CURRENT DRUG THERAPY OF ESSENTIAL HYPERTENSION IN RELATION TO SOME OF THE NON-RENAL FACTORS WHICH PARTICIPATE IN THE MAINTENANCE OF BLOOD PRESSURE*

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So much has been said and written about the kidney as an etiological factor in essential hypertension, almost as a unique cause, that it would be of value to review some other aspects of this disorder. Data on the possible significance of some non-renal mechanisms which function in essential hypertension in relation to the treatment of this condition by the drugs in current use would cover certain features, information on which is rather disseminated in medical scientific literature. This data is particularly important because of the emphasis often given to the results of certain types of therapy interpreted as indicating the existence of a specific etiological factor in essential hypertension controlled by this therapy.

It would seem to me that for discussion this theme falls naturally into three parts: firstly, and very briefly, the mechanism that controls the normal blood pressure; then, secondly, those features we have chosen of the haemodynamic and other changes produced by certain possible non-renal aetiological factors which can cause hypertension; and, thirdly and finally, the comparable haemodynamic and other related changes induced by drugs used in current therapy. It is, of course, exceedingly difficult to avoid bringing the kidney into the discussion, but in the context of this review the kidney will not be discussed in its role as the primary factor in the causation of hypertension.

Essential hypertension, for the purpose of this article, consists of a raised blood pressure with no other recognized disease to which this may be attributed. The blood pressure is considered to be raised when it is at a level (for any specific age,

sex and weight group) that clinical experience has shown is associated with an obvious increase in expected morbidity and mortality.

Mechanisms Which Maintain and Control the Normal Blood Pressure

Mankind was well aware of the fact that the pressure of blood was high in the arteries and low in the veins. Long before formal scientific experiment was considered essential, and in their frequent contacts with each other, they had noticed that blood spurted from the arteries and required considerable pressure to stop it, whereas bleeding from the veins was slow, did not spurt; in fact, was continuous and easily stopped by pressure.

The ejection of blood into the great vessels causes variations in pressure and blood flow in these vessels. The sudden distension of the aorta produces a pressure wave which travels along the aorta and its branches, both in the wall of the vessels and the contained fluid. After the passage of this wave the pressure drops to a minimum level (Lewis, 1924). Since these vessels are elastic, the distended walls of the blood vessel exerts a pressure on the contained fluid. The forcing of additional fluid into this distended blood vessel, if the resistance to its forward passage were greater than the pressure required to distend it, would distend it still further because it is elastic. Resistance by the vessel to this distension results in the storing of 'potential' energy in the vessel wall. At the end of the ejection phase the distended vessel acts through its elasticity and stored energy to continue the forward propulsion of the blood until the vessel's distension and potential energy are reduced to an amount equalling that energy needed for outflow.

It will be realized that the more elastic and less

* This is the opening paper of a symposium on hypertension arranged by the Renal Association and delivered at St. Bartholomew's Hospital on June 28, 1956.

rigid the vessel the lower the pulse pressure and, conversely, increased rigidity increases pulse pressure and lowers diastolic pressure. If the amount of blood ejected into a normal vessel were increased, which would increase diastolic, systolic and pulse pressures, the vessel would become more distended. Were this distension to reach the elastic limit of the vessel, it would behave as a rigid tube. Under these two circumstances, i.e. rigid vessel and increased output, both systolic and diastolic pressures would be elevated, but the pulse pressure would increase considerably. The rate of propagation of the pressure wave in the arteries is a good measure of the elasticity of the wall of these vessels (Bramwell *et al.*, 1923).

In the vessels containing the circulating blood the greatest drop in pressure occurs at the arterioles, since here the surface area is high, and therefore the frictional resistance is high, and also the resistance induced by variation in the cross-sectional area of the arterioles is most marked. The frictional resistance is related to the square of the velocity of blood flow as well as surface area of vessel walls, and this velocity of flow is proportional to the cross-sectional area. Arteriolar control of blood pressure is therefore of major importance.

The pulse pressure is maintained by the close interplay of five factors. These are: (1) the cardiac output, which increases the systolic, diastolic and pulse pressures; (2) the peripheral resistance, increase of which increases the systolic and diastolic pressure, but lowers the pulse pressure; (3) the amount of blood in the arteries, which produces comparable effects to heart output; (4) the viscosity of the blood; and (5) the elasticity of the vessel walls. From what I have already said, the significance of each of these can be readily appreciated. Of all these changes, in human hypertension that of blood viscosity would seem to be the least important. (In late renal disease viscosity is low, whereas in Gaisbock's syndrome the viscosity is high, and both are associated with hypertension.) In essential hypertension viscosity is normal. Changes in cardiac output per minute and per beat, of course, do not occur as aetiological factors in the causation of essential hypertension.

Increased total peripheral resistance is the factor of the greatest importance to us in the theme we are considering, i.e. essential hypertension. Increased total peripheral resistance has a marked effect, particularly upon the diastolic pressure, which is considerably elevated. Decreased peripheral resistance of necessity—other factors remaining constant—reduces the diastolic pressure. Nevertheless, the high pulse pressure of essential hypertension must mean the action of some

additional factor to this, e.g. a change in elasticity of the vessel walls. The systolic and diastolic blood pressures in an artery are much influenced by the degree of contraction or dilatation of its branches.

The arterioles are supplied by vasomotor nerves which effectively produce vasoconstriction or vasodilatation. Sympathetic fibres exert the vasoconstrictor influence and arise in the thoracolumbar chain. The vasomotor effects (i.e. the activity of the vasomotor nerves) are under the influence of a vasomotor centre situated in the medulla. That the vasomotor centre continually exerts what is called a 'tonic' effect on the arterioles is shown by the fact that separation of part of the arteriolar bed from this centre will—for a while, anyway—result in dilatation of the affected vessels and a local fall in blood pressure. However, it is well known since the experiments of Goltz in 1864 that sympathetic denervation of limbs and splanchnic viscera is followed within a few weeks by recovery of blood pressure. In many normotensive animals, e.g. in the dog and cat, even after total extirpation of the paravertebral ganglia, and thoracic and abdominal chains, the blood pressure recovers to practically its normal value (Cannon *et al.*, 1929; Bacq *et al.*, 1934).

The tone of these vessels is controlled via this vasomotor centre, which is in constant receipt of afferent impulses from various regions of the body, including, of course, those from the many specialized areas in the blood vessels (Hering, 1927; Heymans *et al.*, 1933; Katz and Saphir, 1933; Nonidez, 1935; Takino and Watanabe, 1937; Winder, 1937; Dawes, 1952), such as the carotid body and aortic nodes. The centre also receives afferent impulses from the nervous centres of the brain, from the general somatic and visceral afferents (Guttmann and Whitteridge, 1947) and from chemical changes in the blood. Glossopharyngeal and vagal afferent fibres from the baroreceptors of the carotid sinus, aortic arch and elsewhere control blood pressure via arteriolar calibre (and therefore peripheral resistance) and also heart rate. The control of blood pressure with change in posture is usually achieved via this mechanism, effected via the sympathetic nerves. Tilting from the supine to the erect position causes little fall in arterial blood pressure, a slight increase in heart rate, a fall in right auricular pressure and cardiac output and a decrease in upper limb blood flow, which does not occur if the limb is sympathectomized (Brigden *et al.*, 1950).

Emotional factors may affect blood pressure, often in diametrically opposite ways (Hines and Brown, 1933; Alam and Smirk, 1938; Lewis, 1932; Barcroft *et al.*, 1944), via arteriolar tone, either by virtue of their effect on vasomotor

centres, by means of changes in heart activity and even by virtue of their effect on the endocrine glands.

Finally, metabolites and the many known or postulated humoral factors may also act directly on the arterioles and hence affect blood pressure.

Thus carbon dioxide will affect vasomotor tone via the carotid body and aortic bodies, as well as by direct action on the vasomotor centres. The raised blood pressure associated with intracranial lesions would appear to be mediated via chemical changes in the vasomotor centres.

Essential Hypertension

As far as essential hypertension is concerned, an increase in total peripheral resistance due to an increased resistance in the arterioles is in some degree invariably present and is the one constant feature in every description of the condition, as is seen in patients or when it is simulated in certain experimental animals (Wiggers, 1932 and 1938). It is in relation to the factors which lead to the production of this increased resistance that there is so much doubt or even ignorance.

Since in the Goldblatt experiment the hypertension is caused by generalized arteriolar constriction and increased total peripheral resistance, many clinicians and investigators have accepted this type of 'renal mechanism' as the basis for the mechanism of essential hypertension in man. However, there has not as yet been produced evidence revealing a similar mechanism in all or even many cases of human essential hypertension. The treatment of hypertensive patients with substances whose activity is directed against those substances which are postulated to be the cause of hypertension in the Goldblatt animal has been far from successful (Goldring and Chasis, 1944).

That there occur occasional patients with what is clinically a syndrome indistinguishable from essential hypertension, and who are found on full investigation to have a unilateral renal lesion, is well known. Removal of this renal lesion results in a permanent return to normotensive levels in a fortunate few of these. Nevertheless, we cannot neglect the majority without these demonstrable renal lesions, nor can we, on the other hand, neglect the possibility of a disturbance in the renal circulation without a demonstrable disturbance of renal function. Kubicek (1950) and his co-workers have shown that when the sympathetic nerves to the kidney are stimulated the renal blood flow is decreased and the systemic arterial pressure is elevated. However, with continued stimulation the renal circulation, as measured by the standard clearance techniques, returns to normal, although the blood pressure remains elevated. It is interesting to speculate on

this and suggest that nerve stimulation has continued to evoke renal circulatory changes which are important in the maintenance of hypertension, but are not demonstrable by the procedures and techniques as yet available. If this is, in fact, true, then it might invalidate the conclusion that we can exclude renal factors in essential hypertension when our currently used renal function tests are normal.

The maintenance of the circulation and circulatory homeostasis at any level of blood pressure involves the sympathetic-adrenal system and its various afferent paths, and in particular those from the carotid sinus and aortic arch. In this pattern we must include the heart, the small arteries and arterioles, possibly the large arteries, the precapillary sphincters and even the veins.

Section of the afferent pathway (moderator nerves) in man induces an immediate elevation in blood pressure which may be very persistent. The renal element in this neurogenic hypertension is rarely of any significance, since renal denervation results in little fall of blood pressure (Heymans *et al.*, 1935; Grimson, 1941), and in animals even a preceding nephrectomy will not prevent the acute elevation of pressure resulting from moderator nerve section (Thomas, 1941). In neurogenic hypertension the pulse rate is raised, the heart output is raised, total peripheral resistance is normal, but blood flow through the extremities is raised. Nor is the blood pressure level maintained with any degree of constancy; on the contrary, it shows marked fluctuation even greater than that in many 'labile' hypertensives (Green *et al.*, 1935; Boyd and McCullagh, 1938). This pattern is, of course, vastly different from that of essential hypertension, where heart rate and heart output remain normal, total peripheral resistance is elevated, but blood flow through the extremities remains normal.

It is worthwhile recalling here the haemodynamic changes induced by nor-adrenalin and adrenalin, since a phaeochromocytoma may be associated with a persistent elevation of blood pressure, and this may be pertinent to the aetiology of essential hypertension. Nor-adrenalin produces no change or a fall in both heart rate and cardiac output, whereas adrenalin elevates both. Nor-adrenalin increases total peripheral resistance and therefore elevates the diastolic and systolic pressures and lowers the pulse pressure, whereas adrenalin will reduce total peripheral resistance, raising the systolic and lowering the diastolic pressure. Nor-adrenalin will diminish the blood flow through the extremities, whereas adrenalin may increase it. Both will reduce the renal blood flow, but less often the G.F.R., and, of course, the haemodynamic effects of both adrenalin and

nor-adrenalin are nicely blocked by adrenergic blocking agents which have proved themselves of little real use in the treatment of essential hypertension.

Neurogenic hypertension is characterized essentially by a dramatic response to sympathectomy and to the chemical block of adrenergic blocking agents. In human essential hypertension we only very occasionally meet the dramatic and sustained fall in blood in response to sympathectomy. In general, essential hypertension in its responses to these agents far more closely resembles the Goldblatt type of experimental renal hypertension.

Wilkins (1950) quotes an interesting case in this respect. A young adult male with a pheochromocytoma of about four years' duration and an 'almost' sustained hypertension was found to show the renal clearance changes characteristic of essential hypertension. Removal of his pheochromocytoma resulted in an immediate return of his blood pressure to normal levels. Renal biopsy at the time of the operation showed minimal vascular changes in the pre-arteriole, arteriole and glomerulus. Nevertheless, these same renal function tests, repeated 18 months after operation, with his blood pressure still normal, were identical with those found before operation and whilst he was hypertensive. An older patient with whom I am personally acquainted, and with a more intermittent hypertension due to this cause, revealed identical PAH and creatinine clearances during the late stages of the hypertensive episodes and in the normotensive periods both before and after operation.

We can, without generalizing, say that in these patients the functional changes in the kidney, as demonstrated by the clearance techniques, were not responsible for the episodes of sustained hypertension, but could very well have been caused by the hypertension inducing certain persistent changes in the renal vessels.

Pickering (1955), as a theme in his thesis on high blood pressure, has pointed out that examples now apparently exist of the persistence of a high blood pressure, even though the initiating abnormality has been removed or has subsided.

In human 'non-renal' essential hypertension, in which the patient is symptomless and not in heart failure—in fact, in just those cases which are found during routine examinations for insurance and other purposes, beyond the raised blood pressure and increased total peripheral resistance, minimal changes in R.P.F. (renal plasma flow) and G.F.R. (glomerular filtration rate), and small increases in F.F. (filtration fraction) and renal resistance—no other change need be present, be it anatomical, physiological or biochemical, and, in so far as these are not covered already, psychi-

atric or endocrinological. In most cases even the R.P.F. and G.F.R. and the calculations based on these are within the normal range, though usually in the lower levels. Though under basal conditions these patients show no pathological changes, they do not necessarily remain normal when a moderate load is thrown upon them. Thus Perara (1950) was able to show that patients with essential hypertension were more sensitive to the pressor action of DCA and sodium chloride than were normotensive individuals.

Chasis (1950), as a result of his studies, does not, however, favour the view that any change in renal haemodynamics is causally related to the genesis of essential hypertension. To arrive at this conclusion he gives three important observations, namely, the failure to demonstrate changes in the renal circulation early in hypertensive disease, the fact that with the progress of the disease there is an accompanying deterioration of renal circulation explained satisfactorily by the decrease in the number of vascular channels and functional nephrons, and, finally, the fact that the changes in the renal circulation proceed to an equal degree and in a parallel rate in the two kidneys.

There would appear to be evidence to incriminate neurological mechanisms (Wolf *et al.*, 1950; Wolf *et al.*, 1948; Walter *et al.*, 1937; Kottke *et al.*, 1947; Graham, 1945) and data also suggest hereditary (Ayman, 1934; Platt, 1945; Barnes and Browne, 1945) or genetic (Stocks, 1938; von Verschuer *et al.*, 1929; Klemola, 1938; Weitz, 1941; Soby, 1948; Hamilton *et al.*, 1954) factors and possibly to incriminate endocrine changes (Selye, 1946; Heinbecker, 1948) and environmental factors from occupational and social status in a community (Janeway, 1913; Ehrstrom, 1918) to even the level of the state of civilization (Harris, 1927; Donnison, 1929; Fishberg, 1939; Weiss and Prusmack, 1938) or the nutrition of the community itself.

All hypotheses, simple or complex, as to the causation of essential hypertension have succeeded in so far as they have convinced their sponsor of the correctness of his hypothesis and all have also failed. They have failed because they were incapable of proof or could not be proved, either because the hypothesis did not lend itself to any reasonable therapeutic approach to the clinical problem of essential hypertension or because the therapeutic trial was a failure. I might even facetiously suggest that the main appeal to many, of the 'renal' approach to all cases of essential hypertension, is that we can or should be able to some extent influence the function of the kidney or, alternatively, we can remove it, and the same applies to the idea of a 'neurogenic' primary cause.

It would not now be out of place to consider the relationship of the haemodynamic and other changes induced by certain drugs used in the treatment of essential hypertension to the brief and elementary outline which I have so far given.

Changes Induced by Drugs Used in Current Therapy

The list below does not by any means endeavour to cover exclusively all the agents in current clinical and clinico-experimental use, but is, nevertheless, comprehensive enough to indicate the lines of current clinical approach via drug therapy.

SOME HYPOTENSIVE DRUGS USED IN THE TREATMENT OF ESSENTIAL HYPERTENSION

- I. *Adrenergic blocking agents*
 Imidazolines (benzazoline or 'Priscoline').
 β -haloalkylamines (dibenamine and dibenzylamine).
 Chlorpromazine ('Largactil').
- II. *Inhibitors of sympathetic vasomotor activity* (acting centrally)
 Rauwolfia alkaloids (reserpine, rescinnamine, canescine).
 Hydralazine ('Apresoline').
 Dihydrogenated ergot alkaloids.
 ?Chlorpromazine.
- III. *Drugs affecting the vascular reflexes*
 Veratrum alkaloids.
- IV. *Ganglion blocking agents*
 TEA (tetraethylammonium).
 Methonium compounds (hexamethonium, pentamethonium, pentolinium; 'Anso-lysen').
 Azamethonium ('Pendiomide').
 Mecamylamine ('Inversine').
 Chlorisondamine ('Ecolid'; 'Su 3088').
 139c55 ('Presidal').
- V. *Drugs acting directly on vascular smooth muscle*
 Nitrites, papaverine.
 ?Chlorpromazine.
- VI. *Miscellaneous*
 Thiocyanates.
 Sodium nitroprusside.

In recent years combinations of two or more agents have been advocated and tried in treatment. In general, the pharmacology of these mixtures does not differ from that of the individual agents of which they are constituted.

I would like to emphasize that this is a brief review of certain pharmacological effects of some of the hypotensive drugs used in treatment and not a review of the results of the treatment of essential hypertension by drug therapy.

The few drugs mentioned in sections I, V and VI are dealt with first, since they are not used to any great extent as hypotensive agents in the

current long-term therapy of essential hypertension.

The *imidazolines* (e.g. benzazoline or 'Priscoline') and the *benzodioxanes* have been found to be useless in the treatment of essential hypertension.

'Priscoline,' though able to produce considerable and significant adrenergic block and marked peripheral vasodilatation in doses well within the safe tolerated dose in man, nevertheless produces no fall in blood pressure (Ahlquist *et al.*, 1947; Grimson *et al.*, 1948). The cardiac stimulant effect of this drug and the increase in cardiac output more than outweighs the vasodilatation. In fact, a massive dose of 'Priscoline' taken in a suicidal attempt (Moller, 1947) caused no lowering of the blood pressure. Moreover, we know that 'Priscoline' and the benzodioxanes may on occasions cause quite an alarming increase in blood pressure in patients with hypertension.

The β -haloalkylamines combine irreversibly with receptors on the effector cells and have a very long duration of action and might at first seem hopeful therapeutic agents for the treatment of essential hypertension. However, with but few exceptions, their use alone in man for the treatment of essential hypertension has been unsuccessful.

Dibenzylamine, otherwise called dibenylamine or phenoxybenzamine, does not interfere with ganglionic or nervous transmission, but specifically inhibits the activity of adrenalin, nor-adrenalin and many adrenergic pressor substances. It appears essentially to block the motor and not the inhibitory effects and it does this for 5-hydroxytryptamine (Erspamer, 1953) and most sympathomimetic amines as well as adrenalin and nor-adrenalin.

Small doses given intravenously to normotensive humans produce little or no fall in blood pressure, whereas larger doses produce a slowly occurring but moderate fall. In hypertensive patients the fall in blood pressure may be more marked, but is exceedingly variable in degree. Cardiac output, renal blood flow and cerebral blood flow are unchanged. Blood flow in the extremities is considerably increased. Postural hypotension and syncope occur particularly markedly. Reflex pressor responses to asphyxia or anoxia are often reversed (by dibenamine). Compensatory vasomotor reflexes are blocked, but not the compensatory cardiac reflexes elicited by postural hypotension. Tachycardia occurs frequently.

Intravenous or intramuscular injection of 25 to 50 mg. of *chlorpromazine* will in man produce an acute fall in both systolic and diastolic blood pressure with a prominent postural effect. With the hypotension we get tachycardia and a warm, dry skin and usually facial pallor (Dobkin *et al.*, 1954;

Foster *et al.*, 1954). Much of the action of chlorpromazine is due to its anti-adrenalin and anti-nor-adrenalin activity (Courvoisier *et al.*, 1953; Foster *et al.*, 1954), but some of the evidence can be interpreted as suggesting a central effect in reducing vasoconstriction (Foster *et al.*, 1954; Dasgupta and Werner, 1954). The drug has apparently little direct effect on the heart and, except for the tachycardia and a minor effect on the T-wave, it has little effect upon the electrocardiogram (Laborit *et al.*, 1952a and b). The generalized vasodilatation reduces peripheral resistance and lowers the blood pressure. Cardiac output is, however, usually increased (Shackman *et al.*, 1954). Reflex vasoconstriction via the sino-aortic reflexes is reduced or abolished and vasoconstriction after haemorrhage or traumatic shock does not occur. A direct effect on peripheral vessels is shown by intra-arterial infusion, which may increase the blood flow through the infused hand by as much as 50 per cent. (Ginsburg and Duff, 1956).

Nitrites cause a fall in blood pressure with a marked diminution of pulse pressure. In most cases the diastolic fall rarely exceeds 20 mm. and usually is less than 10 mm. Occasional far greater falls may occur.

Usually cardiac output is unchanged or slightly decreased, but with sudden hypotension it may be increased with an increase in heart rate, diminution in stroke volume and a decrease in venous return. The E.C.G. is usually unchanged, though in some hypertensive patients the inverted T-wave in leads V₅ or V₆ may transiently become upright. The G.F.R. is unchanged or slightly reduced and R.P.F. is diminished and F.F. increased.

With the use of sodium or potassium *thiocyanate* (sulphocyanate) orthostatic hypotension does not occur, nor does peripheral vasodilatation. Detailed studies of the cardiovascular and renal effects of this drug in animals, and particularly in man, do not appear to have been carried out. Corcoran and his collaborators (1945) found little change in renal function in man. The heart output of dogs may be reduced. Serum sodium level may be reduced slightly and sodium output may possibly be increased temporarily.

Finally in this section we come to papaverine, which apparently relaxes the smooth muscle of the larger blood vessels, especially the coronary vessels, the pulmonary vessels and the peripheral vessels. It increases cerebral blood flow and coronary blood flow. It has a direct action on heart muscle and may induce various arrhythmias as a toxic effect. It does not cause hypotension and, as far as I know, it is of no value whatsoever in the treatment of essential hypertension.

The substances derived from *Rauwolfia ser-*

pentina and certain related species represent a very frequently used group of hypotensive agents.

The pharmacological activities of the *rauwolfia* alkaloids have been divided into three categories:

- (i) Hypotensive.
- (ii) Sedative or 'tranquillizing.'
- (iii) Miscellaneous:
 - Effect on heat centre.
 - Bradycardia-producing effect.
 - Miosis effect (pupillary constriction).
 - stimulating effect on gut.
 - Antagonistic action to thyroxin.
 - Lowering of convulsive threshold.

This division is not pharmacological, but therapeutic, since the *rauwolfia* derivatives are used now for either their hypotensive or their sedative effects.

Rauwolfia is believed to produce hypotension by acting on the central nervous system at the hypothalamic level, and it is believed that a central inhibition of sympathetic activity causes the hypotension and bradycardia. The vasodilatation which causes the fall in blood pressure is mediated over the sympathetic nerves apparently as the result of inhibition of reflex sympathetic vasoconstriction. Blood pressure changes have been reported in different series as occurring in from 30 to 80 per cent. of cases (Kauntze and Joiner, 1951; Locket, 1955; Wilkins and Judson, 1953). Postural hypotension occurs only rarely. Those alkaloids which are actively hypotensive do not appear to have any adrenolytic, antihistaminic or ganglion blocking activity.

Rauwolfia interferes with certain reflex rises of blood pressure mediated by the central nervous system (normal response to anoxia or carotid sinus occlusion). Cardiac output and arterial oxygen saturation do not appear to be affected, nor is the coronary blood flow reduced during the hypotension induced by the drug. However, with large doses of the alkaloids there would appear to be some slight fall in cardiac output initially in man and a fall after some hours in anaesthetized animals. We have been unable to detect any change in G.F.R. and R.P.F. and creatinine clearance with the mixed alkaloids, though occasionally the G.F.R. may be reduced. Similar results have been obtained by other workers with reserpine (Andreae and Smith, 1955; Moyer *et al.*, 1954; Hughes *et al.*, 1955). Sodium and water retention may occur in some cases and particularly after reserpine.

According to Shore, Silver and Brodie (1955) and Pletscher, Silver and Brodie (1955), reserpine releases 5-HT (5-hydroxytryptamine) in the body, causing depletion of tissue 5-HT and the appearance of a metabolite of 5-HT in the urine. Depletion of 5-HT in brain extracts has been observed by Paasonen and Vogt (1956). That the

flooding of the body with 5-HT released from the tissues is the cause of some of the effects of reserpine is favoured by much of the work to date, including the observation that LSD 25 (lysergic acid diethylamide) will temporarily diminish the apathy in animals caused by intracerebral reserpine (Gaddum and Vogt, 1956).

An intravenous injection of 5-hydroxytryptamine in man produces variable but distinctly unpleasant effects. Tightness in the chest occurs at first with a tingling and pricking sensation all over the body, then generalized aching and numbness, weakness, an unpleasant fullness and irritation in the nose with a desire to sneeze, bradycardia, difficulty in breathing, diarrhoea often with tenesmus, frequency and strangury, and a very variable effect on the blood pressure. It is primarily a vasoconstrictor and cardiac stimulant. In hypertensive patients frequently a pure depressor response may occur; more often it produces increased hypertension comparable to its pressor effect in normotensives (Spies and Stone, 1952). Though it produces a sensation of strangury, it is markedly anti-diuretic. In rats and dogs there may be a reduction in G.F.R. and also some little fall in R.P.F. (Erspamer, 1954; Abrahams and Pickford, 1956).

It is obvious that effects produced by an injection of 5-hydroxytryptamine on the cardiovascular system in man, though similar, are not identical with those of rauwolfia in man.

This group of drugs must be added to morphine and pontine haemorrhage in the differential diagnosis of pinpoint pupils. This pupillary constriction is often one of the first effects of the drug to appear and the last to disappear.

The vascular and probably most of the cardiac effects of *hydralazine* are centrally mediated, but its effect on afferent receptors has not been entirely ruled out. Adrenergic blockade by *hydralazine* probably plays little part in its therapeutic use.

It causes a marked increase in renal blood flow in normal man and also in patients with hypertension. It also increases heart rate, stroke volume and cardiac output (Reubi, 1950; Croseley *et al.*, 1954; Wilkinson *et al.*, 1952). The cardiac effects are independent of alterations in blood pressure. Skin blood flow is usually unchanged and muscle blood flow may decrease. In the spinal animal this reduction in blood pressure does not occur.

In a recent investigation on the acute effects of this drug, Judson and his co-workers (1956) found that intravenous *hydralazine* caused an increase in cardiac output of about 16 to 28 per cent. in all types of heart disease, particularly the 'compensated' hypertensives. Pulmonary arterial pressure showed little change or increased slightly also in 'compensated' hypertensives, but may show a moderate reduction of pressure in occasional

hypertensives in congestive failure. The right ventricular and diastolic pressures followed the same pattern. The fall in systemic blood pressure was comparable in all groups. Tachycardia occurred in almost all patients. The total peripheral resistance fell in all and particularly in those hypertensives with congestive failure. The total pulmonary resistance showed little change.

R.P.F. increased about 35 per cent., the greatest percentage increase being in those hypertensives in congestive failure, and the G.F.R. showed practically no change in the compensated, but might increase up to 23 per cent. in the hypertensives in failure. Sodium and water excretion showed no change in the compensated hypertensives, but showed a considerable increase in those hypertensives in failure with high glomerular filtration rates. Potassium excretion varied, in general following the glomerular filtration rate. When circulatory collapse occurred excretion of sodium and water was considerably reduced. However, *hydralazine* could not counteract or prevent the reduction in sodium and water excretion when a decrease was artificially induced.

Others have found no change or a fall in G.F.R. to accompany the increased R.P.F., this R.P.F. returning to its previous figure with continuing use of the drug. The cerebral blood flow remains unchanged. Transient E.C.G. changes are well recorded, usually ST depression and T-wave inversion, particularly in the chest leads V₄, V₅ and V₆. Centrally mediated cardiovascular reflexes, such as the 'Valsava' overshoot, are inconsistently blocked, but postural hypotension is a not infrequent side-effect in ambulatory patients.

The *dihydrogenated ergot alkaloids* are presumed to act centrally, central stimulation of the vagal nuclei causing the bradycardia, and central inhibition of the sympathetic postural cardiovascular reflexes probably producing a slight decrease in vascular resistance in several areas, particularly in the extremities. Orthostatic hypotension may be very marked. With the hypotension there is usually a considerable reduction of pulse pressure.

'Acute' clinical trials with *dihydroergocornine* showed that it caused postural hypotension, abolition of vasopressor overshoots to blood pressure lowering procedures (e.g. *valsava* procedure), and that it also produced bradycardia. In general, the cardiac output was unchanged or increased, renal and hepatic blood flow fell initially with the onset of hypotension, but tended to return to normal in spite of persistence of the hypotension. The G.F.R. may be diminished, too. The peripheral limb blood flow remained unchanged or even increased and the cerebral blood flow remained unchanged (Freis *et al.*, 1949; Hafkenschiel *et al.*, 1950).

Dihydroergotamine, dihydroergocornine and dihydroergokryptine show antagonism to 5-hydroxytryptamine, though not as marked as LSD 25 (Gaddum and Hameed, 1954).

At least 17 alkaloids have been isolated from *veratrum* species or *sabadilla* seeds. Eleven of these are alkylamine esters, which are the most potent in the group.

The *veratrum* esters stimulate receptors in the left ventricle and possibly lungs, carotid sinus and coronary vessels, the Bezold reflex (Krayner and Acheson, 1946). This afferent activity is transmitted via the vagi to the C.N.S. and in turn causes a reflex diminution in central vasoconstrictor impulses, i.e. a diminution in activity over the splanchnic and probably other sympathetic nerves. This causes vasodilatation and a fall in blood pressure. Increased reflex vagal activity causes a bradycardia (Dontas, 1955). This reflex mechanism is not confined to the *veratrum* alkaloids, but is shown by a miscellaneous collection of substances which includes 5-hydroxytryptamine and certain amidines (Dawes and Comroe, 1954).

There is a high degree of correlation between the emetic dose and hypotensive dose in the pigeon, dog and human for the pure *veratrum* derivatives (Swiss and Mountain, 1955).

At the height of the hypotension the E.C.G. may reveal T-wave inversion in V₃ and V₄, which can be reversed by atropine and *not* oxygen. Postural reflexes are normal and, unless severe hypotension has been induced, in which case postural syncope may occur, vasopressor overshoot reactions are not reduced. Cerebral blood flow remains unaltered (Wilkins, 1951). The R.P.F. and sodium and water excretion may be decreased transiently with little effect on renal function (except in the presence of uraemia (Meilman, 1953)) or cardiac output.

The *ganglion blocking agents* as exemplified by hexamethonium interfere with the transmission of impulses at autonomic ganglia and render the post-ganglionic neurone refractory to pre-ganglionic stimulation. Paton and his collaborators (Paton, 1951, 1952 and 1954; Paton and Zaimis, 1952; Zaimis, 1955) showed that these drugs do not interfere with the release of acetylcholine in the ganglion and do not affect the post-ganglionic nerve trunks or the vascular system directly, nor do they apparently possess histamine liberating, muscarinic or curarizing activity.

The effect on the cardiac output in the recumbent is given variously by different authorities, but the majority find a slight decrease.

Hexamethonium intravenously in small doses may cause a slight fall in blood pressure, but cardiac output measured in the recumbent position

may increase with a fall in total peripheral resistance. Large doses of the drug may produce a slight fall in cardiac output measured in the recumbent position with a variable effect on the peripheral resistance, ranging from a slight fall to a slight increase. In general, however, the total peripheral resistance is unchanged or diminished in hypertensives not in heart failure. Assumption of the erect position is accompanied by a fall in cardiac output (as normally occurs). Hypotension is markedly accentuated. The fall in output when erect and the accompanying fall in venous and possibly right auricular pressure is believed to be due to the failure of occurrence of postural vasoconstriction (Grob *et al.*, 1953). It has been reported that cardio-pulmonary volume has been increased by the drug (Gilmore *et al.*, 1952).

There may be an initial fall in R.P.F., but this is brief and usually not maintained. G.F.R., sodium excretion and urine volumes are reduced in most cases, but rapidly return to their previous figures, except occasionally for urine volume, which may remain depressed for some hours.

Coronary blood flow remains unchanged by hexamethonium (Grob *et al.*, 1953). The blood flow through the foot is increased and usually cerebral blood flow remains unchanged.

In congestive heart failure due to hypertension there is usually an increase in cardiac output associated with a fall in venous and right heart pressure and a fall in blood pressure and total peripheral resistance (Freis, 1953; Kelley *et al.*, 1953).

The normal rise in blood pressure produced by exercise may, after this drug, be converted into a fall and this by doses of drug which only have a slight or moderate effect on the upright blood pressure (Rønnevig-Jessen, 1953; Fowler and Guz, 1954).

The *tetraethylammonium* ion can cause the release of adrenalin and nor-adrenalin from the adrenal glands; it has a neuromuscular blocking action and, interestingly enough, it apparently causes paraesthesiae by stimulating sensory nerve endings.

The drug 139c55 ('Presidal'), we have found follows the pattern of a very potent ganglion blocking agent. We could, however, demonstrate no change in the G.F.R. or R.P.F. in most patients. Bradycardia was usually present during the hypotension and this bradycardia was not appreciably altered by the largest doses of atropine that we could safely give, nor had the atropine any effect on the blood pressure (Lockett, 1956). Effort seemed to augment the hypotensive activity of this drug.

Azamethonium ('Pendimid') follows the expected ganglion-blockade pattern already de-

scribed, but has a few peculiarities of its own. It has been shown that azamethonium interferes with the afferent autonomic pathway and this should be compared with the paraesthesiae of the tetraethylammonium ion (Bein and Meier, 1951).

The initial depression of blood pressure observed with azamethonium is frequently associated with a sharp depression in R.P.F. and an increase in renal vasoconstriction, which usually corrects itself as infusion of the drug continues. Hypotension is associated with decreased G.F.R. water excretion and sodium excretion. Excretion of potassium is low at first, but later will rise even though hypotension persists. Raising the blood pressure to normal with nor-adrenalin corrects all these, even though the azamethonium infusion continues. The same phenomena occurred with hexamethonium, hence the changes recorded must be due to the blood pressure fall and not the drug (Noyer *et al.*, 1955a).

The laboratory observations of some of the original workers with *mecamylamine* (3-methylaminoisocamphaine hydrochloride) (Moyer *et al.*, 1955b) revealed partial ganglion blockade, but could not rule out other additional components participating in the production of the hypotension. In dogs these workers found that the G.F.R. and R.P.F. did not appear to alter during the 30 minutes of initial hypotension, but later showed a significant reduction.

Recently (1956) Freis and Wilson report that they could not demonstrate as marked an inhibition or abolition of homeostatic responses with this drug in man as they have with pentolinium or hexamethonium (they used the overshoot of blood pressure following the valsalva manoeuvre, the cold pressor test, skin temperature gradient between the digits and umbilicus and reflex vasoconstrictor responses as revealed by digital plethysmography).

Changes in heart size and E.C.G. pattern were as with other ganglion blocking agents. Renal function pattern change, too, followed those recorded with other ganglion blockers.

Chlorisoindoline does not differ appreciably from pentolinium in its pattern of action as a ganglion blocking agent (Grimson, 1955; Grimson *et al.*, 1955a and b).

Cavallito *et al.* (1955) and O'Dell *et al.* (1955) recently reported the presence of potent hypotensive activity among a series of unsymmetric bis-quaternary carboline and isoquinoline derivatives and Lape *et al.* (1956) similar activity in a series of unsymmetric bis-quaternary tropane derivatives. Also some members of these three series showed a 'biphasic' hypotensive pattern interpreted as revealing a central as well as a peripheral component in the *hypotensive response*.

Conclusion

From the foregoing recital of data several very obvious points become apparent.

1. If there is strong clinical evidence that some of these more frequently used hypotensive agents are effective in relieving symptoms, inducing a regression in progressive pathological changes and prolonging life, then they must do this by means which do *not* change to normal the haemodynamic-vascular reflex pattern of these ill patients.

2. The only property these agents share is an ability to lower the blood pressure and they are effective clinically only in so far as they cause a fall in blood pressure and independent of any other changes that they may induce.

3. The most universally effective agents would appear to be those most obviously 'neuronal' in their action—not wholly peripheral nor wholly central nor purely humoral.

4. Responses to these agents cannot, therefore, be used as evidence for the existence of any particular aetiological factor in the causation of essential hypertension.

5. Whatever the status of the kidney in this disorder, the effectiveness of the current hypotensive agents in essential hypertension would appear to be entirely independent of any changes produced in the kidney in so far as these are recorded by the R.P.F., G.F.R., F.F., urine volume, renal resistance and sodium and potassium output.

BIBLIOGRAPHY

- ABRAHAM, V. C., and PICKFORD, M. (1956), *Brit. J. Pharmacol.*, **11**, 35.
- AHLQUIST, R. P., HUGGINS, R. A., and WOODBURY, R. A. (1947), *J. Pharmacol.*, **89**, 271.
- ALAM, G. M., and SMIRK, F. H. (1938), *Clin. Sci.*, **3**, 259.
- ANDREAE, E., and SMITH, F. E. (1955), *Amer. J. med. Sci.*, **230**, 45.
- AYMAN, D. (1934), *Arch. intern. Med.*, **63**, 899.
- BACQ, Z. M., BROUHA, L., and HEYMANS, C. (1934), *Arch. int. de pharm. et de therap.*, **48**, 429.
- BARCROFT, H., EDHOLM, D. G., McMICHAEAL, J., and SHARPEY-SCHAFER, E. P. (1944), *Lancet*, **i**, 489.
- BARNES, J., and BROWNE, F. J. (1945), *J. Obstet. Gynaec. Brit. Emp.*, **52**, 1.
- BEIN, H. J., and MEIER, R. (1951), *Schweiz. med. Wschr.*, **81**, 446.
- BOYD, J. D., and MCCULLAGH, G. P. (1938), *Quart. J. exp. Physiol.*, **27**, 293.
- BRAMWELL, J. C., DOWNING, A. C., and HILL, A. V. (1923), *Heart*, **10**, 289.
- BRIDGEN, W., HOWARTH, S., and SHARPEY-SCHAFER, E. P. (1950), *Clin. Sci.*, **9**, 79.
- CANNON *et al.* (1929), *Amer. J. Physiol.*, **89**, 84.
- CAVALLITO, C. J., GRAY, A. P., and O'DELL, T. B. (1955), *Arch. int. Pharmacodyn.*, **101**, 38.
- CHASIS, H. (1950), 'Symposium on Hypertension,' p. 234, University of Minnesota Press, Minneapolis, U.S.A.
- CORCORAN, A. C., and PAGE, I. H. (1940), *Proc. cent. Soc. clin. Res.*, **13**, 38.
- CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H. (1945), *Proc. Amer. Fed. clin. Res.*, **2**, 11.
- COURVOISIER, S., FOURNEL, J., DUCROT, R., KOLSKY, M., and KOETSCHET, P. (1953), *Arch. int. Pharmacodyn.*, **92**, 305.
- CROSELEY, A. P., ROWE, G. G., and CRUMPTON, C. W. (1954), *J. Lab. clin. Med.*, **44**, 104.

- DASGUPTA, S. R., and WERNER, G. (1954), *Brit. J. Pharmacol.*, **9**, 389.
- DAWES, G. S. (1952), *Brit. med. Bull.*, **8**, 324.
- DAWES, G. S., and COMROE, J. H. JUN. (1954), *Physiol. Rev.*, **34**, 167.
- DOBKIN, A. B., LAMOUREUX, L., LETIENNE, R., and GILBERT, R. G. B. (1954), *Canad. med. Ass. J.*, **70**, 626.
- DONNISON, C. P. (1929), *Lancet*, **i**, 6.
- DONTAS, A. S. (1955), *Circulation Research*, **3**, 363.
- EHRSTROM, R. (1918), *Finska LäkSällsk. Handl.*, **60**, 365.
- ERSPAMER, V. (1953), *Arch. int. Pharmacodyn.*, **93**, 293.
- ERSPAMER, V. (1954), *Pharmacol. Rev.*, **6**, 425.
- FISHBERG, A. M. (1939), 'Hypertension and Nephritis,' London, fourth edition.
- FOSTER, C. A., O'MULLANE, E. J., GASKELL, P., and CHURCHILL-DAVIDSON, H. C. (1954), *Lancet*, **ii**, 614.
- FOWLER, P. B. S., and GUZ, A. (1954), *Brit. Heart J.*, **16**, 1.
- FREIS, E. D. (1953), 'Symposium on Hypertension,' Evans Memorial Research Conference, Boston, Mass., September, 1953.
- FREIS, E. D., STANTON, J. R., LITTE, J., CULBERTSON, J. W., HALPERIN, M. H., MOISTER, F. C., and WILKINS, R. W. (1949), *J. clin. Invest.*, **28**, 1387.
- FREIS, E. D., and WILSON, I. M. (1956), *Circulation*, **13**, 856.
- GADDUM, J. H., and HAMEED, K. A. (1954), *Brit. J. Pharmacol.*, **9**, 240.
- GADDUM, J. H., and VOGT, M. (1956), *Ibid.*, **11**, 175.
- GILMORE, H. R., KOPELMAN, H., McMICHAEL, J., and MILNE, I. G. (1952), *Lancet*, **ii**, 898.
- GINSBURG, J., and DUFF, R. S. (1956), *Brit. J. Pharmacol.*, **11**, 180.
- GOLDRING, W., and CHASIS, H. (1944), 'Hypertension and Hypertensive Disease,' Commonwealth Fund, New York.
- GOETZ, R. H. (1956), *Circulation*, **13**, 63.
- GRAHAM, J. D. P. (1945), *Lancet*, **i**, 239.
- GREEN, M. F., DEGROAT, A. F., and McDONALD, C. H. (1935), *Amer. J. Physiol.*, **110**, 513, and **112**, 448.
- GRIMSON, K. S. (1941), *Arch. Surg. (Chicago)*, **43**, 284.
- GRIMSON, K. S. (1955), *J. Amer. med. Ass.*, **158**, 359.
- GRIMSON, K. S., REARDON, M. J., MARZONI, F. A., and HENDRIX, J. P. (1948), *Ann. Surg.*, **127**, 968.
- GRIMSON, K. S., TARAZI, A. K., and FRAZER, J. W., JUN. (1955), *Circulation*, **11**, 733.
- GRIMSON, K. S., TARAZI, A. K., and FRAZER, J. W., JUN. (1955), *Angiology*, **6**, 507.
- GROB, D., SCARBOROUGH, W. R., KATTUS, A. A., JUN., and LANGFORD, H. G. (1953), *Circulation*, **8**, 352.
- GUTTMANN, L., and WHITTERIDGE, D. (1947), *Brain*, **70**, 361.
- HAFKENSCHIEL, J. H., CRUMPTON, C. W., MOYER, J. H., and JEFFERS, W. A. (1950), *J. clin. Invest.*, **29**, 408.
- HAMILTON, M., PICKERING, G. W., ROBERTS, J. A. F., and SOWRY, G. S. C. (1954), *Clin. Sci.*, **13**, 11; **13**, 37; **13**, 273.
- HARRIS, H. A. (1927), *Brit. med. J.*, **i**, 789.
- HERING, H. E. (1927), 'Die Karotissinusreflexe auf Herz und Gefäße,' Dresden, Steinkopff.
- HEYMANS, C., and BOUCKAERT, J. J. (1935), *C. R. Soc. Biol. (Paris)*, **120**, 82.
- HEYMANS, C., BOUCKAERT, J. J., and REGNIERS, P. (1933), 'Le Sinus Carotidien et la Zone Homologue Cardio-aortique,' Paris, Doin.
- HINES, E. A., JUN., and BROWN, G. E. (1933), *Ann. intern. Med.*, **7**, 209.
- HUGHES, W. M., DENNIS, E., and MOYER, J. H. (1955), *Amer. J. med. Sci.*, **229**, 121.
- JANEWAY, T. C. (1913), *Arch. intern. Med.*, **12**, 755.
- JOINER, C., and KAUNTZE, R. (1954), *Lancet*, **i**, 1007.
- JUDSON, W. E., HOLLANDER, W., and WILKINS, R. W. (1956), *Circulation*, **13**, 664.
- KATZ, L. N., and SAPHIR, O. (1933), *Amer. J. Physiol.*, **104**, 253.
- KELLEY, R. T., FREIS, E. D., and HIGGINS, T. H. (1953), *Circulation*, **7**, 169.
- KLEMOLA, E. (1938), *Z. menschl. Vererb.-u. Konstit. Lehr.*, **22**, 69.
- KOTKE, F. J., KUBICEK, W. G., and LAKER, D. J. (1947), *Arch. phys. Med.*, **28**, 146.
- KRAYER, O., and ACHESON, G. A. (1946), *Physiol. Rev.*, **26**, 383.
- KUBICEK, W. (1950), 'Symposium on Hypertension,' p. 158, University of Minnesota Press, Minneapolis, U.S.A.
- LABORIT, H., HUGUENARD, P., and ALLAUME, R. (1952b), *Presse méd.*, **60**, 206.
- LABORIT, H., JAULMES, C., and BENITTE, A. (1952a), *Anesth. et Analg.*, **9**, 232.
- LAPE, H. E., FORT, D. J., and HOPPE, J. A. (1956), *J. Pharmacol.*, **116**, 462.
- LEWIS, T. (1924), *Heart*, **11**, 151.
- LEWIS, T. (1932), *Brit. med. J.*, **i**, 873.
- LOCKET, S. (1955), *Ibid.*, **i**, 809.
- LOCKET, S. (1956), *Ibid.*, **ii**, 56.
- MEILMAN, E. (1953), *J. clin. Invest.*, **32**, 80.
- MOLLER, E. (1947), *Kasuistisk Meddelelse, Nord. med.*, **33**, 610.
- MOYER, J. H., FORD, R., DENNIS, E., and HANDLEY, C. A. (1955b), *Proc. Soc. exp. Biol. (N.Y.)*, **90**, 402.
- MOYER, J. H., HUGHES, W. M., and HUGGINS, R. (1954), *Amer. J. med. Sci.*, **227**, 640.
- MOYER, J. H., MCCONN, R., and MORRIS, G. C. (1955a), *Anesthesiology*, **16**, 355.
- NONIDZE, J. F. (1935), *Amer. J. Anat.*, **57**, 259.
- O'DELL, T. B., LUNA, C., and NAPOLI, M. D. (1955), *J. Pharmacol.*, **114**, 306; **114**, 317.
- PAASONEN, M. K., and VOGT, M. (1956), *J. Physiol.*, **131**, 617.
- PATON, W. D. M. (1951), *Brit. med. J.*, **i**, 773.
- PATON, W. D. M. (1952), *Brit. med. Bull.*, **8**, 310.
- PATON, W. D. M. (1954), *Pharmacol. Rev.*, **6**, 59.
- PATON, W. D. M., and ZAIMIS, E. J. (1952), *Ibid.*, **4**, 219.
- PERARA, G. A. (1945), *J. Amer. med. Ass.*, **129**, 537.
- PERARA, G. A. (1950a), 'Symposium on Hypertension,' p. 257, University of Minnesota Press, Minneapolis, U.S.A.
- PERARA, G. A. (1950b), *Bull. N.Y. Acad. Med.*, **26**, 75.
- PICKERING, G. W. (1955), 'High Blood Pressure,' Churchill, London.
- PLATT, R. (1947), *Quart. J. Med.*, **16**, 111.
- PLETSCHER, A., SILVER, S. L., and BRODIE, B. B. (1955), *Science*, **122**, 374.
- REUBI, F. C. (1950), *Proc. Soc. exp. Biol.*, **73**, 102.
- RÉNNOV-JESSEN, V. (1953), *Lancet*, **ii**, 706.
- SELYE, H. (1942), *Canad. med. Ass. J.*, **47**, 515.
- SELYE, H. (1950), *Brit. med. J.*, **i**, 203.
- SHACKMAN, R., GRABER, I. G., WOOD-SMITH, F. (1947), MELROSE, D. G., and LYNN, R. B. (1954), *Lancet*, **ii**, 617.
- SHORE, P. A., SILVER, S. L., and BRODIE, B. B. (1955), *Science*, **122**, 284.
- SÖBBYE, P. (1948), *Op. dom. Biol. hered. hum. Kbh.*, Vol. 16.
- SPIES, T. D., and STONE, R. E. (1952), *J. Amer. med. Ass.*, **150**, 1599.
- STOCKS, P. (1930), *Ann. Eugen. (Lond.)*, **4**, 49.
- SWISS, E. D., and MOUNTAIN, C. F. (1955), *Proc. Soc. exp. Biol.*, **88**, 19.
- TAKINO, M., and WATANBE, S. (1937), *Arch. Kreislforsch.*, **2**, 18.
- THOMAS, C. B. (1941), *Proc. Soc. exp. Biol.*, **48**, 24.
- VERSCHUER, O. VON, and ZIPPERLEN, V. (1929), *Z. klin. Med.*, **112**, 69.
- WALTER, C. W., and PIJOAN, M. J. (1937), *Surgery*, **i**, 282.
- WEISS, M. M., and PRUSMACK, J. J. (1938), *Amer. J. med. Sci.*, **195**, 510.
- WEITZ, W. (1941), *Fortschr. Erbpäth.*, **5**, 1.
- WIGGERS, C. J. (1932), *Ann. intern. Med.*, **6**, 12.
- WIGGERS, C. J. (1938), *Am. Heart J.*, **16**, 515.
- WILKINS, R. W. (1950), 'Symposium on Hypertension,' p. 407, University of Minnesota Press, Minneapolis, U.S.A.
- WILKINS, R. W. (1950), 'Symposium on Hypertension,' p. 236, University of Minnesota Press, Minneapolis, U.S.A.
- WILKINS, R. W., and JUDSON, W. E. (1953), *New Engl. J. Med.*, **248**, 48.
- WILKINSON, E. L., BACKMAN, H., and HECHT, H. H. (1952), *J. clin. Invest.*, **31**, 872.
- WINDER, C. V. (1937), *Amer. J. Physiol.*, **118**, 379.
- WOLF, S., PFEIFFER, J. B., RIPLEY, H. S., WINTER, O. S., and WOLFF, H. G. (1948), *Ann. intern. Med.*, **29**, 1056.
- WOLF, S., and SHEPARD, E. M. (1950), *Proc. A. Research Nerv. & Ment. Dis.*, **29**, 976.
- ZAIMIS, E. J. (1955), *J. Pharmacol.*, **7**, 497.