BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 12 JULY 1975

New Prospects in Renal Hypertension

From the time the first model of experimental renal hypertension was devised by Goldblatt, leading to the subsequent characterization of the renin-angiotensin pressor system, it has frequently been suggested that increases in renin production might be responsible for certain types of hypertension, probably through the formation of angiotensin II. Rigorous scientific proof of this view has proved elusive, however, and it seems likely that factors other than renin interact with angiotensin both to cause and sustain raised levels of blood pressure in patients with renovascular disease. More recently two new tools have become available which may permit further understanding of the physiological role of angiotensin in hypertension, and which may also have therapeutic implications in their own right.

The first is an inhibitor of the enzyme responsible for converting angiotensin I to angiotensin II. A nonapeptide, it was originally[1] isolated from the venom of *Bothrops aranaca* and then synthesized. Given as a single intravenous injection to a series of patients with renovascular hypertension, S.Q.20881 was found to produce an immediate and statistically-significant fall in blood pressure lasting up to 16 hours.[2] In addition, it caused an increase in plasma renin concentration (presumably by a negative feedback effect) and a fall in plasma aldosterone, confirming that angiotensin II is an important control factor for aldosterone release.

The second tool is a competitive antagonist of angiotensin II itself,[3] and is an octapeptide, saralasin, with a structure only two amino acid residues different from angiotensin. Unlike angiotensin it has little or no pressor activity in its own right, but since it has a similar affinity for angiotensin receptors on blood vessels it blocks the pressor action of angiotensin II. Two potential uses for saralasin have emerged. The first is as a diagnostic test for identifying patients in whom raised blood pressure is maintained by angiotensin. Methods for classifying patients as renal hypertensives have exercised physicians for many years. The recognition of renal abnormalities on radiological investigation and of raised renin levels in peripheral and renal veins have been of some help. Several years ago the size of the pressor response to an infusion of angiotensin II was proposed[4] as an indirect measure of the level of circulating angiotensin—"the angiotensin infusion test"—but it proved disappointing in practice. The studies with saralasin by Streeten *et al.*[5] from the New York Upstate Medical Centre are, therefore, of special interest. Sixty hypertensive patients were given saralasin by intravenous infusion. Sixteen of these patients responded by a fall in diastolic blood pressure, and in 14 of these there was radiographic evidence of renovascular disease. Thirteen of these 16 were found to have raised peripheral plasma renin concentrations, and in 15 a difference was found in the renal vein renin concentration when renin production was increased by either sodium deprivation or frusemide administration. In the same conditions of sodium deprivation as the "responders," only 2 of the 44 "non responders" to saralasin had raised renin concentrations in their peripheral or renal veins.

The critical assessment of any predictive test for renovascular hypertension must be its selection of patients who will respond to renovascular surgery. In Streeten's series only four of the responders were offered surgery, and unilateral nephrectomy was apparently necessary in three of these. In each case a satisfactory fall in pressure was produced, but whether this was sustained without drug therapy was not clear and the duration of the response is not indicated. Those patients whose blood pressure fell with saralasin infusion also responded satisfactorily to treatment with propranolol, supporting the suggestion that patients with high plasma renin concentrations respond preferentially to β blockade.

The second potential use of saralasin is to induce and maintain a reduction in blood pressure in severely hypertensive patients. This aspect has been investigated by Laragh and his colleagues,[6] who found that the blood pressure in 8 of 12 patients with malignant or advanced renovascular hypertension fell in a striking and sustained manner when they were given saralasin. These eight were all found to have raised renin concentrations in their peripheral blood. This may be an important advance in hypotensive therapy; it is common clinical experience that many patients with severe renovascular hypertension are resistant to most drug therapy, and some clinics have resorted to bilateral nephrectomy as the only effective method of treatment of these patients.

Apart from its effect on blood pressure saralasin seems to be relatively non-toxic. Bolus administration has led to paradoxical hypertension in an occasional patient, while in patients on vasodilator drugs saralasin infusion may lead to profound hypotension. A radioimmunoassay method for measuring plasma concentrations of saralasin has also recently been reported.[7] The plasma half life of the compound after stopping an infusion is of the order of 3 minutes, irrespective of the hypotensive response. The half life of the response, as measured by the rise of the blood pressure on withdrawal of the drug, is some 8 minutes. The implications of these data are that an infusion time of something less than 20 minutes is

required to achieve both stable plasma concentrations of saralasin and a constant hypotensive effect, if this is to occur.

As if diagnosis of renovascular hypertension were not difficult enough, its surgical treatment is beset by technical problems. Resection of the offending segment of a renal artery and venous bypass grafting are accepted surgical techniques, but too often unilateral nephrectomy of the protected kidney is the end result—indeed a high price to pay when the other kidney is diseased. In a recent series of cases from Australia[8] a new approach, renal autotransplantation, has been tried with low morbidity and considerable success.

Long experience warns against undue optimism in both the diagnosis and treatment of patients with renovascular disease, but after a relatively long period in the doldrums there seem to be some fresh and hopeful moves in this field.

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Colchicine in Familial Mediterranean Fever

Familial Mediterranean fever (F.M.F., recurrent polyserositis) is characterized by recurrent bouts of abdominal pain and fever. Pleuritic lesions and arthritis affecting one or more of the large joints occur in more than half the cases, and erysipeloid rashes may also appear during the attacks. The disorder is familial and is transmitted by a recessive autosomal gene; most of the reported patients have been Jews, Arabs, or Americans. The first symptoms appear usually before the age of 20, and the disease runs a benign course in most cases, but frequent attacks may cause crippling physical and mental debility. Amyloidosis may supervene in as many as one quarter of the patients and seems to be more common in Sepharadi Jews. When present, it primarily affects the kidneys and is fatal in an average of seven years. Large series of patients with F.M.F. have been published from Israel,[1 2] Lebanon,[3] the United States,[4 5] France,[6] and Russia.[7]

The pathogenesis of F.M.F. is still obscure. The underlying pathological lesion is hyperaemia and an acute nonbacterial inflammatory reaction of the serous membranes. Other organs may be affected as well. An inherited error of metabolism has been suggested[2] but has yet to be demonstrated, while others[1 4] have stressed that the disease carries some of the features of a hypersensitivity disorder.

In the last 30 years patients with F.M.F. have been treated with a wide range of drugs, none of which has been uniformly effective. In 1972 Goldfinger[8] reported that small doses of colchicine prevented the attacks in five patients with F.M.F. Shortly afterwards Eliakim and Licht[9] published similar results in 10 patients followed up for as long as 12 months. Failures in other patients[2 10] were later disproved by more carefully conducted trials by the same authors.[11 12] Additional beneficial results were reported from Egypt,[13 14] France,[15] and the United States.[16 17] Last year three double blind studies[11 16 17] seemed to prove beyond doubt that colchicine in a daily dose of 1·0 to 1·5 mg will prevent attacks in most patients. Indeed suppression of episodes by this drug has been suggested[12] as the only reliable diagnostic test for F.M.F.

The mode of action of colchicine in F.M.F. is not known. Brués and Cohen[18] observed in 1936 that colchicine arrests cellular activity in metaphase. Furthermore, it interferes with phagocytosis by polymorphonuclear leucocytes[19] and prevents the emergence of immature lymphocytes into the blood stream.[20] These actions may contribute to breaking the cycle of inflammation at its inception and so may prevent the development of clinical symptoms. Furthermore colchicine has been found to decrease fibrinogen output by fibroblasts,[21] to increase collagen degradation in vitro,[22] and to diminish fibrosis in rats made cirrhotic by carbon tetrachloride.[23] Preliminary studies have also shown that colchicine may be useful in the management of patients with scleroderma.[24] Recently Kedar *et al.* have shown that colchicine protects mice from casein-induced amyloidosis.[25] One possibility is that the drug may interfere with the assembly of mature amyloid fibrils as it may do with collagen fibres.

Long-term preventive treatment with colchicine raises the problem of chromosomal abnormalities[26] and azoospermia,[27] which may occur and are of great importance in children and in adults wanting to have children. However, colchicine has been used for the prevention of gout for as long as ten years without serious side effects,[28] and except for mild gastrointestinal complaints no untoward reactions have been reported yet in F.M.F. Cessation of therapy three months before a contemplated pregnancy[29] seems to be reasonable at present, and until more knowledge is accumulated caution should be exercised in the treatment of children. Nevertheless, colchicine seems to provide, for the first time, relief of much suffering for many patients with F.M.F. and opens a new horizon as a potential drug in the prevention of amyloidosis.

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