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THE EFFECTS OF BILATERAL REMOVAL OF THE CAROTID BODIES AND DENERVATION OF THE CAROTID SINUSES IN TWO HUMAN SUBJECTS

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The bilateral removal of the carotid bodies and consequent denervation of the carotid sinuses, as a treatment for asthma, provided the opportunity to study the physiological effects of these procedures in the human being.

METHODS

The subjects were two hospital patients with long-established bronchial asthma. Their histories and clinical condition have been described elsewhere (Wood, Frankland & Eastcott, 1965). The clinical details are largely irrelevant to the present paper since each subject was tested before operation and thus provided control observations. Subject A (patient 2 of Wood *et al.* 1965) was a woman of 53 and subject B (patient 3 of Wood *et al.* 1965) was a man of 44.

A box bag respirator (Donald & Christie, 1949) was used to administer gas mixtures for periods of up to 4 min each and to record tidal volume and respiratory frequency.

The gas mixtures were saturated with water vapour at room temperature and had the following composition: room air, 100 % oxygen, 10 % oxygen in nitrogen, 3 % carbon dioxide in air and 6 % carbon dioxide in air. 10 % oxygen was usually administered twice on each occasion. On some occasions arterial oxygen saturation was recorded with an Atlas ear oximeter which was calibrated against samples of arterial blood analysed by manometric Van Slyke estimations and was accurate to within ± 4 %.

Arterial blood pressure and pulse rate were measured at frequent intervals by auscultation and palpation respectively or by a Sanborn pressure transducer and recorder through a needle in the brachial artery. The frequency response was accurate from 0·5 to 15 c/s. Passive changes in posture were produced by tilting the subject on an Eve rocker which had been modified to allow a vertical position. Valsalva manœuvres were performed by the subject blowing against a mercury column.

RESULTS

Chemoreceptor responses

Subject A. Before operation subject A responded normally by hyperpnoea to breathing 10 % oxygen, 3 % CO_2 and 6 % CO_2. There was no cyanosis.

At operation, both carotid bodies were removed and the adventitia was peeled off for about 2 cm on each side of the carotid bifurcations (Wood *et al.* 1965). Recovery was uneventful. Two weeks after operation the

TABLE 1. Mean pulmonary ventilation, l. BTPS/min, while breathing room air and during 4 min periods of breathing gas mixtures. The change of ventilation on each gas mixture is expressed as a percentage of ventilation on room air. The italicized figures indicate that the percentage change is not significant at $P = 0{\cdot}05$

	Room air	10 % O_2		100 % O_2		3 % CO_2		6 % CO_2	
	$\dot{V}$	$\dot{V}$	% change	$\dot{V}$	% change	$\dot{V}$	% change	$\dot{V}$	% change
				Subject A					
Before operation	5·4	8·0	+49	.	.	8·9	+65	9·4	+75
2 weeks after	5·7	4·5	−20	.	.	8·3	+45	9·4	+65
10 weeks after	4·8	5·1	*+6*	5·3	*+9*	3·8	−21	10·4	+116
30 weeks after	5·6	5·7	*+2*	6·6	+16	8·2	+46	10·4	+86
				Subject B					
Before operation	10·8	13·0	+20	6·7	−38	12·2	*+13*	.	.
2 weeks after	5·9	5·9	*0*	5·6	*−6*	6·1	*+3*	8·6	+45
6 weeks after	9·2	*a* 12·3	+29	7·1	*−22*	12·1	+32	.	.
		b 7·8	−17	.	.	.	.	.	.
34 weeks after									
Day 1	6·2	7·1	*+15*	7·1	*+15*	.	.	.	.
Day 3	7·9	.	.	7·2	*−10*	9·4	+19	.	.
43 weeks after	8·0	.	.	.	.	10·7	+34	.	.

responses to gas mixtures were tested again. The most obvious change was depression of respiration caused by breathing 10% oxygen. The effects of hypoxia are illustrated in Fig. 1*a* and *b*, which shows the spirometer records obtained before and 2 weeks after operation. At the end of the recording shown in Fig. 1*b*, the subject was extremely cyanosed though still conscious. The responses to carbon dioxide were the same as before

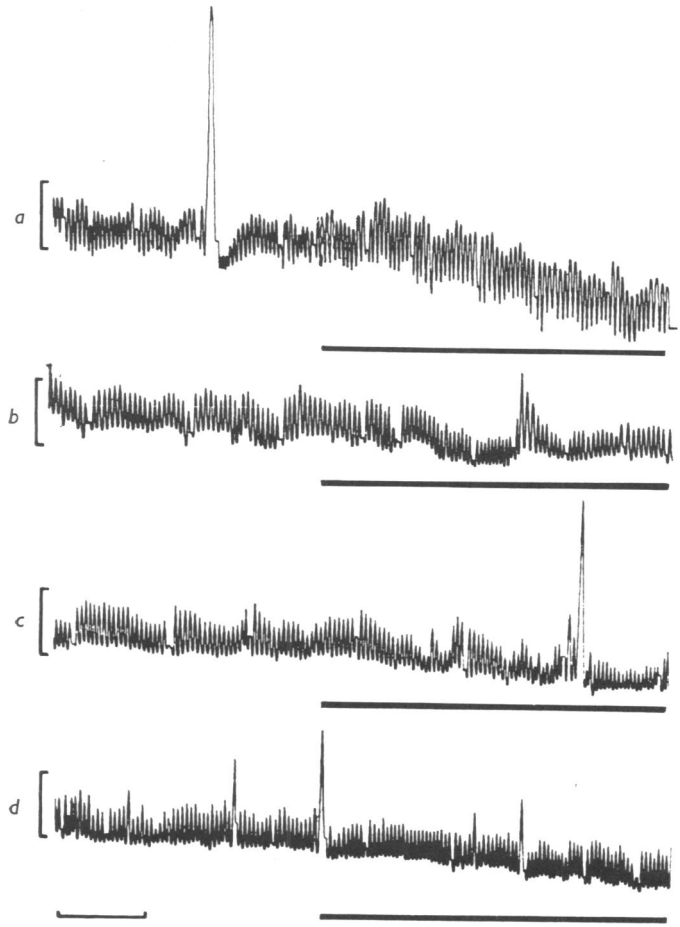

Fig. 1. Spirometer records. Subject A. At the beginning of each record, subject A was breathing room air. 10% oxygen was administered during the period shown by the horizontal line. Vertical calibration 500 ml. Time scale 1 min. *a*, Before operation; *b*, 2 weeks after operation; *c*, 10 weeks after operation; *d*, 30 weeks after operation.

In *a* the marked downward slope during hypoxia is due to increased volume of gas in the respirator as the volume of CO_2 blown off was greater than the volume of O_2 absorbed during hyperpnoea. The much smaller downward slopes in *b*, *c* and *d* can be attributed entirely to decreased absorption of oxygen since there was no hyperpnoea.

operation. The observations were repeated 10 weeks and 30 weeks after operation (Fig. 1*c* and *d* and Table 1). On these two occasions mean minute volume was neither depressed nor stimulated by 10% oxygen and the subject became slightly cyanosed.

The responses to carbon dioxide were normal except that on one occasion, for unknown reasons, 3% CO_2 did not stimulate respiration. The respiratory responses of subject A on the four occasions are summarized in Table 1.

Subject B. Before operation subject B hyperventilated in response to breathing 10% oxygen, but 3% carbon dioxide caused no significant change. However, ventilation was markedly depressed (38%) by breathing oxygen. These results are shown in Table 1.

For several days after operation subject B had episodes of irregular and slow respiration. The measurements which were made 16 days after operation illustrated the clinical findings that respiration was grossly abnormal. Figure 2*b* shows the irregular movements and small minute volume during inspiration of room air and 10% oxygen. Because of the irregularity it is impossible to conclude that ventilation was significantly changed by hypoxia. The *mean* minute volume during two periods of 4 min on 10% oxygen was the same as when breathing room air or 100% oxygen, and was 45% lower than it was on room air before operation (Table 1). Preoperative resting arterial oxygen saturation was 98%. The earpiece oximeter record 16 days after operation (Fig. 3*a*) indicates a lower saturation (90%) while breathing room air. Breathing 10% oxygen for 4 min decreased the saturation to 37% and when the subject breathed room air again arterial saturation rose. However, for the next 20 min breathing became even more irregular and arterial saturation often fell as shown by the earpiece oximeter record. The subject had repeated attacks of slow, very irregular breathing for many hours after this observation. From the third week after operation the spontaneous episodes of hypoventilation gradually decreased in frequency and severity. At this time spontaneous arterial saturations as low as 75% were briefly recorded with the earpiece oximeter. However, attacks of more severe hypoxia occurred only when the oximeter was not used. The intermittent administration of oxygen, in order to calibrate the earpiece, seemed to prevent the attacks.

Subject B was tested again 6 weeks after operation. The results are illustrated in Figs. 2*c* and 3*b* and summarized in Table 1. It can be seen that minute volume while breathing room air was almost the same as before operation and that breathing was regular except for short periods of hypoventilation. The response to breathing oxygen was similar to the response before operation and the response to 3% CO_2 was now a marked stimulation of respiration. 10% oxygen was administered twice. On the

first occasion (*a* in Table 1) there was increased ventilation indicating chemoreceptor reflex activity (Fig. 2*c*). In spite of this, the administration of 10% oxygen resulted in a period of hypoventilation causing hypoxaemia (Fig. 3*b*) after arterial oxygen saturation had returned to normal, that is after about 2 min on room air. During the next 2 min the subject breathed only when commanded to do so. During this and other brief periods of hypoventilation the minute volumes were not representative and have been omitted in calculating the mean ventilation. When 10% oxygen was given for a second period, ventilation was decreased (*b* in Table 1).

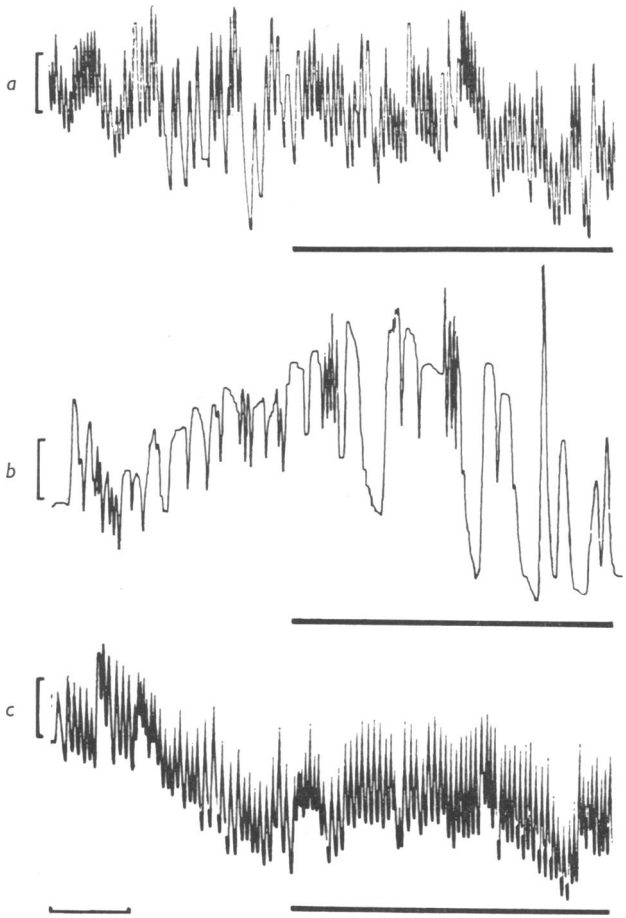

Fig. 2. Spirometer records. Subject B. Calibration as in Fig. 1. *a*, Before operation; *b*, 2 weeks after operation; *c*, 6 weeks after operation.

On each occasion 10% oxygen was administered as shown by the horizontal line. *c* illustrates the *first* of the two periods of hypoxia corresponding to *a* in Table 1 and in the text.

Thirty-four weeks after operation, subject B's responses to gas mixtures were similar to those at 6 weeks and are summarized in Table 1. The regularity of breathing varied from day to day as did the minute volumes while breathing room air. The administration of 10% oxygen resulted in a subsequent period of hypoventilation which was less marked than on previous occasions (Fig. 3*c*).

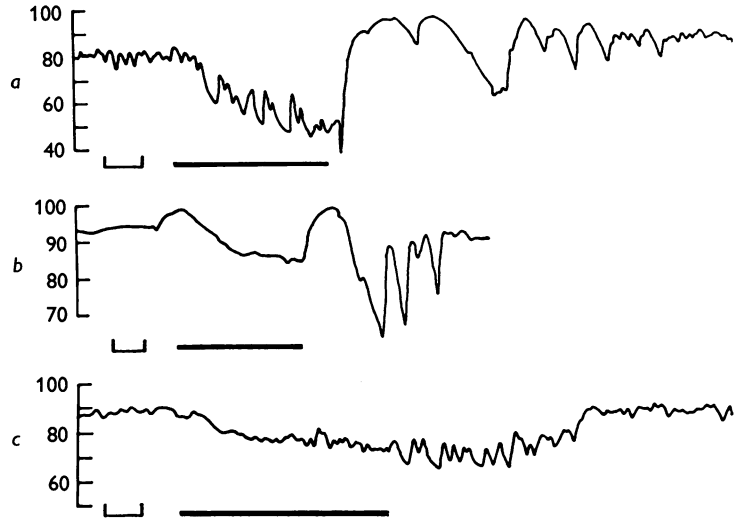

Fig. 3. Ear oximeter records of arterial oxygen saturation (Sa_{O_2}) of subject B. *a*, Two weeks, *b*, 6 weeks and *c*, 34 weeks after operation. 10% oxygen was administered as shown by the horizontal line. Note the 'spontaneous' falls in Sa_{O_2} subsequent to breathing 10% oxygen, while breathing was slow and irregular. Vertical scale Sa_{O_2}. Time scale 1 min.

The cardiovascular effects of breathing oxygen and of hypoxia

In both subjects and on every occasion administration of oxygen caused bradycardia and hypoxia caused tachycardia. These results are shown in Table 2. The effects on heart rate were independent of blood pressure, which was usually unchanged, and they occurred whether ventilation was increased, decreased or unchanged.

Baroreceptor function

The chief effect of denervating the carotid baroreceptors in both subjects was to produce a neurogenic systemic arterial hypertension. Table 3 records the resting arterial pressures of the horizontal subjects before and at various times after operation. Although both subjects were receiving drugs (ACTH or prednisone) which may affect arterial pressure, the sudden change in pressure shown in Table 3 can be attributed to the

TABLE 2. The effect of 4 min breathing 10, 21 or 100 % oxygen on arterial saturation (Sa_{O_2}), pulse rate, blood pressure and ventilation($\dot{V}$). Usually two tests with each gas were made on each occasion. The pulse rates are the means of the readings from the second to the fourth minute of the test. The saturations on 10 % oxygen are the means of the minima

	Sa_{O_2}		Pulse rate (beats/min)			Blood pressure (mm Hg)			$\dot{V}$ Significantly increased (+) or decreased (−)	
Inspired % O_2	10	21	10	21	100	10	21	100	10	100
				Subject A						
Before operation	.	.	88	70	.	.	.	.	+	.
2 weeks after	.	.	119	96	.	.	.	.	−	.
10 weeks after	60	91	99	82	67	165/105	165/105	170/105	0	0
30 weeks after	57	93	105	84	68	144/105	140/95	135/95	0	+
				Subject B						
Before operation	80	98	88	73	68	135/80	135/95	130/85	+	−
2 weeks after	37	90	107	92	86	165/100	165/100	160/110	0	0
10 weeks after	83	94	84	71	64	180/100	180/100	170/100	0	0
34 weeks after	72	90	84	71	59	175/100	170/105	175/100	0	0

operation since the doses of the drugs were the same before and after operation. The increased arterial pressure was accompanied by a rise in resting heart rate. Both heart rate and blood pressure varied considerably from day to day.

TABLE 3. Resting arterial pressure and pulse rate while horizontal and the presence (+) or absence (0) of baroreceptor reflex response to tilting to erect posture. Results marked (T) were obtained with a pressure transducer; all other results were obtained by auscultation

	Arterial pressure (mm Hg)	Pulse rate (beats/min)	Reflex response to tilt
	Subject A		
Before operation	105/65	70	+
10 weeks after	160/100	82	0
30 weeks after	140/95	100	+
61 weeks after	116/96–174/120	66–74	.
	Subject B		
Before operation (T)	120/80	73	+
2 weeks after (T)	170/100	88	0
6 weeks after	170/95	80	.
12 weeks after (T)	160/100	90	+
15 weeks after	145/90	88	+
34 weeks after	170/100	78	.
	180/100	75	.
43 weeks after	140/100	78	+

The cardiovascular responses to tilting the subject from horizontal to erect were studied before and after operation (Fig. 4). Before operation both subjects responded normally; tilting to vertical produced a rise of diastolic pressure at heart level and a slight fall of pulse pressure. In subject B, this was accompanied by tachycardia; in subject A, heart rate was not measured. For a few weeks after operation tilting the subjects produced no change in heart rate or blood pressure (Fig. 4*b*) but at a later stage virtually normal responses returned although the subjects were still hypertensive. These responses are illustrated in Fig. 4*c*, where it can be seen that vertical posture produced a fall in pulse pressure and rise in pulse rate.

The baroreceptor effects of the operation thus occurred in two phases. Initially, all baroreceptor responses were abolished but after a few weeks the responses to changes of pulse pressure returned, although the hypertension persisted. During the second phase, both patients were able to perform Valsalva manœuvres (which they had been unable to do before because of dyspnoea). The results of the Valsalvas were distinct pressure overshoots and bradycardia indicating normal reflex responses (Sharpey-Schafer, 1955).

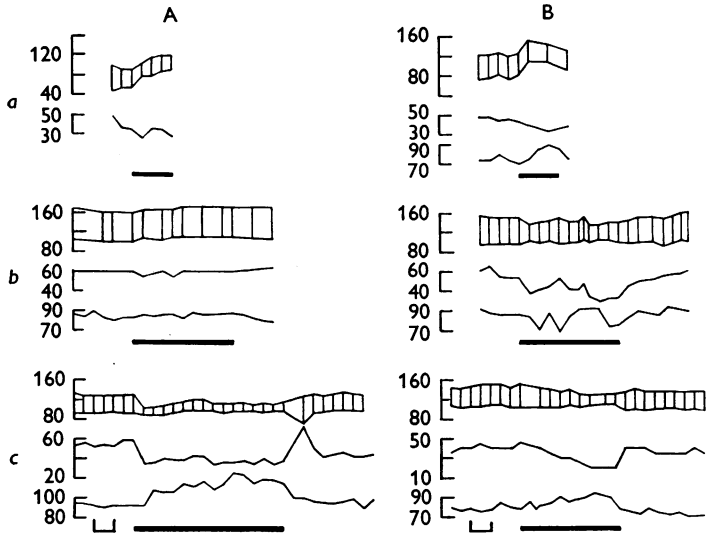

Fig. 4. The effect of passive tilt from horizontal to erect (marked by horizontal line) in subjects A and B. *a*, Before operation; *b*, 10 weeks after operation (subject A), 2 weeks after operation (subject B), *c*, 30 weeks after operation (subject A), 43 weeks after operation (subject B). Records *a* and *b* of subject B were obtained with a pressure transducer; all other results were obtained by auscultation. In each record from above downwards: systolic and diastolic blood pressure (mm Hg) measured at heart level, pulse pressure (mm Hg) and pulse rate (beats/min) (omitted in A, *a*). Time scale 1 min. Note the absence of consistent changes in *b* and the reappearance of reflex changes in *c*.

DISCUSSION

Reflex hyperpnoea in response to acute hypoxia occurs in normal man as in experimental animals. In experimental animals, removal of all chemoreceptor organs, the carotid bodies and the aortic body reverses the response so that hypoxia then causes hypoventilation. Similar observations have been made in a few human subjects; for example, W. I. Cranston, K. W. Cross & G. de J. Lee (personal communication) obtained hypoventilation in response to hypoxia in a tabetic subject who was presumed to have no intact chemoreceptors, and R. D. Wright (personal communication) reported similar findings in a patient after removal of bilateral carotid body tumours.

These observations suggested that human chemoreceptor organs have the same function as those of experimental animals but in these subjects the lesion was not clearly defined nor was it possible to observe the individuals before the lesion had occurred. We were fortunate in being able to test the same two subjects before and after clearly defined surgical lesions. In both subjects, hypoxia caused normal hyperpnoea before operation, but hypoventilation or no change two weeks after bilateral removal of the

cartiod bodies. The finding was unexpected since it is generally believed that the aortic body has chemoreceptor activity in man (Cotes, 1964), as it has in most animals (Gernandt, 1946; Heymans & Neil, 1958).

Chemoreceptor function returned in subject B within 6 weeks of operation. In subject A, the evidence is less convincing. However, at 10 weeks and 30 weeks after operation her breathing was neither stimulated nor depressed by hypoxia in contrast to the marked depression at 2 weeks. The abolition of this hypoventilation suggests some return of the chemoreceptor reflex.

The mechanism of these changes in reflex hyperpnoea cannot be elucidated from our observations. Both peripheral and central factors must be considered. The absence of reflex hyperpnoea occurred because there was insufficient chemoreceptor activity to overcome the depressing effect of hypoxia on the respiratory centre. Since chemoreceptor responses to hypoxia are decreased by increased arterial pressure (Heymans & Neil, 1958; Lee, McCloskey & Torrance, 1964), the post-operative arterial hypertension in our subjects may have contributed to the abolition of the reflex. Subsequent recovery can be attributed to increased activity at either site or both sites. The peripheral receptors are presumably situated in the aortic body since regeneration and reinnervation of the carotid bodies is unlikely. The individual receptors might have become more sensitive to the combination of hypoxia and arterial hypertension or the number of functioning receptors might have increased. Alternatively, some or all of the renewed response might be due to adaptation in the central nervous system to information from the aortic body receptors.

In normal subjects and in every-day situations the chemoreceptors are not very important. It is, however, well known that they become of great importance in subjects who are insensitive to CO_2 (Campbell, Dickinson & Slater, 1963), and who therefore rely on chemoreceptor drive for normal breathing. Subject B was relatively insensitive to carbon dioxide but had sufficient chemoreceptor drive to maintain his ventilation at the normal level before operation. This was not regarded as a contra-indication for removal of the carotid bodies since it was thought that the aortic body would provide adequate chemoreceptor activity. This assumption was not justified. Two weeks after removal of his carotid bodies subject B's ventilation was 45% lower than it was before operation (Table 1). That is to say, total ventilation was depressed by the operation to about the same extent as when the chemoreceptor reflex had been abolished preoperatively by the administration of oxygen. At this time hypoxia did not always cause a prompt hypoventilation but after a delay breathing was depressed for some hours. This delayed effect was observed again, but to a smaller extent, 6 weeks after operation, at which time chemoreceptor

function had recovered. The mechanism of the delayed depression is a matter for speculation but it probably involves supramedullary regions of the brain. In neither subject was the response to inspired CO_2 decreased after removal of the carotid bodies. This is in accordance with the findings in animals of all species and in man (W. I. Cranston, K. W. Cross & G. de J. Lee, personal communication; R. D. Wright, personal communication), bur disagrees with the reports of Nakayama (1961) that CO_2 hyperpnoea was abolished by the operation. It is not clear from Nakayama's paper what were the details of his observations, and resolution of the apparent contradiction between our results and his must await clarification.

The cardiovascular effects of hypoxia which have been reported in the literature and are discussed by Heymans & Neil (1958) include vasoconstriction, hypertension, tachycardia and bradycardia. Daly & Scott (1964) have analysed the responses in the anaesthetized dog and have shown that the primary reflex effects from chemoreceptor stimulation are bradycardia and vasoconstriction and that the tachycardia which normally occurs in hypoxia is partly secondary to hyperventilation. However, they also observed tachycardia in constantly ventilated dogs when the chemoreceptor reflex effects were abolished and concluded that it could not be due wholly to alterations in respiration. This is in agreement with the conclusion of Heymans & Neil (1958) that hypoxic tachycardia in anaesthetized cats is not due to a chemoreceptor reflex but it is a direct action of low oxygen tension either on sympathetic centres or on the pacemaker region of the heart. The only marked cardiovascular effect of hypoxia in our subjects was tachycardia. This response remained and was even intensified at a time when the respiratory response to hypoxia was absent after removal of the carotid bodies. This finding suggests that in unanaesthetized man hypoxic tachycardia is not secondary to hyperventilation nor due to reflex stimulation of carotid chemoreceptors but could be explained by the hypothesis of Heymans & Neil (1958). In our subjects there was little, if any, change of arterial pressure and hence the response was probably not due to general sympathetic stimulation but could have been due to liberation of adrenaline from the adrenal glands or to a direct effect of hypoxia on the heart. On the other hand, our observations do not exclude the possibility that in man hypoxia causes reflex tachycardia as a result of stimulation of aortic body chemoreceptors. This would be in accordance with the findings of Comroe (1939) that in dogs the carotid bodies are mainly responsible for respiratory responses whereas the aortic body plays a major part in initiating cardiovascular reflexes. However, Comroe did not observe a complete separation of function between the two reflex areas and the partial separation that he reported was more marked in dogs than in other species.

The results of the observations on the cardiovascular responses to changes in arterial pressure in our subjects may be summarized as a temporary disappearance of all baroreceptor responses, later reappearance of some part of the response, and long-lasting hypertension.

The complete loss of all baroreceptor activity, which lasted for a few weeks after carotid sinus denervation, suggests that the aortic baroreceptors were not functional in these subjects. At this stage our subjects may be compared with the tabetic subjects investigated by Sharpey-Schafer (1956). The tabetic subjects, like ours, had no reflex responses to tilt or Valsalva manœuvres, but, in contrast to our subjects, the tabetics had normal blood pressures while horizontal and postural hypotension when vertical. These different findings are due to differences in the efferent part of the reflex control of peripheral resistance. In our subjects, sympathetic tone was probably high because of the lack of reflex inhibition and peripheral arterioles and veins must have been constricted sufficiently to prevent any fall of blood pressure on tilting to vertical. In the tabetic subjects on the other hand, sympathetic tone was not abnormally increased and peripheral resistance was presumably too low to prevent pooling of the blood when vertical. The difference may be associated with the probable longer duration of deafferentation in the tabetic subjects.

After the first few weeks, our subjects regained some baroreceptor activity. At this stage, both subjects showed decreased pulse pressure and tachycardia in response to tilting to vertical and the normal reflex responses to Valsalva manœuvres. The effective stimulus in these reflexes is a change in pulse pressure. There was no marked increase of diastolic pressure when the subjects were vertical, indicating that little, if any, increase in vasoconstrictor tone occurred. Systolic pressure fell and thus caused a fall in pulse pressure. Presumably the tachycardia was a baroreceptor response to this fall in pulse pressure. Both subjects were still hypertensive. This suggests that their baroreceptors were responding to changes in pulse pressure but not in mean pressure. In animals, carotid sinus baroreceptors are more sensitive to a pulsatile pressure than to a steady pressure (Ead, Green & Neil, 1952). While there is evidence that the same receptor may respond to both types of stimulus (Bronk & Stella, 1935), at least some of the receptors respond to a pulsatile pressure but not to a steady pressure of the same mean value (Ead *et al.* 1952). The site of the pulse pressure sensitive receptors in our subjects is not known. It seems unlikely that the carotid sinuses had become re-innervated, but other baroreceptor areas have been found in the aortic arch and other regions of the circulation (Heymans & Neil, 1958). Presumably one or more of these baroreceptor areas had developed a latent response to changes in pulse pressure during the weeks that elapsed since carotid sinus denervation. If this is the

explanation the question arises of why these baroreceptors failed to abolish the hypertension. In animals denervation of the carotid sinuses while sparing the aortic baroreceptors results in a short-lived hypertension, whereas denervation of both regions causes permanent hypertension in dogs (Nowak, 1940; Schafer, 1944), but not in rabbits (Boyd & McCullagh, 1938). Although animals with intact aortic baroreceptors do not become chronically hypertensive, it is possible that human subjects do because of human erect posture. Since the carotid sinuses are nearer the head than the aortic arch, information from the former might be expected to have more control over blood pressure than information from the latter. It is also necessary to consider the efferent mechanism of hypertension. In dogs, total sympathectomy abolishes neurogenic hypertension (Heymans, 1938; Schafer, 1944). When the operations are performed in the reverse order, however, hypertension still develops after total sympathectomy (Nowak & Walker, 1939). Thus there is evidence that the sympathetic nervous system constitutes the major efferent pathway but it may not be the only one. The possibility of species difference must also be borne in mind.

SUMMARY

1. Two patients were examined before and at intervals after bilateral removal of carotid bodies and denervation of carotid sinuses.

2. Chemoreceptor responses were tested by administration of oxygen, 10% oxygen in nitrogen, 3 and 6% carbon dioxide in air. In both subjects the response to hypoxia was hyperpnoea before operation but hypoventilation two weeks after operation. Several weeks later hypoxia produced no change in ventilation. Carbon dioxide produced hyperpnoea on all occasions.

3. Baroreceptor responses to passive tilt from horizontal to erect posture were normal before operation, absent for a few weeks after operation, and returned after the first few weeks.

4. Both patients became moderately hypertensive immediately after operation and remained so throughout the period of observation.

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