SOME APPLICATIONS OF PHYSIOLOGY TO MEDICINE.

IV.—HIGH BLOOD PRESSURE FROM THE PHYSIOLOGICAL ASPECT.*

BY

J. A. MACWILLIAM, M.D., F.R.S.,

REGIUS PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF ABERDEEN.

(From the Physiological Laboratory.)

It need hardly be said that the problem of the causation and mechanism of persistent high blood pressure has proved one of exceptional complexity and difficulty. High pressure is a condition or symptom, like pyrexia, probably of different types and modes of causation.

Methods of Estimation.

As regards the measurement of the pressure a combination of the auscultatory and tactile methods is by far the best—very superior as regards accuracy and convenience to various oscillatory and other methods that have been proposed. It may be taken that the readings obtained are in the vast majority of cases an approximately correct estimate of the pressures actually present within the artery. In a very limited number of cases with thickened *contracted* arteries local resistance to compression in the arterial wall may lead to an over-estimation of the intra-arterial pressure, an error that can be obviated by the method of repeated or continued armlet compression. But it is to be noted that in a certain number of cases the method of repeated compression may in turn introduce sources of fallacy if the auscultatory method *per se* is used. For in some individuals compression, repeated a number of times or kept on for some time, may cause serious disturbance in the auscultatory indices—for example, the systolic reading may come to be much too low, while the diastolic reading becomes too high. The error is detected by combination with the tactile method; the tactile systolic index is now found to be considerably higher than the auscultatory systolic, the pulse beat being easily felt at the wrist long before the armlet compression has been reduced sufficiently to allow the sound constituting the auscultatory systolic index to be recognized. This is one of the instances which illustrate the necessity of checking the auscultatory systolic index by the tactile method—recommended as a routine procedure by Professor Spencer Melvin and myself²³ many years ago. The source of fallacy in question is in my experience seldom, if ever, of importance in high-pressure cases, so the matter need not be further pursued in the present connexion.

Systolic and Diastolic Pressure Levels.

Since Melvin and Murray²⁷ stated the systolic and diastolic pressure levels in young adults in 1914, evidence on a large scale has become available as to the "normal" pressures in healthy persons—systolic readings 110 to 125 mm. being most common (sitting position), while the value may sometimes be as low as 100 to 105 mm. in subjects in good training, or may be as high as 130 to 140 mm. in some young persons in good health, there being evidently a setting of the normal pressure at different heights. The diastolic level in young adults is usually between 60 and 80 mm.; the pulse pressure has ordinarily a value of 40 to 45 mm.

The relation of age to the pressure values is a matter on which much evidence has accumulated in recent times, thanks largely to the American insurance statistics (Symonds,⁴⁰ Rogers and Hunter,³⁵ MacKenzie,²¹ and others), in which records from hundreds of thousands of individuals are available; also to the work of Stocks and Karn²⁸ in this country. The results led to a correction of a current idea as to there being an extensive rise of pressure in normal persons as life advances and as body weight increases. It

is true that there is a very appreciable rise in the later half of life, but this is much more limited than has been currently believed by clinicians, dealing with persons who come under their observation for some ailment or other. Thus the average systolic pressure, in the enormous numbers examined, has been found to show only a comparatively small increase, whatever may be the significance of the much higher pressures recognized in some individuals who enjoy good health.

When the averages of very large numbers are dealt with, it is evident the rising pressure of childhood undergoes some acceleration about puberty and reaches the normal adult level somewhere in the age period of 17 to 20; there is some evidence of a slight subsequent lowering in the early adult years. The pressure then alters little up to the age of about 40, after which a more definite progressive rise becomes manifest. But the actual increase under the combined influences of age and the usually associated increase of weight is on an average under 15 mm., in some statistics much less.

The statistics bear strong testimony to the relative constancy of systolic pressures at different ages, when estimated with the necessary allowances and corrections; they make clear that exceptionally high pressures in healthy persons must be very infrequent, otherwise the averages would be much higher. It is noteworthy that the statistics have largely been obtained in America, with its stress and hurry of life. The importance of hereditary influences or familial tendencies is marked in regard to the occurrence of unusually high pressures, and the association of high pressures with obesity is a notable one, though by no means invariable. At all ages persons of heavy build have higher average systolic pressures (for example, 10 mm., etc.) than persons of light build.

The importance of the diastolic pressure reading and the consequent obtaining of the pulse pressure value need hardly be emphasized. Diastolic pressure represents the resistance against which the contracting left ventricle has to force open the aortic valves, and it represents the constant stress which the arterial walls have to stand. Its importance with regard to the bursting of a weakened artery is great, more than the transient systolic rise caused by each heart beat. This is illustrated by the comparative rarity of cerebral haemorrhage in cases of aortic regurgitation, with its high systolic but low diastolic pressures. Systolic pressure taken by itself may give very defective and misleading indications, for the systolic readings may be at the same level in profoundly different conditions of the circulation.

The diastolic pressures afford data valuable for interpretation of the condition present. Normal or supernormal systolic pressure taken by itself does not necessarily indicate efficiency as regards the mass movement of the blood in the circulation.

Modes of Death in Subjects of High Pressure.

Taking the average results of very large numbers as regards health and duration of life, it is clear that the dice are loaded against the subjects of high pressures, though of course there are many individual examples of long life and activity under those conditions.

In excessively high pressures the fatal ending seems to come by cerebral haemorrhage in about 20 per. cent., changes having supervened in cerebral vessels by this time. The not infrequent occurrence of cerebral haemorrhage (like pulmonary and gastro-intestinal haemorrhages) during sleep was long a puzzling phenomenon in view of the accepted conclusion that the blood pressure is lowered during sleep. Why should the haemorrhage take place during a period of reduced pressure? Observations by the present writer²² on the remarkable rise of pressure that may be associated with disturbed sleep, exciting dreams of motor effort, nightmares, etc., afford an explanation. In contrast with the definite lowering of pressure attending on sound sleep, the steep rise during disturbed sleep may reach an elevation attained in the same individual in the waking state only during vigorous or even violent muscular exertion—for example, systolic pressure rises to 182 and 200 mm. from normal levels of 125 to 130 mm.

* Read at the James Mackenzie Institute for Clinical Research, St. Andrews, October, 1926. Previous articles of this series were published in the BRITISH MEDICAL JOURNAL, 1923, vol. i, p. 51; vol. ii, pp. 215, 278, and 1196.

respectively, while diastolic pressure rises from 75 to 105 mm., etc.

It is significant that an American observer (Krumhaar²⁰) has recently found that a relatively large number of ruptures of the heart occur during sleep. In about 50 per cent. of high-pressure cases death is ascribed to cardiac failure. Of course the work of the heart is greatly augmented by the excessive resistance against which it has to pump out its contents. But the reserve power of the healthy cardiac muscle, as Sir James Mackenzie repeatedly emphasized, is very great; the heart is an organ of phenomenal power and endurance, granted a good supply of normal blood to its walls. What usually happens is not simply the wearing out of such a heart by excessive work, but the defeat of a labouring heart impaired by defective nutrition due to lesions of the coronary circulation, and deficient quality of blood resulting from damaged kidneys and other organs. The remaining proportion of deaths has been attributed mainly to uraemic conditions, but are really complex in causation in presence of widespread derangements of function in the later stages.

Interpretation of High Pressures.

The phenomenon of persistent elevation of the arterial pressure may be regarded from different standpoints and given quite different interpretations. It may be looked on as a result of irritative and deranging influences (circulatory toxins or other causes) frequently leading to the development of symptoms of ill health, increasing the work of the heart and tending to cardiac failure, stressing the vascular walls, promoting their degeneration and predisposing to cerebral haemorrhage, kidney changes, etc.

From another point of view the high pressure may be looked on as essentially a compensatory process, while attended in the long run by certain unfavourable effects on the heart and blood vessels. The raised pressure is regarded as compensatory in the sense of its maintaining the circulation or driving more blood through some vital organ that requires it—for instance, the brain, kidney, heart muscle, etc.—either when the flow has been subnormal or when a higher pressure and more rapid flow would be useful in view of functional or structural defects in the tissue.

Janeway¹⁷ concluded that in some persons an average pressure far above the normal is necessary to ensure the requisite capillary blood flow, the optimum arterial pressure sometimes being 200 mm. or more, instead of 100 to 145 mm. Oliver²² remarks: "We are apt to forget that high arterial pressure is not infrequently a necessary evil and should sometimes be regarded as one of the natural defences of the body." Herringham,¹⁶ referring to certain high-pressure cases, says: "I make little doubt that a high blood pressure is necessary for the life of these patients."

Clifford Allbutt¹ wrote long ago: "High pressure is an attempt of the organism to maintain the equilibrium of the circulation." In his last work² he remarks: "The truth is that as high pressures creep on stealthily, the system as silently adapts itself to them; so that blindly to try to reduce excessive pressures permanently to the normal would be as harmful in practice as fallacious in reason." While advising gradual reduction towards the level suitable for the particular individual, he severely criticizes the teaching, based on the belief that high pressure is compensatory, that treatment should not be applied to high pressures: "If an ergot-like poison were crimping up one's arteriolar system or directly irritating the vasomotor centre, would one decline to relax the system for fear of destroying compensation? Certainly not."

While it is well known that a lowering of pressure is sometimes attended by unfavourable symptoms, this does not necessarily prove that the elevated pressure had primarily been compensatory. The rise may have been due to irritative morbid influences in presence of which habituation or adjustment had at length developed, a new pressure level being established. Later, if a fall occurs, readjustment at this phase may not be practicable, especially in presence of failing heart action with defective regulating mechanisms and probably deterioration in kidney efficiency, structural lesions, etc.

It is obvious that with declining heart power relaxation

of the arterioles by vaso-dilator drugs would naturally produce unfavourable results, since the physiological mechanism which tends to keep up the aortic pressure by vaso-constriction in presence of defective cardiac output would be upset. But such considerations do not establish the beneficial or compensatory nature of high pressures while the heart is efficient.

It was long ago suggested that high blood pressure might be useful, as far as the kidney is concerned, when there is an excess of material of some sort to be excreted or when the functional power of the organ is defective from structural or other causes. A recent paper from this laboratory by C. Reid,²⁴ dealing with a mixed series of high pressures, some with and some without renal involvement, yields evidence that does not support the idea of a compensatory function with regard to renal function. Substantial lowering (20 to 60 mm., etc.) of pressure by drugs of the nitrite series or by venesection did not impair the power of the kidney to concentrate urea or diminish the total urea excretion in the vast majority of cases; the urea and non-protein nitrogen of the blood were not increased during the periods of reduced pressure—there was no accumulation of these bodies in the blood to indicate defective excretion. Evidently renal function was well maintained, so far as urea and non-protein nitrogen are concerned. Some clinical observations as regards phenolsulphonephthalein by Gruber, Shackelford, and Ecklund,¹⁴ and on guanidine by Major,²⁴ afford similar indications; the excretion of these substances in the urine was not lessened during periods of lowered pressure.

Causation of High Pressures.

It is hardly necessary to recall the various influences that have been invoked to account for the development of high pressures: (1) nervous, (2) endocrine, (3) toxic, and (4) renal.

While it is obvious that some powerful agency is at work, the search for definite pressor bodies (from any source) in the circulation has proved to be singularly inconclusive. Clifford Allbutt said: "Such catch phrases as intestinal toxins, kidney inadequacy, endocrine disorder, and the like are but dust in our eyes."

Mechanism of High Pressures.

Ideas as to the relations of high pressure and the frequently associated arterial sclerosis have varied much. The old view of von Basch regarded sclerosis as the cause of the high pressure, while the later one of Huchard made the high pressure primary and the sclerosis secondary. At the present time it is accepted that there are two distinct conditions; there may be sclerosis without high pressure at any stage, and high pressure without sclerosis, though persistent high pressure favours the development of sclerosis.

Studies on the viscosity of the blood in high-pressure conditions have not provided any explanation applicable on a wide scale, though a limited group of high-pressure cases associated with polycythaemia and augmented viscosity has been recognized. In the absence of a great increase in blood viscosity or of blood volume (conjoined with ineffectiveness of the normal mechanism of accommodation of such increased volume) it is evident that high pressure must depend on excessive frictional resistance or diminished capacity of the vascular system, or a combination of these factors. The factor commonly accepted as the main one is increased peripheral resistance—increased frictional resistance to the onward movement of the blood from the arteries, dependent on narrowing of the outlet by active contraction of the arterioles or by structural change.

In view of the work of Krogh, Lewis, Dale, and others, which has emphasized the independent powers and strong contractility of the capillaries, the question naturally arises as to the part which these may play in determining excessive resistance in high-pressure conditions, as distinguished from the normal state in which the capillary resistance seems to be slight. Some observations on capillary pressures on the skin, made by modern methods, are described (Boas and Frant⁸) as showing the presence of excessively high values in some types of high arterial pressure, in contrast to cases of simple high pressure (hyper-

piesia, primary or essential hypertension, etc.); this suggests the possible existence of two categories of high arterial pressure, one with and the other without high capillary pressures.

It is to be remarked, with reference to the numerous studies of capillary pressures that have been made by different observers, that measurements of capillary pressure in the skin afford no valid evidence as to the average pressure in the capillary system as a whole, or as to the friction in the total capillary bed. For the capillary pressures in the skin (finger, etc.) are profoundly influenced by local conditions of arterial tone, with the result that the digital capillary pressure may rise while the pressure in the brachial artery falls, and vice versa. And the conditions in the skin area and the splanchnic area of the circulation are frequently opposed, as in muscular exercise, etc. There are no means of determining the relations between the pressures in the skin capillaries and in those of internal organs.

It is not warrantable to speak of "capillary pressure" in the same sense as "arterial pressure," for the latter has a definite value practically identical in all the larger arteries, while the former shows diverse and varying pressure values in the multitude of capillary districts. Still, if it should be confirmed that the skin capillary pressures fall into two categories in cases of high arterial pressure, such a differentiation may prove to have clinical significance. Apart from the question of capillary resistance playing an important part, it is evident that a diminished capacity of the capillary system would have important effects on the circulation. But there are no means of gauging the size of the total capillary bed.

In the healthy person at rest the arterial pressure which is normal for that individual is remarkably constant within narrow limits, apart from ascertainable disturbing conditions; the regulating nervous mechanism (medullary centres) is very efficient, as shown by there being little or no change in aortic pressure when the peripheral resistance is markedly increased by artificial compression of large arterial trunks like the brachial or femoral. But in the high-pressure subject this regulating mechanism has ceased to be adequate; the pressure remains at an abnormally high level, and is often subject to sudden and extensive variations, sometimes in the absence of any recognizable cause or from slight exciting influences that would have little effect in the normal individual. The normal regulating mechanism includes the depressing or inhibitory effect on the vasomotor centre of high blood pressure acting (1) directly on the centre and (2) through afferent impulses from the heart, aorta, sinus caroticus,* etc. In addition, there is the controlling influence of the vagus centre on the cardiac pump, this centre being also influenced directly by the blood pressure in it and reflexly by afferent impulses from the heart, aorta, and sinus caroticus. Additional recent evidence with regard to this mechanism is to be found in experimental inquiries by Anrep and Starling⁴ (cross-circulation experiments), Hering,¹⁵ Nash³⁰ (sinus caroticus), Daly and Verney.¹² The observations of Eyster and Hooker¹³ on the influence of afferent impulses from the aorta have recently been corroborated.

Some Occasional Postural Effects in Man.

Recent observations by me have shown that in some persons the sudden assumption of the horizontal position may cause an abrupt fall of general arterial pressure of variable amount, sometimes associated with a marked though transient attack of giddiness; the latter is probably due to the pressure change, being absent in these subjects when the pressure fall is not very considerable. Evidently what happens is that the increase of blood pressure in the head on lying down flat, due directly to the hydrostatic factor—the difference in the influence of gravity—depresses the vasomotor centre, causing vascular relaxation and a marked fall of aortic pressure, sufficient sometimes to disturb the equilibrating mechanism of the brain. These unusual cases, not subjects of high pressure so far as has been observed, are explicable as depending on an exaggera-

tion of the normal depressing or inhibitory action exercised on the vasomotor centre by a local rise of blood pressure. The fall of pressure is not explained by depressed heart action, there being little alteration in the rate of the beat; pronounced vagus slowing is not observed. Here the vagus centre is not made to show enhanced controlling power over the heart by the increase of blood pressure in the head, which is sufficient to produce strong though very temporary depression of the vasomotor centre. Hence an excessive susceptibility of the vasomotor centre is postulated in the subjects showing this reaction. The brief duration of the marked fall of pressure is a point of difference from the experimental results of Anrep and Starling, who found a continued effect on the vasomotor centre from increased blood pressure in the head in their cross-circulation experiments. The reaction in man described above is in contrast to the less uncommon occurrence of giddiness on suddenly standing or sitting up from the recumbent posture, associated with a lowering of the blood pressure in the head from the direct influence of gravity—as well as other possible causes of disturbance of the equilibrating mechanism. In the cases above referred to giddiness did not occur on suddenly standing or sitting up—only on lying down.

Relation of the Medullary Centres to High Pressures.

Increased peripheral resistance, raising the arterial pressure, evidently depends essentially on constriction of the minute vessels, due to the overactivity of the vasomotor centre or to causes acting directly on the vascular tubes. But there is more involved than a simple increase in peripheral resistance, however produced; for a rise of pressure from this cause acting alone would, in accordance with Marey's law, induce slowing of the heart by enhancing the controlling action of the vagus centre. But in high-pressure cases this slowing is wanting, the pulse usually being normal in rate or more or less extensively accelerated. Thus in a series of 241 cases Mannaberg²⁶ found 55 per cent. with normal pulse rates, 43 per cent. with quickened pulses (mostly in women), and only 3 with slow pulses. The high pressure fails to bring out the normal controlling influence of the vagus centre on the heart rate, an indication that alongside of the constricted state of matters in the peripheral vessels there is an altered condition in the medulla, affecting the vagus centre and no doubt the closely related vasomotor centre—overaction of the vasomotor centre producing excessive general vascular constriction, alongside of altered behaviour of the vagus centre.

Accepting the conclusion that in high pressures overactivity of the vasomotor centre is caused by pressor agencies, whether nervous or chemical, it is evident that such pressor action may act in two ways: (1) by a direct irritative action on the centre, or (2) indirectly, by impairing the blood supply and oxidation in the centre, and thus exciting it to overactivity, as such conditions are known to be very effective in doing.

Starling²⁷ has suggested a local impairment of this kind as being possibly due to claudication of the vessels supplying the centre, or to toxic damage of its capillaries or interference with the oxidative process, and that such may be responsible for certain forms of high pressure. Following upon this suggestion Bordley and Baker⁹ have recently reported the finding of arterio-sclerosis in the medulla in a number of high-pressure cases, in contrast to the findings in subjects who had had normal pressures. But it remains to be seen whether such sclerotic changes are primary or secondary.

There are various phenomena of high-pressure cases that are difficult of explanation on the hypothesis of limitation by structural causes of the medullary blood supply.

1. The frequently marked effects of continued mental and muscular rest—often involving a lowering, for the time being, of the pressure more extensive than can easily be accounted for by the slowing of the heart and the absence of the pumping movements of the skeletal muscles which promote the venous return to the heart during movement, etc.

2. The remarkable lowering of many abnormally high pressures that has been noted during sleep (Brooks and Carroll,¹⁰ Müller,²⁹ Blume,⁷ Katsch and Pansdorf¹⁹). A

* The "sinus caroticus" is a name applied to the first portion of the internal carotid artery immediately above the bifurcation of the common carotid. It receives afferent fibres from a twig of the glossopharyngeal nerve.

notable constancy of pressure levels during sleep (for example, 5 mm. variation during sleep) has been observed, in contrast to the extensive variations often seen in the waking state. Katsch and Pansdorf found an unusual range of reduction during sleep in essential hypertension, in contrast to other forms of hypertension where there was little or no reduction.

3. The occurrence in some cases of extensive variations of pressure from day to day or at shorter intervals (hours)—apparently not accountable for by changes in heart action.

4. The apparently "spontaneous" recoveries from high pressures sometimes seen.

5. The pressure-reducing effects of the ingestion of large amounts of water, to be referred to later (Orr and Innes).

There is obvious difficulty in reconciling such considerations with the idea of a high-pressure mechanism depending on the existence of established structural changes in the vessels of the medulla or the general circulation; they point to a notable variability of resistance, as contrasted with a fixed increased of resistance set up by structural alterations in the vascular circuit. An assumption that such variability of pressures is explicable by changes in the cardiac action is not warranted.

It would appear that the incidence of the pressor influence responsible for high blood pressures is primarily on the central nervous system, not directly on the peripheral vessels as a whole. The disturbance of the medullary regulating mechanism is evidently due either to (1) interference with the normal blood supply to the brain or the medullary portion of it, or (2) the influence on the centres of some abnormal disturbing agent arriving in the blood, or (3) nervous impulses reaching the centres from other parts of the brain or from peripheral structures.

As regards (1) it remains to be seen whether indications may be derived from a study in high-pressure subjects of the behaviour of the respiratory centre, which from its close topographical and functional relations with the vagus and vasomotor centres would naturally be affected by inadequacy of the blood supply to this part of the brain stem.

Suggested Pressor Substances.

Salt, cholesterol, urea, adrenaline, "renin" (from damaged renal tissue), and many other substances have been under trial, and have either been acquitted or given a verdict of "not proven."

There has long been a presumption that protein derivatives—products of incomplete or perverted metabolism or results of microbic action in the alimentary canal or the tissues—are frequently concerned in the genesis of excessively high blood pressures, though a pressor agent in the blood has not been identified or isolated. Experimental investigations (feeding, etc.) on this subject have given conflicting results in recent years. Thus Mosenthal,²⁸ Squier and Newburgh,³⁶ Strouse and Kelman,³⁹ and Anderson³ report no elevation of pressure from increased protein feeding in high-pressure cases, while some other observers—for example, Nuzum⁴¹ and others among recent workers—have reported different findings. Foster describes a reduction of pressure from long-continued low protein diet, and Benedict a reduction from normal under a diet of low calorie value and low protein content. Again, in a collection of low-pressure cases it has been found that high protein feeders are 28 per cent. less numerous than among normal blood pressures.

Allbutt concluded that there is no evidence of the accumulation of non-protein nitrogen in the blood or default in the urine, that intestinal disorder is incidental, and that there is no proof of the absorption of intestinal poisons to be got from examination of the urine. It is to be remarked that feeding experiments deal more directly with the amount and completeness of protein metabolism rather than with possible perversions of this process in certain types of this subject.

In view of the recognized hereditary liability to the development of high pressures—as strikingly illustrated in many families—under the influence of nervous strain, worry, unfavourable habits of life, dieting, etc., there may well be inborn susceptibility to derangement in the metabolism of proteins and associated substances in these subjects.

Orr and Innes,³³ working in this laboratory, a few years ago made the remarkable observation that ingestion of large amounts of water tend to induce a notable lowering of elevated blood pressure—a result attributed to the washing out of intermediate metabolites, presumably of protein origin. Whatever be the ultimate explanation, the pressure change is often both marked in extent and of much longer duration than is commonly the case with depressor agencies. Reduction from such a pressure as 200 mm. to normal, maintained over many months, has been effected. Decided results seem to be obtainable in a considerable proportion of high-pressure subjects. The application of this method is being made the subject of further investigation; it is clearly worthy of being given an extended trial. The slight preliminary rise of pressure which may follow the ingestion of large amounts of water does not seem to have been attended by any unfavourable results in primary or essential hypertensions.

A pressor agent recently suggested by Major and Stephenson²⁵ is guanidine—a substance which, on intravenous or intramuscular injection, gives a rapid and extensive elevation of arterial pressure. The excretion of guanidine was found to be markedly interfered with in experimental uraemic nephritis (dogs), and in a number of high-pressure patients a diminished output was observed and compared with the normal daily average of about 100 mg. It is suggested that guanidine, as being somewhat difficult of excretion, might be partially retained in developing kidney defect at a phase too early to be recognized by the usual tests. In this connexion it would be interesting to have evidence as to the blood pressure in tetany—for example, from parathyroid defect, where guanidine has been found in the blood by Noël Paton and his associates; also whether any high-pressure cases are favourably affected by parathyroid feeding and calcium salts. Hyperthyroidism, though sometimes associated with high blood pressure, is ruled out as a common cause by the results of examination of the basal metabolism.

Relation to Kidney Conditions.

While kidney conditions have long been prominently in question, whether in primary or secondary relations, it is now generally accepted that high pressures frequently occur (hyperpiesia, primary or essential hypertension, etc.) apart from any recognizable lesion or functional defect of the kidneys as examined by modern methods. Still there can be no question that the presence of kidney defect, whether it be primary or secondary, constitutes a formidable handicap on the subject of high pressure and profoundly influences his chances of health and duration of life. This is so, whether the detriment arises through (1) limitation of the excretory function of the organ, leading to the retention of noxious irritant substances in the circulation, or (2) to the entry into the blood of some product of damaged renal tissue—for instance, the "renin" of Tigerstedt and Bergman, suggested as a causal agent by Batty Shaw⁵ in some high-pressure cases.

Experimental reduction of the amount of kidney tissue below a certain limit (for example, to one-third) has been shown to lead to a rise of blood pressure; this has been assumed to be due to the action of retained substances (of unknown composition) which ought to have been excreted. The actual presence of such bodies of a pressor nature has not been demonstrated in the blood. In these reduction experiments there is the complication of the possible absorption into the circulation of pressor substances from damaged renal tissue, as indicated by the recent evidence adduced by J. R. Cash⁴¹ in which 50 to 85 per cent. diminution of renal substance was associated with a pronounced rise of arterial pressure.

Relation to Depressor Substances.

Defect of depressor substances in the circulation is evidently one of the conceivable causes, assuming that the normal blood pressure is maintained by the interplay and balance of pressor and depressor influences. As is well known, chemical substances of depressor nature are very widely distributed in the animal tissues, and many observers question whether the substances are mainly of the nature of histamine and choline or are quite separate from these bodies—a question which is in dispute, as shown

by the recent contributions of Vincent and Sheen⁴¹ and others. If high pressure can result from default of depressor substances the failure of the search for separate pressor agents in the blood might conceivably be accounted for.

A tissue extract that has recently been the subject of active investigation is liver extract, which has been found to have pronounced depressor effects, studied by various observers. As prepared by James, Laughton, and Macallum,¹⁸ the active extract is stated to be free from the shock-producing substance histamine and from choline. Fresh extract is necessary, and while the experimental effects are marked, the clinical data in high-pressure cases in man are not conclusive. Major reports striking and lasting effects in certain high pressures of recent origin without recognizable lesions, while not overlooking the occurrence of occasional "spontaneous" recoveries in such cases. In "fixed" pressures of long standing there was little evidence of specific effect with the liver extract. Some observers interpret the depressor effects of the liver extracts which they used as being due to histamine and choline (Best, Dale, Dudley, and Thorpe⁶).

Conclusion.

From the foregoing considerations it is evident that while the incidence of the disturbing agency on the medullary regulating centres is clearly indicated, precise and adequate knowledge of the causation and mechanism of high pressures is defective. The fact of high pressures coming under observation in man only, and the consequent inapplicability of many of the methods of experimental research, have to be borne in mind as limiting the modes of attack upon the problem. While it is obvious that much more knowledge is necessary for the definite solution of the question involved, it has seemed advisable to take stock of the present situation as it appears to a physiologist, in order to avoid the waste of laborious work in accumulating data such as are already available. It is necessary to keep an open mind as to the possibility of a solution being found in an unexpected direction—in the discovery of a precise causal agent or agencies different from those that are mostly in question at the present time as bearing on the condition of high pressures, which may prove to be multifactorial in causation and mechanism as also in clinical type.

REFERENCES.

- ¹ Allbutt: *Diseases of the Arteries*, London, 1915.
- ² Allbutt: *Arteriosclerosis*, London, 1925.
- ³ Anderson: *Arch. Int. Med.*, 1925, xxxviii, 297.
- ⁴ Anrep and Starling: *Proc. Roy. Soc.*, 1925, B, xcvi, 463.
- ⁵ Batty Shaw: *Hyperpiesia and Hyperpiesia*, London, 1922.
- ⁶ Best, Dale, Dudley, and Thorpe: *Communication to Physiol. Soc.*, March, 1926.
- ⁷ Blume: *Ugeskrift for Laeger*, Copenhagen, 1922, lxxxiv, 1126.
- ⁸ Boas and Frant: *Arch. Int. Med.*, 1922, xxx, 40.
- ⁹ Bordley and Baker: *Bull. Johns Hopkins Univ.*, 1926, xxxviii, 320.
- ¹⁰ Brooks and Carroll: *Arch. Int. Med.*, August 15th, 1912.
- ¹¹ Cash: *Proc. Soc. Exper. Biol. and Med.*, 1926, xxiii, 609.
- ¹² Daly and Verney: *Journ. Physiol.*, 1926, lxi, 268.
- ¹³ Eyster and Hooker: *Amer. Journ. Physiol.*, 1908, xxi, 273.
- ¹⁴ Gruber, Shackelford, and Ecklund: *Arch. Int. Med.*, 1925, xxvi, 366.
- ¹⁵ Hering: *Flüger's Archiv*, 1924, cxxv, 772.
- ¹⁶ Herringham: *Kidney Diseases*, London, 1912, 219.
- ¹⁷ Janeway: *The Clinical Study of Blood Pressure*, New York and London, 1910.
- ¹⁸ James, Laughton and Macallum: *Science*, lxi, 181; *Journ. Amer. Med. Assoc.*, 1926.
- ¹⁹ Katsch and Pansdorf: *Munch. med. Woch.*, lxi, 1915.
- ²⁰ Krumbhaar: *Journ. Amer. Med. Assoc.*, 1925, lxxxiv, 1691.
- ²¹ MacKenzie: *Proc. Assoc. Life Ass. Med. Dir.*, 1916, vi, 92, 1915, 221.
- ²² MacWilliam: *Quart. Journ. Exper. Physiol.*, 1923, xiii, BRITISH MEDICAL JOURNAL, 1923, ii, 1195; *Physiol. Reviews*, 1925, v, 303.
- ²³ MacWilliam and Melvin: *Heart*, 1914, v, 153; BRITISH MEDICAL JOURNAL, 1914, i, 693.
- ²⁴ Major: *Journ. Amer. Med. Assoc.*, 1926, lxxxvii, 311; *Bull. Johns Hopkins Univ.*, 1925, xxxvi, 357.
- ²⁵ Major and Stephenson: *Bull. Johns Hopkins Univ.*, 1924, 140, 186.
- ²⁶ Mannaberg: *Wien. klin. Woch.*, 1922, xxxv, 145.
- ²⁷ Melvin and Murray: *Quart. Journ. Exper. Physiol.*, 1914-15, viii, 125.
- ²⁸ Mosenthal: *Amer. Journ. Med. Sci.*, 1920, clx, 808; *Med. Clinic. of North America*, 1922, 1189.
- ²⁹ Müller: *Acta Med. Scand.*, 1921, lv, 443.
- ³⁰ Nash: *Proc. Physiol. Soc.*, *Journ. Physiol.*, 1926, lxi.
- ³¹ Nuzum: *Journ. Amer. Med. Assoc.*, 1925, xxxvii, 733.
- ³² Oliver: *Studies in Blood Pressure*, London, 1916.
- ³³ Orr and Innes: *Erit. Journ. Exper. Pathol.*, 1922, iii, 61.
- ³⁴ Reid: *Quart. Journ. Med.*, 1926, xix, 411.
- ³⁵ Rogers and Hunter: *Proc. Assoc. Life Ass. Med. Dir.*, 1921-22, viii, 130; 1919, vi, 92.
- ³⁶ Squier and Newburgh: *Arch. Int. Med.*, 1921, xxviii, 1.
- ³⁷ Starling: BRITISH MEDICAL JOURNAL, 1925, ii.
- ³⁸ Stocks and Karn: *Blood Pressure in Early Life*, London, 1924.
- ³⁹ Strouse and Kelman: *Arch. Int. Med.*, 1923, xxxi, 151.
- ⁴⁰ Symonds: *Journ. Amer. Med. Assoc.*, 1923, lxxx, 232; *Proc. Assoc. Life Ass. Med. Dir.*, 1923, 321.
- ⁴¹ Vincent and Sheen: *Journ. Physiol.*, 1903, xxix, 262; *Lancet*, 1926, i, 1142.

THE INSECT TRANSMISSION OF ONCHOCERCA VOLVULUS (LEUCKART, 1893),

THE CAUSE OF WORM NODULES IN MAN IN AFRICA.*

BY

D. B. BLACKLOCK, M.D., D.P.H.,

PROFESSOR OF TROPICAL DISEASES OF AFRICA, UNIVERSITY OF LIVERPOOL.

AMONG the families of parasitic nematodes which infest man none surpasses in diversity of interest the family Filariidae. This is due both to the pathogenic effects produced by some species, and also to the strange biological adaptations in the human host and in those insect vectors so far known. Complex problems are presented by the larval habits of different species, some living in the blood stream, others having their chief habitat in the skin; some showing the remarkable phenomenon of periodicity, the causes of which are still obscure. No less important are its historical associations; since it was with the species *Filaria bancrofti* of this family that Manson worked when, in 1878, he made the discovery—destined to revolutionize the tropics—of the part played by insects in the transmission of human disease. From this observation dates all that research into the association of insects with disease which has already produced such significant results and which is daily achieving fresh discoveries in the ever-widening domain of human and animal parasitology.

The Genus Onchocerca.

Included in the family Filariidae is the genus *Onchocerca* (Diesing, 1841), which has one species, *O. volvulus*, parasitic in man in Africa, another species, *O. caecutiens*—so closely allied with *O. volvulus* that some authorities consider it identical—parasitic in man in Central America, and several species parasitic in domestic and other animals in various parts of the Old and the New World. Naturally the two species which are parasites of man are of great direct importance. They have a restricted geographical distribution, the ill effects produced by them being confined to the limited regions in which they occur. Of a different order, and affecting man much more widely, are the indirect ill effects produced by those species which infest domestic animals, especially cattle.

Onchocerca volvulus (Leuckart, 1893) infests man in tropical Africa with an intensity which varies in different localities. In West Africa there are large areas in which a very high percentage of the total population is infested. Prout (1901) in Sierra Leone was one of the first to describe it. The worms live in nodules in the subcutaneous and deeper tissues, and give rise to larvae which find their way into the skin; an infested area of skin may contain vast numbers of larvae, so much so that not even the smallest portion can be removed without numerous larvae being found. Different observers have attributed to the worm an etiological significance in the production of very diverse pathological effects, which depend on the distribution of the worm itself in the body and of the larvae in the skin. Several forms of skin disease, itch, ulcers, as well as glandular enlargements, hydrocele, and elephantiasis, are some of the conditions with the production of which this worm is credited.

Mode of Transmission of Onchocerca.

The transmitting agents of several of the Filariidae are already known, if we accept invasion of the proboscis as evidence of the insects being capable of transmitting; up to the present time, however, no one has succeeded in demonstrating by what means any species of the genus *Onchocerca* is transmitted from man to man or from animal to animal. As a result of investigations carried out at intervals during the past four years I believe that I am now in a position to state that the conditions essential to transmission of *O. volvulus* are fulfilled by a biting insect, a species of the genus *Simulium*, named very appropriately *Simulium damnosum*. These investigations were undertaken in the Konno district of the Sierra Leone

* An address delivered before the Sierra Leone Branch of the British Medical Association.