Brit. J. Pharmacol. (1958), 13, 372.

CARDIAC OUTPUT DURING EXCITATION OF CHEMOREFLEXES IN THE CAT

BY

GWENDA R. BARER AND E. NÜSSER

From the Nuffield Institute for Medical Research, University of Oxford

(RECEIVED APRIL 23, 1958)

In cats under chloralose anaesthesia the reflex fall of blood pressure and heart rate caused by injection of veratrine, amidines, diphenhydramine, or ethyl acetoacetate was accompanied by a fall in cardiac output. After veratrine and amidines there was a fall in mean pulmonary arterial pressure and after veratrine no significant change in pulmonary vascular resistance. After diphenhydramine and ethyl acetoacetate there was a rise in mean pulmonary arterial pressure and after diphenhydramine an increase in pulmonary vascular resistance. The effects of veratrine and amidines, but not those of diphenhydramine and ethyl acetoacetate, were abolished by section of the vagi. The main change leading to the fall of cardiac output after amidines was bradycardia.

The chemoreflexes which can be elicited from receptors in the heart and lungs (Dawes and Comroe, 1954) are manifested by a fall in heart rate, a fall in systemic arterial pressure, rapid shallow breathing or arrest of respiration and, frequently, increased bronchial tone. It was not known if they had any effect on the pulmonary circulation or cardiac output. It was therefore decided to make direct measurements of pulmonary arterial blood flow and pressure during the administration of drugs which stimulate these receptors.

METHODS

Cats were anaesthetized with chloralose (50 or 60 mg./kg. i.v.). The chest was opened widely through a midline incision and positive pressure ventilation was maintained with a Starling Ideal pump. Heparin (10 mg./kg., Boots) was given and either a bubble flowmeter or a density flowmeter (Dawes, Mott, and Vane, 1953) was inserted into the main or left pulmonary artery or left lower lobe artery. Since the results obtained with the two types of flowmeter were identical it has not been stated in the tables which type was used for a given experiment. Blood flow in the main pulmonary artery is equal to the total cardiac output and a mean value in these experiments was 280 ± 68.7 ml./min. or 114 ± 20.6 ml./min./kg. (16 cats). The bubble flowmeter consisted of a loop of polyethylene tubing marked in ml. with a bubble trap at the distal end. The pressure drop across the flowmeters was as follows. The drop with the bubble flowmeter for main pulmonary artery was 6 mm. Hg at a flow rate of 800 ml./min. (saline) and for the left pulmonary artery was 4 mm. Hg at a flow rate of 150 ml./min. (saline). The drop with the density flowmeter for main pulmonary artery was 4.4 mm. Hg at a flow rate of 1,840 ml./min. (saline) and for the left pulmonary artery was 2 mm. Hg at a flow rate of 128 ml./min. (saline). The details of insertion of these flowmeters have already been described (Barer and Nüsser, 1957). Pulmonary arterial pressure was recorded with a mercury manometer attached to the flowmeter circuit close to the distal cannula. Left atrial pressure was read directly in cm. of blood in a vertical tube tied into the auricular appendage. Pulmonary vascular resistance was calculated in Peripheral Resistance Units from the formula: Resistance (PRU) = Mean pulmonary arterial pressure − mean left atrial pressure (mm. Hg)/pulmonary blood flow ml./min.

In six experiments a Starling resistance was inserted into the main pulmonary artery and the lungs were perfused at constant pressure (Barer and Kottegoda, 1958).

We are indebted to Dr. F. L. Rose for phenyldiguanide hydrochloride, to Professor O. Krayer for veratridine and to Dr. W. F. Short for 2-α-naphthylethyl*iso*thiourea hydrochloride. Diphenhydramine hydrochloride (Parke, Davis), ethyl acetoacetate (B.D.H.), Chlorbismol, a fine suspension of bismuth oxychloride (May and Baker), and veratrine B.P.C. (B.D.H.) were also used. Ethyl acetoacetate was made up in Tyrode solution or 0.9% tap water saline in order to diminish its acidity (ethyl acetoacetate *p*H 1.7, in Tyrode solution 6.7, in tap water saline 7.1). All drugs were given intravenously or into the flowmeter tubing.

RESULTS

Veratrine and Veratridine.—Veratrine and the pure alkaloid veratridine stimulate sensory receptors in both the heart and lungs (Dawes and

TABLE I

THE EFFECT OF DRUGS EXCITING CHEMOREFLEXES FROM THE HEART AND LUNGS ON PULMONARY BLOOD FLOW

The blood flow in the main pulmonary artery was measured in all experiments except those marked with an asterisk in which left pulmonary arterial blood flow was recorded. The numerals in brackets in the first column denote the number of cats used with each drug. † Denotes that the effect was sometimes diphasic (as in Fig. 3). I.v. denotes intravenous injection, i.p. injection into the pulmonary arterial tubing.

Drug	Dose and Route of Administration	Effect on Pulmonary Arterial Blood Flow (% Change)	Effect on Mean Pulmonary Arterial Pressure (mm. Hg)	Effect on Mean Systemic Blood Pressure (mm. Hg)
Veratridine (5)	15–70 μg. i.v. and i.p.	−30 to −50	−7 to −16	−34 to −86
Veratrine (3)	10–25 μg. i.p.	−15 to −60	−2 to −7	−36 to −66
Veratrine (6)*	30–100 μg. i.p.	−8 to −60	−1 to −3	−24 to −90
Phenyldiguanide (13)	100–300 μg. i.p.	−13 to −60	0 to −11	−18 to −66
2-α-Naphthylethylisothiourea (9)	75–100 μg. i.v. and i.p.	−20 to −60	−2 to −10	−36 to −74
Ethyl acetoacetate (8)	100–200 mg. i.v. and i.p.	−15 to −60†	1st phase −2 to −14 2nd phase +8 to +10	†−22 to −64

Comroe, 1954). Both substances when injected either intravenously or into the pulmonary flowmeter circuit caused a profound diminution in pulmonary blood flow, and a fall in mean pulmonary arterial pressure (Table I and Fig. 1). The increase in pulmonary arterial pulse pressure has also been demonstrated with a condenser manometer and may be due to increased stroke volume consequent upon bradycardia. There was usually a slight rise in left atrial pressure. These effects were abolished by section of the vago-sympathetic trunks in the neck.

Measurements of pulmonary vascular resistance before and after administration of veratrine in 7 cats showed very slight changes in either direction (Table II).

Amidine Compounds.—A large number of these compounds give rise to reflexes originating in the heart and in the lungs (Dawes, Mott and Widdicombe, 1951). The two compounds investigated were phenyldiguanide and 2-α-naphthylethyl*iso*thiourea, both of which caused a fall in cardiac output, an increase in pulmonary pulse pressure (observed in condenser manometer records) a rise in left atrial pressure, and, usually, a slight fall in mean pulmonary arterial pressure (Table I, Fig. 2). These effects were abolished by section of the cervical vago-sympathetic trunks.

An attempt was made to find out whether the fall in cardiac output after these substances was due to diminished venous return following peripheral vasodilatation, bradycardia, or increased pulmonary vascular resistance.

Experiments in which a Starling resistance was inserted into the main pulmonary trunk and the lungs were perfused at constant pressure showed that the fall in cardiac output was not directly due to increased pulmonary vascular resistance. Injection of phenyldiguanide in six such preparations still caused a fall in *right ventricular output.* To test the importance or otherwise of peripheral vasodilatation, the fall in arterial pressure was minimized in four cats by the insertion of a pressure stabilizer into the abdominal aorta. The fall in blood pressure after injection of phenyldiguanide was greatly reduced by this procedure, but the fall in cardiac output was as great or greater

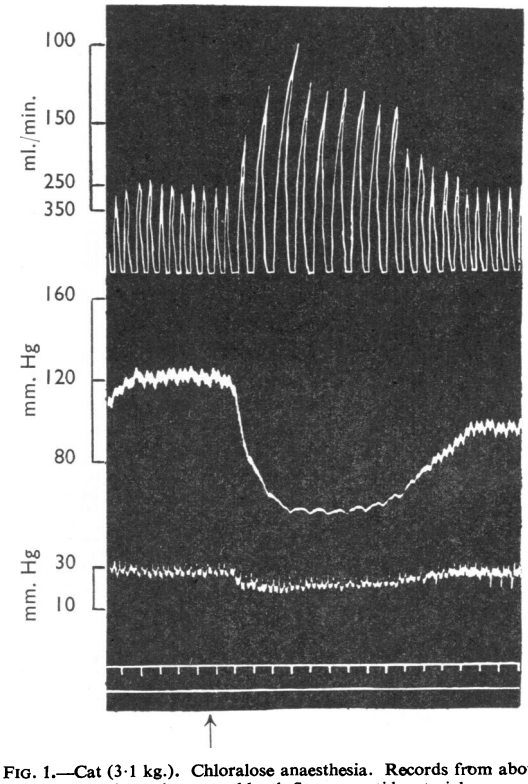

FIG. 1.—Cat (3·1 kg.). Chloralose anaesthesia. Records from above downwards, pulmonary blood flow, carotid arterial pressure, pulmonary arterial pressure and time, 10 sec. Veratrine (10 μg.) was injected at the arrow into the distal pulmonary cannula.

TABLE II

THE EFFECT OF VERATRINE ON PULMONARY VASCULAR RESISTANCE

30 to 100 μg. of veratrine was injected into the pulmonary arterial tubing. "Before" and "After" refer to measurements made before and after the injection of veratrine. Where successive measurements are given, these were made at corresponding times for flow pressure and resistance estimations.

Expt. No.	Left Pulmonary Arterial Blood Flow (ml./min.)		Mean Pulmonary Arterial Pressure (mm. Hg)		Mean Left Atrial Pressure (mm. Hg)		Resistance P.R.U. (mm. Hg/ml./min.)	
	Before	After	Before	After	Before	After	Before	After
1 (a)	56	48, 55	26	26, 24	8	8, 8	0·32	0·37, 0·29
(b)	54	32, 31	24	22, 19	7	7, 8	0·31	0·47, 0·36
2	47	38, 35, 37	17	16, 16, 14	2	3, 3, 3	0·32	0·34, 0·37, 0·3
3	50	36, 34	18	16, 15	2	2, 1	0·32	0·39, 0·41
4	51	50, 52, 47	25	25, 24, 25	3	3, 4, 4	0·43	0·44, 0·38, 0·45
5	27	24, 24	30	22, 29	5	5, 6	0·93	0·71, 0·96
6	50	48, 36, 38	17	17, 15, 14	4	4, 4, 4	0·26	0·27, 0·31, 0·26
7	42	33	27	22	3	5	0·57	0·52

than before. Both right and left atrial pressures rose considerably, so it is probable that an adequate venous return was maintained. In five cats, atropine (1 mg./kg.) was given to abolish the bradycardia. There was then little or no fall in cardiac output on administration of phenyldiguanide, and the fall in blood pressure was reduced to only 10 to 24 mm. Hg.

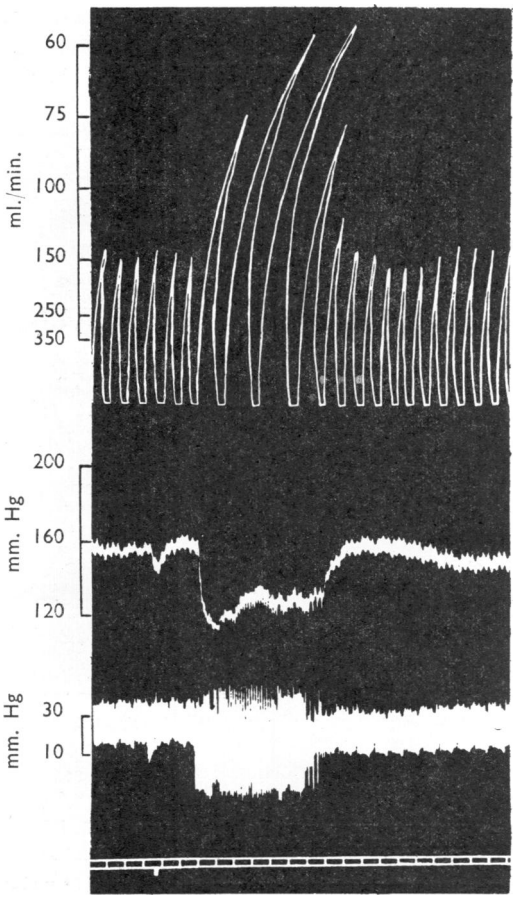

FIG. 2.—Cat (2·1 kg.). Chloralose anaesthesia. Records as in Fig. 1. 30 μg. of 2-α-naphthylethyl*iso*thiourea was injected into the distal pulmonary cannula at the signal mark.

Diphenhydramine. — Diphenhydramine and other antihistamines elicit reflexes from the lungs of the cat similar to those caused by amidines (Jones, 1952). In the dog, the two classes of compound act differently (Dawes, Mott, and Widdicombe, 1952) and in the cat differences were detected in their respective effects on tidal air (Barer and Nüsser, 1953). Table III shows that diphenhydramine differed from amidines and veratrine in that, although it caused a diminution in pulmonary blood flow, this was accompanied, in all but one cat, by a rise in mean pulmonary arterial pressure, and both these changes still took place after section of the vago-sympathetic trunks in the neck. In 4 isolated cat lungs perfused at constant blood flow, the pulmonary arterial pressure rose after administration of diphenhydramine in doses of 0.5 to 5 mg. There was therefore an increase in pulmonary vascular resistance. When a flowmeter was inserted into the left pulmonary artery, intravenous diphenhydramine caused first an increase and then (in 2 out of 3 experiments) a decrease in left pulmonary arterial blood flow (Table III, Expt. Nos. 5, 6 and 7). The preliminary increase was presumably due to the fact that the drug reached the right lung first and caused vasoconstriction and a temporary diversion of blood flow to the left lung before the drug reached this through the flowmeter circuit. When diphenhydramine was injected directly into the left pulmonary artery only a diminution of blood flow was observed (Table III, Expt. No. 6).

Ethyl Acetoacetate.—This substance was shown by Bagoury and Samaan (1940) to initiate reflexes from the lungs of dogs which resemble those excited by veratrine and amidines in cats. Its interest lies in its closer relationship to a physio-

TABLE III

THE EFFECT OF DIPHENHYDRAMINE ON PULMONARY BLOOD FLOW

LPA denotes left pulmonary artery; MPA, main pulmonary artery. In all experiments the bubble flowmeter was used except in Expt. Nos. 3 and 4 where the density flowmeter was employed. After the injection of the drug, the successive pulmonary blood flow measurements were made as rapidly as possible. I.v. denotes intravenous injection; i.p., injection into the pulmonary arterial tubing.

Expt. No.	Site of Flowmeter	Dose (mg.) and Route of Administration	Vagi	Pulmonary Blood Flow (ml./min.)		Effect on Arterial Pressure (mm. Hg)	
				Before Injection	After Injection	Pulmonary	Carotid
1	MPA	5 i.v.	Intact	188	36	+10, −4	−38
2	,,	5 i.v.	,,	215 207	60	+12	−66
	,,	5 i.v.	Cut	207 207	86	+ 8	−42
3	,,	5 i.p.	,,	167	117	+ 3	−36
4	,,	10 i.p.	Intact	197	86	+1, −3	−76
5	LPA	10 i.v.	,,	13 13	27 28 11 14	+28	−48
		10 i.v.	Cut	30 30 29	40 35 7 15	+20	−60
6	,,	13 i.v.	,,	43 43	42 46 55 27 29 37 44	+20	−50
	,,	10 LPA	,,	40 41	20 15 17 16 16	+ 6	−40
7	,,	10 i.v.	,,	16 16	25 38 30 21 23	+ 8	−44

logical substance (acetoacetic acid) than the other drugs which give rise to pulmonary chemoreflexes. Similar effects were produced in cats, but the doses required, 100 to 200 mg., were much higher than those used by Bagoury and Samaan (1940) in dogs. In cats, intravenous injection of ethyl acetoacetate caused a fall in blood pressure, arrest of respiration, sometimes rapid shallow breathing and occasionally a diminution in tidal air. That the effect on respiration was a reflex due to receptors in the lungs was shown by the fact that there was no change in breathing when ethyl acetoacetate was injected into the left atrium, or after intravenous injection when the vago-sympathetic trunks had been cut. This pulmonary respiratory reflex resembled the pulmonary amidine reflex in that it was not abolished until the cervical vagi were cooled to 0 to 2.5°, which is a much lower

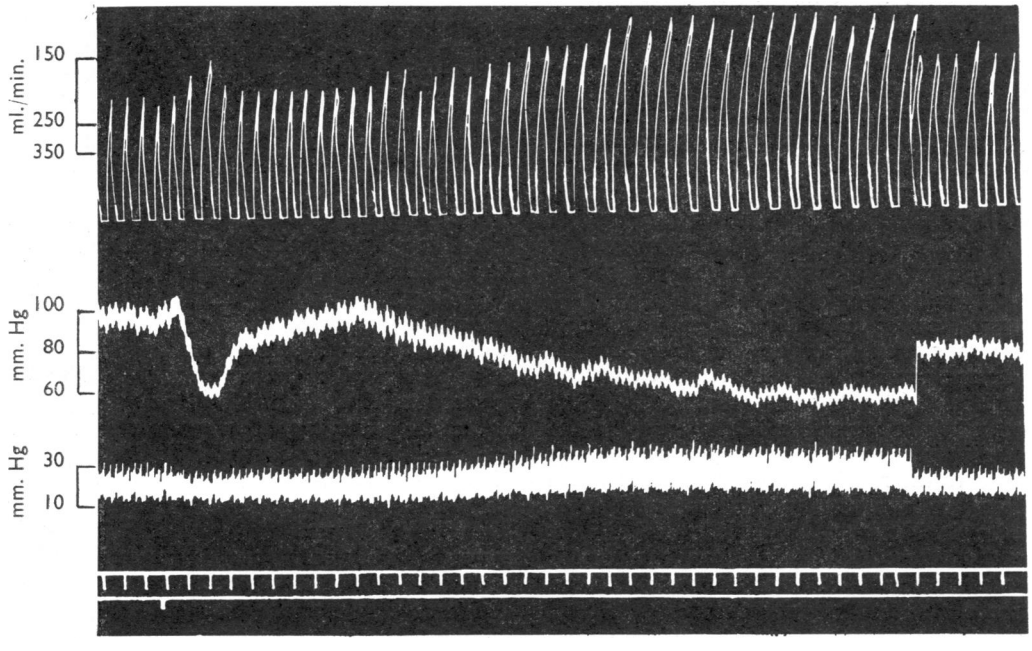

FIG. 3.—Cat 3.0 kg. Chloralose anaesthesia. Records as in Fig. 1. Ethyl acetoacetate (150 mg.) was injected into the distal pulmonary cannula at the signal mark. Partial recovery after an interval of 14 min. is shown on the right.

temperature than that required to inactivate the pulmonary stretch receptors (Dawes and Comroe, 1954). The effect of ethyl acetoacetate on cardiac output and pulmonary arterial pressure was complex (Table I and Fig. 3). There was always a fall in cardiac output, but this was frequently in two phases. The first phase was accompanied by a slight fall or no change and the second by a rise in mean pulmonary arterial pressure, and all these effects were still present after section of the vago-sympathetic trunks. The solution of ethyl acetoacetate was nearly saturated and slightly unstable, so that the two liquids occasionally separated. It was therefore considered possible that the second phase might be due to this effect happening *in vivo*, the droplets of ethyl acetoacetate acting as minute emboli. For comparison chlorbismol was injected in 4 vagotomized cats as a means of producing emboli, and caused a decline in cardiac output and a rise in pulmonary arterial pressure similar to that following administration of ethyl acetoacetate.

Discussion

All the substances tested produced a fall in cardiac output, accompanied either by a fall (veratrine, amidines, ethyl acetoacetate, first phase) or a rise (diphenhydramine; ethyl acetoacetate, second phase) in mean pulmonary arterial pressure. The actions of veratrine and the amidines were abolished by section of the vago-sympathetic trunks in the neck, while those of diphenhydramine and ethyl acetoacetate were not. The known features of the pulmonary and cardiac chemoreflexes are therefore a fall in blood pressure, bradycardia, arrest of respiration or rapid shallow respiration, a fall in cardiac output, frequently a decrease in tidal air, an increase in left atrial pressure, and variable changes in pulmonary arterial pressure.

The small and variable changes in pulmonary vascular resistance following veratrine suggest that it has no important direct or reflex effect on the diameter of the pulmonary vascular bed. The small changes seen were more likely due to passive effects on vessel diameter caused by the decrease in flow, or to the rise in left atrial pressure which sometimes follows its administration. Thus Green, Lewis, Nickerson, and Heller (1944) have shown that there is a non-linear relationship between pressure and flow in certain regions, and therefore an alteration in resistance, which is probably due to a passive expansion of the vessels at high rates of flow and a diminution in their size at low rates of flow. Such non-linear pressure/flow curves have been demonstrated in the lungs of dogs by a number of workers and in isolated perfused cat lungs (Carlill, Duke and Jones, 1957). Similarly in cats with the thoracic contents exposed to the atmosphere in which a flowmeter was inserted into the left pulmonary artery, although there was a linear relationship between pressure and flow over a wide range of variation in flow, this straight line, when extrapolated, cut the axis at a positive pressure probably representing the critical closing pressure (Barer and Nüsser, 1957). The resistance as calculated from the ratio pressure/flow therefore increased as blood flow decreased. Carlill and Duke (1956) showed that raising the left atrial pressure in isolated perfused cat lungs led to a considerable reduction in pulmonary vascular resistance, especially when the left atrial pressure was less than 15 cm. saline. Although it was possible that second order reflexes, such as those described by Daly and Daly (1957a and b), might be initiated by the changes in systemic pressure which these substances produce, and thereby lead to changes in pulmonary vascular resistance, there is, as stated above, no *prima facie* evidence of such changes.

The similarity between the changes in the pulmonary vascular system after amidines and veratrine suggests that the former compounds have also no important direct or reflex action on the pulmonary vessels. Preliminary measurements of resistance after 2-α-naphthylethyl*iso*thiourea (not included in this report because only substituted values for the left atrial pressure were used) showed very small changes in either direction as after veratrine.

Since diphenhydramine and ethyl acetoacetate in the second phase of their action caused a fall in pulmonary blood flow and a rise in pulmonary arterial pressure which persisted after section of the vago-sympathetic trunks, they may have had a direct constrictor effect on the pulmonary vascular tree similar to that caused by 5-hydroxytryptamine (Ginzell and Kottegoda, 1953), which also elicits pulmonary chemoreflexes. Experiments on perfused lungs showed this to be true for diphenhydramine. Diphenhydramine has probably also a direct effect on bronchial muscle (Barer and Nüsser, 1953), which might in itself increase the pulmonary vascular resistance indirectly (Daly and Hebb, 1941). The results obtained with diphenhydramine also emphasize the need for caution in interpreting the effects of drugs on the pulmonary circulation when the flow through only one lung is measured.

The fall in cardiac output which accompanied all the reflexes investigated could have been due to increased pulmonary vascular resistance, diminished venous return, bradycardia, or a combination of these factors. Increased pulmonary vascular resistance can be ruled out as a cause because only after diphenhydramine and ethyl acetoacetate was there a rise in pulmonary arterial pressure, and this was certainly not sufficient to cause right heart failure. For amidines, the most thoroughly investigated substances, it was shown that the right heart output declined even when the output resistance was constant. When the arterial pressure was maintained with a compensator, the right heart output was still reduced, but when the bradycardia was abolished by atropine, a procedure which may also have affected the venous return, there was no longer any significant fall in cardiac output. Taken together, these results suggest that the bradycardia is probably the most important if not the sole factor responsible for the diminished right heart output when these reflexes are excited.

We wish to thank Dr. G. S. Dawes for his help and criticism and Mr. W. A. Ryder for technical assistance.

References

Bagoury, M. M., and Samaan, A. (1940). *J. Egypt. med. Ass.*, **24**, 211.

Barer, G. R., and Kottegoda, S. R. (1958). *J. Physiol. (Lond.)*, **143**, 1.

—— and Nüsser, E. (1953). *Brit. J. Pharmacol.*, **8**, 315.

—— —— (1957). *J. Physiol. (Lond.)*, **138**, 103.

Carlill, S. D., and Duke, H. N. (1956). Ibid., **133**, 275.

—— —— and Jones, M. (1957). Ibid., **136**, 112.

Daly, I. de B., and Daly, M. de B. (1957a). Ibid., **137**, 427.

—— —— (1957b). Ibid., **137**, 436.

—— and Hebb, C. O. (1941). *Quart. J. exp. Physiol.*, **31**, 211.

Dawes, G. S., and Comroe, J. H. (1954). *Physiol. Rev.*, **34**, 167.

—— Mott, J. C., and Vane, J. R. (1953). *J. Physiol. (Lond.)*, **121**, 72.

—— —— and Widdicombe, J. G. (1951). Ibid., **115**, 258.

—— —— —— (1952). *Arch. int. Pharmacodyn.*, **90**, 203.

Ginzel, K. H., and Kottegoda, S. R. (1953). *Quart. J. exp. Physiol.*, **38**, 225.

Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L. (1944). *Amer. J. Physiol.*, **141**, 518.

Jones, J. V. (1952). *Brit. J. Pharmacol.*, **7**, 450.