Jubilee Editorial

Hypertension

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Over the past 40 years hypertension has been a special focus of interest for research workers in Britain. Great contributions have been made by researchers in other lands but this editorial must be forgiven a mildly parochial outlook because it is part of a series written to celebrate the Golden Jubilee of the British Cardiac Society. In a wide field of investigation there are four areas in which the contribution of the United Kingdom was particularly notable. The first of these was the description of the pathological features of severe hypertension.

Pathology

In a sense it all began when, long before the first measurements of blood pressure in man, Richard Bright observed that patients dying of nephrosclerosis often had enlarged hearts.1 But the meticulous pathological observations of Volhard and Fahr in Germany2 marked the beginning of the modern vascular pathology. Fahr's description of "partial infarction" of the kidney has never been surpassed. The only real flaw was an excessive emphasis upon vasospasm as a cause of the abnormality. Serious work on experimental hypertension came only after Goldblatt's discovery of the renal artery clip in the 1930s.3 His methods were taken up by Clifford Wilson and Frank Byrom at the London Hospital, who used them in several important experiments on the time course and reversibility of hypertension produced by the renal artery clip.4

The visual impact of later studies by Byrom of the pial arteries of the hypertensive rat, observed through an implanted transparent skull window, was stunning.5 I can still remember the impression they made on me at a Medical Research Society demonstration at the start of my own research career. At about the same time Kincaid-Smith, McMichael, and Murphy6 completed an extensive correlative study of the clinical and pathological features of a large series of patients with accelerated hypertension seen at Hammersmith just before the dawn of the modern era of treatment.

Because of their accessibility the fundus oculi have always had a special place in research on hypertensive vascular disease. Many physicians assume that it all began with Keith, Wagener, and Barker's famous paper from the Mayo Clinic in 1939, in which they correlated retinal features with prognosis.7 In fact they were far from the first to describe the features or identify the prognosis. As early as 1859, Liebreich, in Germany, had described linear streaks of blood, milk white spots, a reddish papilla, engorged veins, and abnormal retinal arteries in patients with Bright's disease.8 In 1886 Bull in the United States followed up 86 patients with neuroretinitis and found that 57 died within a year.9 Notable descriptions of the more subtle arterial and venous changes in the hypertensive fundus were made by the British ophthalmologists Marcus Gunn (1898) and Foster Moore (1916).1011 But Keith, Wagnener, and Barker had the blood pressure readings as well as the clinical description, and their paper deserves its reputation.

The Glasgow ophthalmologist Robert Leishman established the clinicopathological correlation of the fundal changes in hypertension.12 The coming of fundus photography, and particularly fluorescein angiography, made it possible to follow the evolution of areas of fibrinoid necrosis in retinal arteries in man and experimental animals, which showed up as areas of fluorescein leakage. From these studies the pathogenesis of the cotton wool spot was deduced.1314 It was my singular good fortune to participate in that exciting era of retinal research with Paul Henkind and Norman Ashton from the Institute of Ophthalmology.

Epidemiology

The second great contribution of the British in-
vestigators was to the epidemiology of hypertension. The family studies carried out by Pickering, Hamilton, Fraser Roberts, and Sowry and St Mary's were highly original in their conception. No doubt history is right to give George Pickering most of the credit for conceiving this study but the contribution of the statistician Fraser Roberts goes largely unrecognised. Yet it was probably his skill that converted a good piece of clinical research into a classic study. Later this work became one of the centrepieces of the famous Platt–Pickering controversy that enlivened the columns of the *Lancet* in 1963.

A different view of the genetics of hypertension had emerged in Robert Platt's department in Manchester. Vivid arguments about the relative merits of camels with two humps and dromedaries with one echoed up and down the land. By general agreement Pickering won the argument by demonstrating that the bimodal distribution of blood pressure in Platt's data was an artefact of digit preference and avoidance. One consequence was a much more exact approach to clinical blood pressure measurements in which Geoffrey Rose was a leader notably with his ultimate weapon against digit preference—the London School of Hygiene and Tropical Medicine sphygmanometer.

It is fascinating to speculate that Platt's ghost may ride again when the molecular biologists crack the hypertension genes. Hypertension demonstrates polygenic inheritance and the risk is graded with the pressure. But the number of important genes will probably turn out to be small and it would not be surprising to find that the cardiovascular risks conveyed by each of them are different. Who would be judged the victor then? Perhaps both Platt and Pickering—we shall see.

Prospective studies of defined populations have played a very important part in understanding the risks of mild increases in blood pressure. The early studies by Miall in the mining valleys of South Wales were of a high standard, but later the palm crossed the Atlantic and all the really important prospective studies, such as Framingham, Albany, Tecumseh, were done in the United States. Why didn't the United Kingdom play a bigger part? Perhaps the gulf that existed between many clinicians and epidemiologists at the time was unbridgeable.

**Pathogenesis**

The study of pathogenesis is the third area in which there have been substantial contributions from the United Kingdom. Stanley Peart took leave from St Mary's to work with Elliott at the National Institute for Medical Research and together they elucidated the peptide sequence of angiotensin. Nowadays sequencing a short peptide is a simple matter but then it was a tour de force. Peart's work on the renin-angiotensin system was continued at St Mary's, and later at Glasgow, by the troika of Brown, Lever, and Robertson. Perhaps their greatest contribution was to take apart the assay of renin so that it became an accurate measurement of renin content, calibrated against a defined biological standard. Much of our knowledge of the role of renin in conditions like renal artery stenosis and Addison's disease came from that era. John Dickinson, while still at University College Hospital, used his electronics know-how and mechanical ingenuity to devise a system for giving prolonged suppressor infusions of angiotensin to rabbits. The progressive increase in the pressor effect which he observed is one of the few positive feedback loops known in biology. Currently, attention in the renin angiotensin field has shifted to renin in the vessel wall and several groups in the United Kingdom are actively engaged.

Modern interest in the role of sodium retention on the regulation of blood pressure can be traced back to Borst's experimental work with liquorice in Holland. Borst was not a charismatic figure and received little credit in his own country or elsewhere but his observations were important and original. Work on sodium retention received a tremendous boost when the Taits, working at the Middlesex Hospital Medical School, used the novel paper chromatographic methods for steroid separation that had been devised by Ian Bush, identified a new salt retaining steroid in the adrenal gland and called it "electro-cortin". A short time later electrocortin became aldosterone. Considering the importance of the discovery, they must have come close to winning the Nobel prize, but Jim Tait and Ian Bush received only modest recognition in their own land. The names we tend to remember are those of the Americans Arthur Guyton and Jerome Conn rather than those of Borst, Bush, and Tait. Both Guyton, who constructed computer models of the haemodynamic and renal interactions that led to an increase in blood pressure, and Conn, who discovered primary hyperaldosteronism, made great independent contributions; but we had our own heroes. Jack Ledingham at the London devised ingenious methods for measuring cardiac output in conscious rats so that the changes that took place as the blood pressure rose after a renal clip could be studied.

These experiments did much to establish Guyton's model. Cuthbert Cope at Hammersmith, who made many contributions to the study of the steroids, was only days behind Conn in hunting for electrocortin excess in a patient with "potassium losing renal disease".
Drug treatment

The fourth component of hypertension research in the United Kingdom has been the study of drug treatment of hypertension. As it is the part of the story which I know best I hope that I may be forgiven for devoting greater attention to it.

Early clinical memories are always the most powerful. My first memory of severe hypertension is as a very junior clinical student in the early 1950s. I was clerking a patient admitted to an ear, nose, and throat ward with an epistaxis who was found to have a very high blood pressure and papilloedema. After the bleeding stopped she was discharged on the grounds that the condition was untreatable. I was shocked because during my intercalated BSc in physiology, a few months before, I had read papers about pentolinium tartrate. Three years later as a house officer with Melville Arnott in Birmingham I had first hand experience of how difficult it was to manage patients with malignant hypertension with pentolinium and mectamylamine. At that time some patients with the most refractory hypertension had bilateral adrenalectomy and under replacement with cortisone. The aim was to find a precocious ledge between death from Addisonian crisis on the one hand and malignant hypertension on the other. It was a challenging experience for a preregistration house officer. If the blood pressure was brought under control there was dramatic clinical improvement. Pulmonary oedema vanished like magic, deterioration of renal function halted, and retinal cotton wool spots and papilloedema quickly regressed.

I leap forward 29 years to a press conference at the Medical Research Council in July 1986 at which members of the MRC Hypertension Trial Working Party, chaired by Peart, were trying to explain to a distinctly unimpressed group of journalists how they had screened half a million people, treated 18,000 of them with very mild hypertension for five years, and had prevented 60 strokes and 5 myocardial infarcts and saved 12 lives.28 So much had happened in between.

The dawn broke with the synthesis of a series of polymethylene quaternary ammonium compounds. This was followed by precise pharmacological studies by Paton and Zaimis at the Royal College of Surgeons.29 The clinical initiative was seized by Smirk in Dunedin.30 He had been a Professor of Pharmacology in Cairo (as had Gaddum before him) before becoming a Professor of Medicine so had a prepared mind and a proper sense of the priorities. His abstract in the New Zealand Medical Journal in 1950 describing the reversal of the clinical features of malignant hypertension represents the beginning of the modern era of antihypertensive treatment. His findings were quickly confirmed by McMichael at Hammersmith and Rosenheim at University College Hospital. May and Baker, the British subsidiary of the French company Rhone Poulenc had an important role in developing the quaternary ammonium compounds for clinical use.

There followed a period of explosive discovery of active compounds in the pharmaceutical industry and ever widening indications for their use. Mecamylamine (Merck, United States) and pemipidine (May & Baker, Dagenham) overcame the problems of poor bioavailability and tolerance that hampered the use of the quaternary ammonium ganglion blocking drugs.31 32 Bretylium tosylate (Burroughs Wellcome, Beckenham) was the first selective inhibitor of adrenergic neurones and spared patients from the miserable parasympathetic side effects of ganglion blockade.33 I have a memory of leaving a meeting about bretylium in conversation with Max Rosenheim around 1960. To him bretylium represented the ultimate that was likely to be achieved in selective sympathetic blockade. Nearly three decades and several generations of more selective drugs later this seems hard to believe. Despite its high initial promise bretylium, like pentolinium a quaternary ammonium compound, was felled by the rapid development of tolerance. Fortunately, quanethidine discovered by the Ciba company in the United States was close behind.34 The same company had earlier developed hydralazine but this drug was not much used in Britain at the time. The late Franz Gross, who played a leading role in the development of hydralazine,35 was wont to say that British doctors nearly destroyed the drug by giving excessive doses and causing a great deal of avoidable toxicity. Reserpine was another important drug discovery from a medicinal plant long known in India. Its properties were drawn to the attention of the Western world by an article by Vakil in the British Heart Journal.36 Use of high doses and suicides among several patients in Britain and New Zealand blackened the name of this drug but it is still widely used on the mainland of Europe.

The real revolution began with the discovery of chlorothiazide by Karl Beyer and his colleagues at Merck, Sharp & Dohme in the United States.37 Chlorothiazide and its many congeners were well tolerated, easy to regulate, and potentiated the action of most other antihypertensive drugs. They opened the door to an era of mass treatment. Methyldopa, whose blood pressure lowering action was discovered by Oates and Sjoerdsma at the National Institutes of Health,38 was also developed by Merck, Sharp & Dohme. These two drugs played a central part in the ever widening use of antihypertensive drugs during the decade between 1960 and 1970. It
was also a time that saw clinical pharmacology beginning to come into its own because of the need to study the new powerful drugs in a more systematic way than the clinical anecdotes and testimonials of the past.

Meanwhile the search for more specific drugs went on and after some encouraging indications from other workers the team under James Black at Imperial Chemical Industries produced pronethalol and later propranolol. Angina was the main clinical target; it was during a carefully conducted angina trial that Prichard observed a small but systematic reduction in blood pressure. His persistence in studying the hypotensive effect of beta blockade in comparison with other powerful established drugs (and in the face of some opposition) finally led to the wide recognition that propranolol was an essential therapeutic agent. Through its introduction hydralazine and other vasodilators gained a second lease of life. Propranolol began to replace reserpine in the “combos” beloved on the Continent and the “stepped-care” of North America.

The calcium antagonists verapamil and nifedipine from Knoll and Bayer in Germany also came into antihypertensive treatment by way of the treatment of angina. By contrast, the angiotensin converting enzyme inhibitors were discovered by the Squibb company in the United States as a result of a deliberate search after the original observations of biological activity in snake venom.

Throughout this period the United Kingdom maintained a good reputation for accurate and critical studies of new antihypertensive drugs. To do so at a time when enormous commercial forces were unleashed was no small contribution. Two factors seem to have helped. The first was the expertise of the specialist hypertension clinics that had been founded in a number of major hospitals (Hammersmith, University College Hospital, Oxford, Manchester, Sheffield, Chelmsford) to handle the ganglion blocking drugs. The existence of the National Health Service made long term specialist follow up easier than it was in the private fee-based systems in other countries.

Another positive influence was the rise of clinical pharmacology as a clinical and laboratory discipline. Possibly it was not in the long term interest of clinical pharmacology that so many of the founding fathers of the subject in the United Kingdom adopted hypertension as their disease but it did mean that considerable expertise was deployed. Antihypertensives, especially the \( \beta \) blockers, became the model for exact studies of pharmacodynamics and kinetics in man. With the occlusivecocaneous syndrome with practolol, diabetes with diuretics, haemolytic anaemia with methyldopa, systemic lupus with hydralazine, and nephrotic syndrome with captopril it also became the training ground for clinical toxicologists.

In the first decade of modern treatment, when almost all the patients had very high pressures, there was convincing clinical evidence of benefit. Retinal haemorrhages, cotton wool spots, and papilloedema resolved and pulmonary oedema melted away. In the second decade, most patients still had pre-treatment diastolic pressures above 110 mm Hg. On treatment their heart often got smaller, electrocardiographic evidence of left ventricular hypertrophy regressed, symptoms such as morning headaches disappeared, and deaths from cerebral haemorrhage or rapidly progressive renal failure became rare. In the third decade (from about 1970 onwards) the nature of the problem changed. Many patients had diastolic pressures of only 100 mm Hg or lower and few had any signs or symptoms related to hypertension. The aim of treatment was to prevent cerebral and coronary vascular disease and clinical assessment was of little help. This was the stage when the large trials of outcome came into their own.

It would be wrong to end this account of a glorious period of discovery and innovation in drug treatment like the end of a Hollywood movie with the heroes walking off into the sunset. Only a few of the new drugs were developed from the outset as antihypertensives. Most of the others arose from intelligent pursuit of chance observation in animals or man. Some of the most spectacular examples of drug toxicity have arisen with antihypertensives. Much of the toxicity was (and is) dose related and therefore potentially avoidable. Often the first descriptions of toxicity came from the United Kingdom. Some reports were the result of excessive enthusiasm for high doses but often alert long term follow up led to the early recognition of toxicity and some estimate of incidence. The British record on outcome trials has been patchy. Hamilton carried out a promising but very small trial in Britain, but it was Freis in the United States who initiated the only substantial placebo controlled trials of treatment of moderate and severe essential hypertension during the period that treatment was being rapidly extended. By the early 1970s the issue was becoming pressing because millions of patients with mild hypertension were being considered for treatment. In 1971 the Medical Research Council agreed to conduct a trial in mild essential hypertension. I had some part in the decision, having written to the Secretary of the Medical Research Council to suggest a trial; the Medical Research Council received similar advice from its epidemiology committee at about the same time. Bill Miall, and later Gillian Greenberg with the collaboration of many general practitioners performed the
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vast work of recruiting patients and guiding the trial to a successful conclusion. And so it was that 14 years later we met at the Medical Research Council head office under the chairmanship of W S Peart to tell the press what we had discovered. It did not seem much: a 45% reduction in stroke (the trial numbers had been calculated on the basis of a 40% reduction); a powerful adverse effect of cigarette smoking; and no more than a hint of benefit for myocardial infarction in one subgroup. But my overriding impression of the 36 years since Smirk is not that we put too much effort into outcome trials but that we put far too little. The prospect for the next 10–15 years is not encouraging with many new drugs and little new outcome data (the trial pipeline is almost empty). It is not the best legacy to have left our successors.

References

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