the circulation in the foetal and new-born rabbit

Dornhorst & Young (1952) observed very little change in heart rate when adrenaline or noradrenaline was injected into rabbit foetuses, whereas the great majority of our foetuses showed an increase of heart rate on the injection of adrenaline or noradrenaline. The heart rate always decreased if the mean arterial blood pressure reached after the injection of pressor amine exceeded 80 mm Hg. It is clear that, in general, the higher the mean arterial pressure is raised by adrenaline or noradrenaline, the greater is the resultant bradycardia (Fig. 7). The fact that the heart usually does not slow on injection of adrenaline in foetal rabbits may be due to the low absolute level of the peak rise in blood pressure. Bauer (1939) put the threshold of the depressor reflex at 65 mm Hg. Our results suggest that it may be lower, and that the depressor reflex may be evoked at birth on injection of adrenaline.

According to Soltmann (1877) stimulation of the peripheral end of the vagus scarcely slowed the heart at all in the new-born rabbit. Kellogg (1927) obtained variable results. We found that the vagus of the new-born rabbit was

very easily damaged, and that the results then obtained were indeed variable. But if an undamaged portion of nerve was excited, there was profound slowing of the heart. Moreover, it was not uncommon to observe a slowing of the heart in the new-born rabbit on injection of adrenaline, a slowing that was abolished by cutting the vagi (Fig. 5).

The fact that in most foetal and new-born rabbits oxygen lack caused only a fall of blood pressure and heart rate suggests that the chemoreceptor reflexes were not yet functional. Yet hexamethonium caused a fall of blood pressure and heart rate in very young rabbits. Autonomic nervous control of the circulation is evidently only just becoming established in the rabbit at birth, although the cardiovascular system is fully sensitive to adrenaline and noradrenaline, as judged by the changes in blood pressure.

SUMMARY

1. In confirmation of Bauer (1939) it was found that asphyxia or anoxia caused little or no increase in blood pressure or heart rate in mature foetal and new-born rabbits.

2. The sensitivity of the cardiovascular system of the mature foetal rabbit to injected adrenaline or noradrenaline was equal to that of the new-born or adult, as judged by the percentage rise of blood pressure and on a weight-to-weight basis.

3. In rabbits of different ages the change of heart rate on injection of adrenaline was related to the absolute peak blood pressure attained. If the blood pressure rose to less than 40 mm Hg the heart accelerated, while above 80 mm Hg it slowed.

4. The bradycardia in response to injection of adrenaline in the adult rabbit was reduced, but not abolished, by cutting the vagi and depressor nerves and denervating the carotid sinuses.

5. Stimulation of the peripheral cut end of the vagi in the new-born rabbit caused a profound fall of blood pressure and heart rate.

6. Injection of hexamethonium caused a proportionately greater fall of blood pressure in older rabbits, whose initial blood pressure was higher.

7. These observations are discussed in relation to the development of cardiovascular reflexes in the rabbit and other species.

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