Renal Ischaemla and Hypertension

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ESSENTIAL hypertension in its various aspects was the subject of a previous review.[1] Attention was drawn to renal ischaemia as an aetiological agent, to surgery in treatment and to Cecil's words[2] "the factor which directly determines such spasm (of arterioles) remains one of the most important unsolved problems in medicine." This factor will be discussed in the light of recent evidence along with additional experimental, pathological and clinical data. This article is to be considered as a continuation and review of the last one.

The Kidney and Blood Pressure.

For many years controversy raged as to whether or not the kidney played any part in the production of high blood pressure. Kidney pathology was associated with high blood pressure, but to many this appeared as a secondary involvement. In 1928 Goldblatt[3] began a series of experiments based on the following working hypothesis: "If organic disease of the kidney be the initiating factor in the pathogenesis of benign essential hypertension, then this disease is, in all probability, the arteriolar sclerosis which is so frequently associated with this condition. If arteriolar sclerosis limited to the kidneys can be the primary factor in initiating this type of hypertension, then the necessary conditions for the establishment of the renal origin of essential hypertension upon an experimental basis should be the production of hypertension in animals by any method which will produce at least the physiological effects of such renal vascular disease." This effect was produced by constricting the main renal arteries with silver clamps. A reduced blood flow through the kidneys resulted, i.e. renal "ischaemia", and blood pressure was elevated. If the occlusion was severe the hypertension was accompanied by arteriolar necrosis and a fatal uraemic state—the clinical picture of malignant hypertension. Extensive sympathectomy did not prevent the development of hypertension, nor did it abolish it once established. Thus hypertension could be produced by reducing the blood flow through the kidneys and the process was independent of the nervous system. Could a humoral substance cause the hypertension? Such a factor could not be detected in the blood of hypertensive patients, but some evidence pointed to its presence in the blood from the renal vein of a dog with ischaemic kidneys.[4] After a review of the subject Ballock[5] concludes that negative evidence leads one to postulate a renal pressor substance. These experiments have proven a great stimulus to experimental and clinical research on the relation of renal ischaemia to hypertension.

Pathology.

If one accepts renal ischaemia as the causative factor in the production of essential hyptension, what produces the renal ischaemia? Is it, as

Ascroft suggests, [4] abnormal vasoconstriction of the afferent glomerular arteriole due to nervous impulses, or is it some organic lesion of the renal arterial system? Obstruction of renal blood flow by a lymphosarcoma involving both renal arteries (Blatt and Page [6]), Wilm's tumor (Koons and Rush [7]) thrombosis of the renal vein (Perry and Taylor [8]), pyelonephritis Weiss and Parker [9]), and by renal ptosis — "orthostatic hypertension" (McCann [10]), and accompanied by high blood pressure, have been reported clinically. But in the majority of cases no such lesion is present i.e. essential hypertension. Here it is well recognised that at autopsy marked arteriolar sclerosis is present, not only in the kidneys, but in the arterioles throughout the body. Is this sclerosis of renal arterioles secondary to hypertension, or is it primary, leading to renal ischaemia and hypertension? Moritz and Oldt [11] believe that it is primary. They selected one hundred non-hypertensive and one hundred hypertensive cases and investigated the pathological picture at autopsy. In non-hypertensives arteriolar sclerosis is widespread throughout the body, but rare in the kidney, where it is of mild form when it exists. On the other hand only three hypertensives did not show a marked arteriolar sclerosis in the kidneys, and all showed more widespread and severe lesions throughout the body than did non-hypertensives. Arteriolar sclerosis is a primary vascular disease of a degenerative nature. When it affects the renal arterioles hypertension results, and the normal "wear and tear" on the arterioles is intensified. All three cases which showed no arteriolar sclerosis had marked renal arteriosclerosis with narrowing of the lumen of the renal arteries, a natural clamp. Blackman [12] reports similar cases associated with hypertension. Weiss and Parker [9] agree with Moritz and Oldt that the primary fault is renal disease. From their observations they conclude: "These findings seem to strengthen the belief that 'primary' malignant hypertension is a generalized vascular disease, while hypertension following pyelonephritis is primarily a renal vascular disease. It is of interest that in diseases associated with generalized arteritis, such as lupus erythematosus, periarteritis nodosa, and rheumatic fever hypertension is present only when the arterioles of the kidney are extensively affected. Even when the arteritis is generalized but affects only the larger vessels, marked arterial hypertension does not develop. This suggests that in these diseases, too, hypertension depends on renal vascular changes."

Goldblatt clamped the renal arteries and produced arteriolar necrosis in the dog, except in the kidneys. By producing a perinephritis due to cellophane, Page [13] observed hypertension and extra-renal arteriolar sclerosis. Wilson and Byrom [14] were able to produce arteriolar necrosis in the kidney of a rat by rendering the other kidney ischaemic; this was accompanied by only slight depression of renal function. Thus arteriolar sclerosis and necrosis can be secondary to high blood pressure, and the ischaemia could be caused by the sympathetic nervous system. But Moritz and Oldt's investigation lend strong support to those who would regard renal arteriolar sclerosis as the primary fault. If the sclerosis is

advanced then the malignant phase appears, with arteriolar necrosis, haemorrhages and renal failure. That renal blood flow is reduced in essential hypertension has been demonstrated by Golding,[15] measuring diodrast excretion.

In pregnant dogs whose kidneys are rendered ischaemic an eclamptic-like syndrome appears, terminated by cardiac failure and showing focal necrosis and haemorrhages in the liver.[16] Evacuation of the uterus abolishes the condition.

Pyelonephritis and Hypertension.

This subject is of great clinical interest in studying the relation of renal ischaemia to hypertension.

In an extensive review Weiss and Parker[9] deal with the problem of pyelonephritis and hypertension. Last year mention was made[1] of the treatment of hypertension, secondary to pyelonephritis, by nephrectomy. The literature on the subject has been accumulating in the interval. Patch [17] reports a case of unilateral pyelonephritis, and discusses twenty-two other cases where hypertension secondary to renal disease has been treated by nephrectomy. Improvement has been only transitory in some and negligible in others, but the results have been good enough to warrant further investigation into this promising field. Barker and Walters[18] treated five cases of unilateral pyelonephritis by nephrectomy with good results.

Pyelonephritis is not always associated with hypertension, but under fifty years of age the incidence of hypertension in pyelonephritics (18 per cent) is twice that of the incidence in a control group (9 per cent[19]).

Such findings have led to an investigation of the urinary tract in hypertensives. Palmer[20] studied two hundred and twelve hypertensives by intravenous pyelography. In forty-seven cases (22 per cent) renal pathology could be detected, in thirty-one (16 per cent) the lesion being unilateral. Of nine such cases selected for surgery only one showed improvement; this, however, was one of the two showing marked arteriolar changes in the kidney. Of the forty-seven cases, 76 per cent had a family history of cardio-vascular-renal disease, while in a control of forty-three cases of pyelonephritis with no hypertension, 40 per cent had a cardio-vascular-renal history. This would suggest that urinary lesions may act as a precipitating factor in those who show hereditary susceptibility. Pearman[21] urges caution in assuming a causative relationship between various renal lesions and hypertension.

In the selection of cases for nephrectomy the lesion should be unilateral, the hypertension present for not more than two years with minimal retinal lesions, and the patient in the younger age groups.[17]

Surgery.

The position of the surgery of the sympathetic nervous system in the treatment of essential hypertension has shown no advances. Though denying an aetiological rôle, widespread lumbar sympathectomy could conceivably improve the blood supply to an ischaemic kidney in very early arteriolar sclerosis. It is such cases which show most benefit. Hein-

becker[22] has recently published a survey of the position of the surgeon with reference to essential hypertension. Page and Heuer[23] review the subject and report on seventeen cases, with some success in reducing the blood pressure and good subjective improvement. Revascularization by muscle graft and omentopexy has been attempted by de Takàts and Seupham[24] with disappointing results. Only four cases are reported, and these all advanced hypertensives, when the preglomerular arteriole would be well sclerosed. They make the interesting suggestion that in the cases such as Blackman's,[12] with arteriosclerosis of the renal artery, revascularization of the kidney might be of value. Fishberg[25] sees little hope for surgery. But the fact remains that with careful selection of cases 25 per cent of patients show definite improvement by extensive lumbar sympathectomy.[26]

Pressor and Depressor Substances.

Tigerstedt and Bergman[27] were the first to produce an increase in blood pressure by a saline extract of kidney. Goldblatt's experimental work on renal ischaemia has once more set investigators on the track of a renal pressor substance. Blalock discusses renin in his review.[5] The active substance can be precipitated from the saline extract of an acetone extracted kidney by 2M phosphate. It is a protein substance, non-dializable and destroyed by heat. It causes a slow rise in blood pressure, but repeated injections cause decreasing effects, i.e. tachyphylaxis. Its action is not potentiated by cocaine, as is adrenine, nor abolished as is tyramine. Nor is its action abolished by ergotamine.[28] Page and Helmer[29] have prepared a crystalline pressor substance, which they call angiotonin, by the interaction of renin with renin-activator obtained from blood plasma. It is heat stable and exhibits only a mild tachphylaxis. Intravenous administration of renin causes a decreased renal blood flow, along with an increased blood pressure.[30] A perfusate from a completely ischaemic kidney will increase blood pressure on intravenous infusion; a perfusate from a limb under similar conditions causes no increase.[31] The substance which produces the rise, like renin, is heat-labile, shows tachyphylaxis and has a similar pressor curve. Saline extracts of normal kidneys show less pressor effect than extracts of ischaemic kidneys, both from dogs and humans.[32] It is true that pressor substances have been prepared from tissues other than kidneys,[33] but these show quite different pressor curves and are antagonized by large doses of ergotamine. Landis[34] has shown that a renal pressor substance is unique in increasing blood pressure without reducing the peripheral blood flow or skin temperature.

Extracts of kidneys which will reduce blood pressure in hypertensive dogs and humans have been reported.[35,36,37] Extraction by various methods yields a non-dializable, non-protein substance, active on intramuscular or oral administration. It produces its effects slowly and the fall in blood pressure persists after the administration is stopped. It will not reduce normal blood pressure. Grollman and Harrison[38] prefer to regard their data as incomplete, though these point to successful clinical application. They compare thirteen known depressor substances, and show that the kidney

extract is unique. Page et al[39] have published an article this year reviewing the position of renal depressor substances, and giving data on the treatment of six cases. Their extracts may be prepared by a variety of methods, and may contain small amounts of renin as an impurity. Much remains to be done on the biochemical differentiation of renal pressor and depressor substances. That an anti-pressor substance is present in vivo has been demonstrated by the fact that nephrectomized dogs, which are normally hypersensitive to renin, lose this hypersensitivity when transfused from normal dogs. Tachyphylaxis can be explained on the basis of the existence of a substance in plasma which reacts with renin, or by the formation of a depressor substance But as the addition of renin and renin-activator to tachyphylactic plasma elicits no response on the perfused rabbits ear, it would appear that a depressor substance has been formed as the result of the renin injections. Page can control the blood pressure of dogs suffering from malignant hypertension. Dramatic effects have been obtained from the adminstration of these extracts to patients with benign and malignant hypertension; e.g. one patient in a comatose state was sitting up in bed within two days. On experimental grounds Blalock[5] concluded that: "The most hopeful line of investigation from the therapeutic viewpoint lies in the possibility of finding a specific anti-pressor substance"

These investigations, though incomplete, indicate strongly that a humoral substance is present and functional in hypertension associated with renal ischaemia, and help to strengthen the view that renal ischaemia is the causative factor in essential hypertension.

The discovery of a depressor substance, and the promising results from its clinical use holds out new hope for an effective therapeutic agent in the treatment of hypertension. A proper understanding of its nature, action and effectiveness will depend on the results of future investigation.

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To the Editor,
Dalhousie Medical Journal

Dear Sir:

It is the nostalgic remembrance of bygone days that prompts us to write to those who are now doing what we once did to tell them that in the hearts of Dalhousians at the St. John General Hospital there is a longing for the student life of the University. In the pursuit of the practical application of our years of academic training, we have journeyed many miles to an institution which is a credit to the city in which it is located. There we have met men who symbolize everything that is fine in the profession. We are thankful for the opportunity that has been given us.

The last years of our formal training have been darkened by the turn of international events. Men whom we thought of as merely upperclassmen are now serving with the Canadian forces. There is that longing for the days that can no longer be when we and they thought only of lectures, professors and examinations.

Some of us have just returned from the photographers where we got into our academic robes to have our pictures taken for the year book. The thought came to mind that new worries, serious problems, responsibilities, have come to dull the sharpness of concentration which the student at the University can bring to the solution of hypothetical propositions. It is our loss.

At Christmas time, we had some visitors to the quarters at the hospital—students home for the vacation. The Med. Journal arrives soon after it comes off the press. Every week we get our Dalhousie Gazettes. The ties that bind us to Dalhousie also have their material expression.

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