THE CIRCULATION IN ARTERIAL HYPERTENSION*

BY

G. W. PICKERING, M.A., M.B., F.R.C.P.

Professor of Medicine in the University of London; Director of the Medical Clinic, St. Mary's Hospital Medical School

LECTURE I

Raised arterial pressure has been suspected in man for over a century, and its degree has been measurable for over 40 years. The diseases with which it is associated are some of the commonest contemporary causes of death. The factors regulating arterial pressure have been the subject of earnest inquiry by physiologists from the time of Ludwig on. Yet we know comparatively little of what causes arterial hypertension in man, or indeed of what changes in the circulation it is the result. It is not surprising, therefore, that when confronted with a patient presenting raised arterial pressure the role of the physician, except in certain rare instances, is no more than that of comforter and friend.

In the last ten years a beginning has been made in analysing the nature of the circulatory disturbances which underlie hypertension in man, and in this first lecture I propose to outline the, as yet imperfect, picture which these investigations have revealed. This leads naturally to the subject of my second lecture—an inquiry as to how far the action of known pressor agents succeeds in reproducing the circulatory conditions encountered in disease.

Arterial hypertension is, like contracted pupils or enlarged heart, no more than a symptom or sign of disease, and, like them, may arise in more than one way. Hypertension is known to occur in acute and chronic nephritis, chronic pyelonephritis, polycystic kidney, pituitary basophilism, tumours of the adrenal medulla, pregnancy kidney, coarctation of the aorta, and in benign and malignant essential hypertension. To avoid the fundamental fallacy of confusing conditions essentially unlike, each of these conditions must be separately considered. So little is known of the circulation in some of these that they will not detain us long.

ESSENTIAL HYPERTENSION

In essential hypertension, which is by far the commonest of such maladies, we know that the raised arterial pressure is not due to increased output of the heart or to increased blood viscosity, for these have been measured and found normal. We may infer, therefore, that hypertension is due to narrowing of the vessels at some point or points in the vascular circuit. From measurements, by indirect methods, of the intravascular pressure at various points it would appear that the site of the vascular narrowing is in the small arteries and arterioles.† Thus in hypertension the rate at which the blood circulates round the body as a whole is normal; the hydrostatic pressure of blood within the vessels is abnormally high in the aorta and arteries, gradually falls to reach approximately the normal level as the blood traverses the arterioles to the capillaries, and remains normal as the blood flows through venules and veins back to the heart. If we concede the possibility that the rise

of arterial pressure may serve some useful function, then the structure likely to benefit should be one on the arterial side of the circulation, such, for example, as the glomerulus of the kidney.

On this general background two important details remain to be filled in—namely, the distribution of this vascular narrowing, which determines the share of blood the individual tissues receive, and the nature of the agent constricting the vessels.

It is convenient first to consider to what extent structural changes in the vessels can directly account for raised pressure. Increased rigidity of the aorta and its main branches can be dismissed briefly. On theoretical grounds this can only lead to increased pulse pressure, the mean arterial pressure remaining unaltered. It is probably the cause of the pure systolic hypertension (diastolic pressure being normal); and it probably accounts for the relatively high systolic as compared with the diastolic pressure found in elderly subjects with hypertension of all kinds. It is not the cause of the raised mean arterial pressure. Atheroma, or nodular arteriosclerosis, need not detain us long. It is more frequent in subjects with raised than with normal pressures, and, occurring as it does in the larger arteries supplying organs such as brain and heart, is an important cause of symptoms and death in subjects with hypertension past middle life. Its occurrence and distribution are too irregular to account for the hypertension, and it involves the wrong order of vessels. As we have seen, it is in the small arteries and arterioles that we should look for the vascular narrowing, and here two kinds of structural change have been observed. A fatty hyaline thickening of the intima is found in the arterioles of the kidney (particularly the afferent glomerular arterioles) in about 98% of cases of essential hypertension, and less frequently in the spleen, pancreas, liver, and brain. But because these changes are often slight and affect relatively few vessels, and because they usually spare the important vascular territories of gut, muscle, and skin, histologists are agreed that they are not directly the causes of the raised pressure (see Fishberg, 1939). The cause of these changes is obscure, for they have not been produced experimentally; but it is to be mentioned that they also occur, though less frequently, in elderly subjects with normal arterial pressure, in which, however, as Moritz and Oldt (1937) have pointed out, the kidneys tend to be spared. The second change is that first described by Fahr as necrosing arteriolitis, a condition in which a granular mass staining brightly with haematoxylin and eosin appears in media or intima and greatly reduces the lumen. This change never occurs in the benign type of essential hypertension and is invariable in the malignant form, appearing chiefly in the kidney and to a lesser extent in the gut and other viscera; it is probably the chief factor determining the rapid course of malignant hypertension to the usual death in uraemia. Arteriolar necrosis, as it is now generally termed, is due to grossly raised intravascular pressure, as has been shown experimentally (Wilson and Pickering, 1937-8; Wilson and Byrom, 1939). It is therefore an effect of the hypertension and not its cause.

Further evidence for the view that structural arterial lesions are not directly responsible for the raised arterial pressure of

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† The evidence for this conclusion is reviewed in a previous article (Pickering, 1939). See also Oppenheimer and Prinzmetal (1937).

essential hypertension is the normal vasodilator responses of the forearm and hand vessels to heat and reactive hyperaemia (Prinzmetal and Wilson, 1936; Pickering, 1935-6b; Stead and Kunkel, 1940) and the normal depressor response to intravenous injection of 0.1 mg. of histamine acid phosphate (Pickering and Kassin, 1935-6).

Thus it would seem that, while structural changes in the small arteries and arterioles may contribute, they are not the chief factors in the increased peripheral resistance which is the cause of the raised arterial pressure. The chief factor is evidently vasoconstriction, which may be of nervous or humoral origin. Its nature will become clearer when we consider the distribution of the vascular narrowing.

Experimental physiology has taught us that the vessels of the body behave as a series of units in their response to certain reflexes affecting the circulation and in response to vasoactive substances. Thus the skin vessels tend to behave similarly all over the body and in a way that is different from the vessels to muscle or brain when, for example, the body temperature is raised or adrenaline is injected intravenously. If the vascular narrowing in hypertension affected all the vessels to a similar degree, then in the first place we should expect each organ to receive its normal quantity of blood, and in the second we should have to search for some agent as the cause of essential hypertension which had a uniform action on different vessels. Alternatively, if the vascular narrowing were unequal, then blood would be diverted from organs in which the vessels were narrowest to those organs in which the vessels were wider; we should thus find some organs receiving less and some more blood than normal, and our agent should have a similar differential action on the vessels. One further and important point can be learned from a study of tissue blood-flow. If the vasomotor nerves are responsible for the abnormal vasoconstriction in hypertension, then if it were possible temporarily to eliminate their influence over one vascular territory while leaving the arterial pressure unchanged, the blood-flow through that territory should rise to much higher levels than in normal people subjected to a similar procedure; for, the effective agent being removed, the vessels to the part would be reduced to the same state in normal and hypertensive subjects, and blood-flow would be directly dependent on arterial pressure. These are the lines of thought which have led us to investigate the conditions of blood-flow through individual tissues in an attempt to identify the causative agent.

The Forearm

The first part to be investigated was the forearm. Early in 1936 Prinzmetal and Wilson, and I, independently, published measurements of the forearm blood-flow by the plethysmographic method of Hewlett and van Zwaluwenburg, using Lewis and Grant's plethysmograph. We each found similar rates of blood-flow in normal subjects and subjects with persistent hypertension, both at rest and in response to the vasodilator stimulus of circulatory arrest for 10 minutes. In addition Prinzmetal and Wilson found similar rates of flow in response to local heat and to warming the body or anaesthetizing the cervico-dorsal sympathetic ganglia with novocain. For our present purposes these observations are largely of historical interest, and for two reasons: we did not know that the blood-flows also represented in part hand-flow, as Grant and Pearson (1937-8) later showed; and the forearm consists of two tissues—muscle and skin—in addition to bone.

The Skin

The circulation in the skin in the normal resting subject undergoes relatively large fluctuations directed to the maintenance of body temperature. This is particularly true of the hand, where blood-flow is estimated most easily; for the hand contains relatively enormous numbers of arteriovenous anastomoses (Grant and Bland, 1929-31).

While the skin circulation is thus not suited to demonstrating small variations in blood-flow under resting conditions, it is in the hand admirably designed for investigating the nature of the agent narrowing the vessels, for sympathetic vasoconstrictor tone is easily removed by warming the body (Lewis and Pickering, 1931-3), and the main nerves to the hand are accessible to anaesthetization.

To investigate the blood-flow through the hand (Pickering, 1935-6b) the calorimetric method of Stewart was used in preference to the plethysmographic method because, although it does not actually measure blood-flow in c.cm. per 100 c.cm. per min., it is simple and robust, and the possible sources of error are more easily detected and controlled. To remove vasoconstrictor nervous tone from the hand, body temperature was raised by immersing the opposite forearm in water at 44° C. Evidence will be found in the original paper to show that heat elimination provided a true reflection of skin blood-flow in subjects with normal and raised pressures, and that the degree of body-warming employed did in fact completely remove vasoconstrictor nervous tone from the hand vessels without stimulating vasodilator nerves (Lewis and Pickering, 1931-3; Grant and Holling, 1937-8) and without significantly altering arterial pressure. In this way it was shown that the blood-flow through the skin of the hand from whose vessels vasomotor nervous tone had been removed was no greater, but sometimes a little less, in 15 subjects with benign and malignant hypertension than in 21 subjects of comparable age with normal pressures (Fig. 1). Evidently, then, in essential hypertension the hand

FIG. 1.—Shows the heat elimination from the hand (in cal. per min. per c.cm. hand) after removal of vasoconstrictor nervous tone from it in a series of subjects with normal and persistently raised pressures. The heat elimination, which is a measure of blood-flow, is similar in the several groups.

vessels are narrowed by a non-nervous agent, and this narrowing is of an order such that if generally distributed through the body it would account for the hypertension. Since the skin vessels are rarely and inconsiderably involved in the arteriosclerosis of hypertension, the narrowing is presumably not of structural but of humoral origin. That the vasoconstriction, thus inferred in the hand vessels in essential hypertension, is not great enough to produce any detectable diversion of blood from the skin becomes an important point when we come to consider vasoconstrictor agents.

The Muscles

The observations on forearm blood-flow published in 1936 have been repeated by Abramson and Fierst (1942), who also used the Lewis-Grant forearm plethysmograph, but excluded the hand by arresting its circulation. If we assume that the plethysmograph was placed as high on the forearm as possible, then Grant and Pearson's investigations would indicate that about 85% of the tissue whose blood-flow they measured was muscle. They found that with the plethysmograph maintained at 32° C. (a normal skin temperature for the forearm) the blood-flow averaged 2.86 c.cm. per 100 c.cm. per min. in subjects with hypertension and 1.77 c.cm. in normal subjects. Moreover, if the subjects were grouped according to their systolic pressures it was found that the higher the arterial pressure the greater was the forearm blood-flow. Similar results were obtained in the calf. Abramson and Fierst unfortunately did not attempt to classify their subjects with hypertension, and we have to assume that their observations refer to essential hypertension, since this is by far the commonest condition. From their observations it seems, therefore, that the muscle vessels are either uncontracted or less constricted relative to the other vessels in the body, so that at rest the muscles get more than their normal share of blood. Observations on the effects of exercise on muscular blood-flow are difficult to make

really quantitative, but, so far as they go, both Stead and Kunkel and Abramson and Fierst have found normal flows in hypertension.

The Brain

If it is assumed that the metabolism of the brain is the same under different pathological conditions, any changes in cerebral blood-flow should be reflected by changes in the carotid-jugular O_2 and CO_2 differences. Williams and Lennox (1939) have found the values in 21 patients with hypertension to be within the normal range. They also found normal values in cerebral arteriosclerosis and high intracranial pressure, and stress the importance of the local regulating effect of CO_2 on the blood-flow through the brain.

Although it is therefore probable that the blood-flow through the brain as a whole is normal in essential hypertension, it is widely maintained that from time to time the cerebral arteries show intense contractions leading to transient ischaemia of the area of brain supplied. A careful consideration of the evidence and of my own experience in this and other conditions has convinced me that this hypothesis is unnecessary to explain the phenomena of hypertensive encephalopathy, which I believe to be due either to thrombosis in small cerebral arteries or, more rarely, to acute cerebral oedema. My evidence against the hypothesis of vascular spasm chiefly depends on a series of cases of transient cerebral disturbances occurring in mitral stenosis and auricular fibrillation and undoubtedly due to cerebral embolism. This evidence will be presented elsewhere.

The Kidney

The circulation through the kidney has always evoked the greatest interest because of the idea, subsequently fortified by Goldblatt's work, that this organ might be the primary source of the hypertension. The ingenious and careful experiments of Homer Smith (1937, 1939, 1941) and his colleagues have thrown an unexpected light on the renal circulation. Briefly, they have shown that a non-metabolized polysaccharide, inulin, is excreted in man entirely by glomerular filtration. Its clearance—that is, the volume of blood cleared of inulin per minute by the kidneys—thus measures the rate of glomerular filtration, which in its turn is dependent on the pressure in, and the rate of blood-flow through, the glomeruli. The rate of renal blood-flow can be measured by the diodrast clearance; for this substance is excreted chiefly by the tubules, and at low plasma concentrations its rate of excretion in normal subjects is such that, even assuming the kidney removes all the diodrast from the blood traversing it, the renal blood-flow must be of the order of 1.3 litres per min., or about one-third of the cardiac output.

In comparing the normal kidney and that in essential hypertension the position is complicated by the variable amount of destruction of the renal substance, which becomes extreme in the malignant phase of essential hypertension. But here again the ingenuity of Smith and his colleagues is equal to the occasion. For they have shown that when the plasma diodrast is raised to a high level the excretion reaches a maximum value unaffected by further plasma rise. This value is proportional to the amount of functional tubular tissue and is termed the tubular excretory mass. Thus by relating the inulin and diodrast clearances to the tubular excretory mass it is possible to obtain a surprisingly complete picture of the circulation through the functionally intact tissue of the kidney in hypertension.

Goldring, Chasis, Ranges, and Smith (1941) have investigated by such methods the renal circulation in 60 cases of essential hypertension of all grades of severity to the terminal malignant phase. The tubular excretory mass was reduced in all but 3 cases, and in the 8 patients in the malignant phase was between 6% and 38% of the normal value. The effective renal blood-flow inferred from the diodrast clearance was also reduced, being between 41.7 and 1,176 c.cm. per min.; in 45 of 60 cases it was more greatly reduced than the tubular mass, suggesting that some factor is operating in hypertensive subjects to produce a relative ischaemia in the residual functional tubular tissue. The rate of glomerular filtration is much less reduced than the tubular functions, so that the fraction of the renal blood-flow filtered off in the glomeruli is increased: "Since the relative ischaemia in these subjects is correlated with a rise in filtration

fraction we conclude that the ischaemia is the result of increased resistance beyond the glomeruli—i.e., probably in the efferent glomerular artery."

Goldring, Chasis, Ranges, and Smith believe the constriction of the efferent glomerular arterioles to be of humoral origin, because it is not nervous and it can be relaxed. The vasoconstriction is not nervous in origin, because in essential hypertension the renal blood-flow is not increased, nor is the filtration fraction lowered, by operations in which the sympathetic nerves supplying the kidneys have been divided. The vasoconstriction can be relaxed through the induction of fever by intravenous injections of pyrogens which, in essential hypertension as in normal subjects, increase the effective renal blood-flow while leaving the filtration rate unaltered. The tubular excretory mass is usually not increased by the pyrogenic reaction, but in some subjects with essential hypertension it rises significantly, suggesting that substantial amounts of tubular tissue may be ischaemic under basal conditions. This argument rests chiefly on the decreased ability of the kidney in essential hypertension to excrete diodrast. I am, however, unable, after careful consideration, to see any satisfactory alternative to the explanation of their results adopted by these workers.

It seems, then, that there are intrinsically two changes in the kidney in essential hypertension: first, a reduction in the amount of functional renal tissue, inferred to be progressive and accompanied by a corresponding reduction of renal blood-flow; and, secondly, a relative ischaemia of the remaining functional tubular tissue due to narrowing of the efferent glomerular arteries. The first of these changes has long been suspected by those working on post-mortem material and attributed to structural vascular lesions, especially of the afferent glomerular arterioles. In malignant hypertension these arteriolar lesions are striking, and on experimental grounds have been attributed to the effects of a grossly raised intravascular pressure. The histologically distinct lesions in benign hypertension are of more uncertain causation. Smith and his colleagues also consider that the efferent glomerular vasoconstriction is an effect of the process of hypertension rather than in any sense its cause—a conclusion supported by Chasis and Redish's (1941) observations that vasoconstriction usually affects equally the two kidneys in essential hypertension.

Other Tissues

In a man of 1.73 sq. m. body surface the resting cardiac output, according to Grollman, is 3.8 litres, and the renal blood-flow, according to Smith, 1.3 litres per min. If we take Testut's figure of 30 kg. for the muscle in a man of 70 kg., the total muscle flow on the mean of Abramson and Fierst's figures would be 500 c.cm. per min. This leaves 2 litres per min. for distribution to skin, brain, gut, heart, and liver. In the subject with hypertension the cardiac output is similar; the renal blood-flow is variable, but we may take 0.8 litre as representative, and, accepting Abramson and Fierst's figures, 800 c.cm. would go to the muscles, leaving 2.2 litres per min. for skin, brain, gut, heart, and liver. So far as we know, brain and skin get similar supplies in the two instances. While any calculation based on composite figures, as this is, must be treated with reserve, the suggestion is that in the remaining tissues the blood-flow in hypertension is not grossly abnormal—except, of course, when structural vascular disease, especially atheroma, produces localized ischaemia.

Comment

The available evidence suggests that raised arterial pressure in essential hypertension is due to arteriolar constriction, and that this constriction probably affects the vessels to voluntary muscle little if at all; while in the skin vessels, and probably also in the cerebral vessels, its degree is just great enough to counter the effects on blood-flow of raised arterial pressure. In the kidney the efferent glomerular arterioles are constricted, and this narrowing is great enough to reduce the renal blood-flow. Finally, there is evidence, both from the skin and from the kidney, that the agent is not nervous but chemical.

COARCTATION OF THE AORTA

When studying the circulation through the skin of the hand (Pickering, 1935-6b) I was surprised to find that in coarctation, as in essential hypertension, the blood-flow was normal after

removing vasoconstrictor nervous tone. A chemical cause for the vascular narrowing thus demonstrated seemed out of the question, in view of the much lower arterial pressures recorded in the legs, where Lewis had found a normal blood-flow; and the vascular narrowing above the aortic constriction was attributed to a local change. Steele (1941) has since shown, by direct recording, that the diastolic arterial pressure is often nearly as high below the aortic constriction as above it, thus removing the argument against a humoral mechanism. A further similarity with essential hypertension is to be found in Friedman, Selzer, and Rosenblum's (1941) finding of a reduced effective renal blood-flow and normal glomerular filtration rate, inferred from the diodrast and inulin clearances.

NEPHRITIS

Chronic.—Vasoconstriction of non-nervous origin has been demonstrated in the skin of the hand in chronic nephritis as in essential hypertension (Pickering, 1935-6b). No information is available concerning muscle or cerebral flow; reduced blood-flow through the kidneys has been inferred (Chesley *et al.*, 1940), but there is no information as to what vessels are involved and how. Allegations that the hypertension behaves differently in chronic nephritis and essential hypertension have on repetition been unconfirmed (Pickering and Kissin, 1935-6; Pickering, 1935-6b).

Acute.—While all the varieties of chronic hypertension which I investigated behaved similarly in showing evidence of vasoconstriction in the hand after removal of sympathetic vasoconstrictor tone, acute nephritis behaved differently (Pickering, 1935-6c). During the phase of hypertension the blood-flow (as reflected by calorimetry) was in the upper normal range or above it, and in 4 of 6 cases was significantly greater than when the arterial pressure had returned to normal. The increase in maximum heat elimination from the hand produced by a given rise in arterial pressure—all other known factors, including the tone of the hand vessels, remaining constant—had been determined in a case of femoral arteriovenous fistula in which compression of the artery proximal to the fistula raised diastolic arterial pressure by 15 mm. Hg. In the four cases of acute nephritis the increase in heat elimination per unit rise of diastolic pressure was quite similar (Fig. 2); there was thus

FIG. 2.—Shows the relationship between diastolic pressure and the heat elimination from the hand, from which vasoconstrictor nervous tone had been removed, in 4 cases of acute nephritis (solid circles, solid triangles, solid squares, open triangles) and in a case of arteriovenous fistula (open circles).

no evidence of non-nervous vasoconstriction of the hand vessels during the phase of hypertension. It was concluded, therefore, that the mechanism of raised arterial pressure in acute nephritis differed from that in chronic hypertension,* and that while the latter was probably due to a chemical agent the former probably was not. Similar results in 5 cases were obtained by Arnott and Matthew (1939). While no observations by

* It will be seen that in acute nephritis the "control" is provided by the same patient after recovery, and thus the factor of individual variation is excluded. I have had only two opportunities of measuring the heat elimination from the hand after removing the vasoconstrictor tone in different stages of chronic hypertension, and these support the conclusions already described. Thus in a case of progressive chronic nephritis arterial pressure was 138/80 and heat elimination 525 cals. per min. on Feb. 6, 1936; on Sept. 12, 1936, the corresponding figures were 146/96 and 480. In a case of essential hypertension passing from the benign to the malignant phase arterial pressure was 195/124 and heat elimination 281 cals. per min. on Nov. 1, 1935; on June 9, 1936, the corresponding figures were 234/144 and 290.

the most modern methods have yet been published on the renal circulation in acute nephritis, Goldring and Smith's preliminary results, published in 1937, "suggest that renal hyperaemia may exist during a phase of acute glomerular nephritis." Unfortunately they did not state whether hypertension was present in this phase.

Published records give us a very incomplete picture of the circulation in nephritic hypertension, but, so far as they go, they suggest that in chronic nephritis the circulation behaves in much the same way as it does in essential hypertension, and is probably likewise humoral in origin. In acute nephritis the hypertension seems to arise from a different cause. If a chemical agent is involved it is peculiar in that it constricts neither the vessels of the hand nor apparently those of the kidney. A nervous mechanism is possible, though none has been demonstrated.

PREGNANCY TOXAEMIA

In a brief summary of work done before the war Kellar and Sutherland (1941) state that the heat elimination from the hand after elimination of vasomotor nervous tone was normal in 35 cases of toxæmia, but give no details. The renal circulation has been investigated by Corcoran and Page (1941), Chesley *et al.* (1940), and by Wellen, Welsh, and Taylor (1942), who are in substantial agreement. The glomerular filtration rate and the tubular excretory mass tend to be normal, while the effective renal blood-flow is increased. It is suggested that these changes are the result of efferent glomerular dilatation with possibly thickening of the glomerular basement membrane.

In pregnancy toxæmia, therefore, the circulation apparently presents some features similar, and some dissimilar, to acute nephritis. We must await further evidence to decide.

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(Lecture II, with a list of references, will appear next week.)

THE DIFFERENTIAL DIAGNOSIS OF SPINAL ARTHRITIS IN YOUNG SUBJECTS*

BY

C. W. BUCKLEY, M.D., F.R.C.P.

Physician to the Buxton Clinic for Rheumatism; Consulting Physician to the Devonshire Royal Hospital, Buxton

The symptoms of arthritis of the spine in young subjects may present a diagnostic problem of considerable difficulty and at the same time of the greatest importance in view of the rapid progress and grave developments in the more serious forms.

The Typical Form

The form most commonly seen in young people is that which is associated with the names of Marie and Strümpell, although its characteristic features had been described many years earlier by Hilton Fagge (1877) and others. The descriptive name of "ankylosing spondylitis" is now generally used; but Gilbert Scott (1942) advocated the name "adolescent spondylitis," as it usually begins at that period of life. Its rapid development and relentless progress to complete rigidity of spine, hips, and thorax, and later other joints, have been described elsewhere (Buckley, 1931). The earliest symptoms are vague pains in the back and limbs; sometimes at the outset they may be chiefly complained of in the limbs, but low back pain usually appears soon and is associated with flattening of the normal lumbar curve. At this stage the condition may be confused with adolescent kyphosis, but in the latter the gradually increasing curvature of the dorsal spine is usually associated with a compensatory increase of the normal lumbar curvature. As the disease progresses, the gait and facies are characteristic and striking.

The sequence of events is synovitis and inflammatory hyperaemia of the apophyseal joints of the lumbar spine and usually of the sacro-iliac joints, followed very soon by implication of the costo-vertebral joints and extension to the dorsal spine. Osteoporosis of the bones forming these joints appears at the

* Based on a communication to the East Midlands Society of Physicians at Leicester, April 3, 1943.