The history of hypertension: 1950–1970

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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In the previous instalment of *Tattersall's Tales*, Robert Tattersall explored the history of hypertension up to 1950. This instalment details the developments that took place between 1950 and 1970. The final instalment will take us to the present day.

In 1950 most physicians believed that if blood pressure was lowered in hypertensive patients, the result would be uraemia or a stroke. This was based on the old dictum that high pressure was a beneficial adaptation to force blood through the narrowed arteries. In any case, there was no effective hypotensive agent and this reinforced the view that there was no need for treatment. At this time, in the words of Oage (1981), hypertension had 'no class, no charisma, and almost no advocates'. What kept the physiologists, the pharmaceutical chemists and a few physicians interested was the prospect of finding a treatment for the relatively rare malignant hypertension, which was fatal in 90% of cases within a year.

In 1946 it was noticed by chance that an antimalarial drug, pentaquine, produced orthostatic hypotension in volunteers and in 1947 it was tested in three patients with malignant hypertension, in whom it cured the headache and led to resolution of retinopathy and heart failure. Unfortunately the side effects were too severe for clinical use but it showed the error of the prevailing opinion that lowering blood pressure was dangerous (Freis and Wilkins, 1947).

Hypotensive agents

By 1955 four classes of hypotensive agents were available: (1) veratrum alkaloids, (2) ganglion blockers such as hexamethonium or pentolinium, (3) hydralazine and (4) rauwolfia alkaloids.

Veratrum alkaloids

Veratrum alkaloids were prepared from the roots or seeds of *Veratrum viride*, a plant related to the lilies, one variety of which was known, for obvious reasons, as the sneezewort. They had been used in the 19th Century as emetics and cathartics and as the source of an organic caterpillar killer. In the 1920s tincture of veratrum was used to treat eclampsia and it was said that 'if the pulse was kept at or below 65 beats per minute, the woman could not have convulsions.' In 1950 it was confirmed that veratrum alkaloids caused profound, if transient, falls in blood pressure but they were soon abandoned because the effective hypotensive dose was barely different from that which caused nausea and vomiting (Meilman and Krayer, 1950).

Ganglion blockers

The ganglion blocker hexamethonium, first used in 1950, was often described as 'a chemical sympathectomy', although it also blocked the parasympathetic system. A 1950 trial in 15 patients with malignant hypertension showed regression of retinopathy, reduction in heart size and clearing of the signs of heart failure (Restall and Smirk, 1950) and in a 1955 symposium, McMichael and Murphy (1955) from the Royal Postgraduate Medical School reported a 3-year survival of 40% compared with none in historical controls. Apart from the fact that it had to be given two or three times a day by subcutaneous injection, a bugbear was that the hypotensive effect was exclusively postural. (I remember, as a house physician in 1967, treating a patient with a ganglion blocker; he lay on a tilt table so that we could adjust his blood pressure by altering his inclination. My registrars thought this was great fun but it was hell for the patient, who had been converted into what my pharmacology textbook called 'hexamethonium man'. He had to stand up for as much of the day as possible, was not able to read, had constipation and difficulty urinating, had a dry mouth and was impotent.) Clearly this was a desperate treatment for a desperate disease, and not something to give to people with asymptomatic hypertension.

Hydralazine

Hydralazine, which is still used in some parts of the world, was developed soon after the ganglion blockers and was shown to be a vasodilator which increased renal blood flow. It was effective but the side effects of palpitation, headache and a lupus-like syndrome were pointed out by what one might call the 'therapeutic nihilists'.

Rauwolfia alkaloids

Rauwolfia serpentina, or snake root, is an Indian climbing shrub, extracts of which had long been used as a sedative. A pure compound, reserpine, was isolated in the Ciba laboratories in Basle in 1952. It only worked in 50% of cases and, although its side effects were often described as mild by doctors, they included nasal congestion, weight gain and depression – the last one sometimes led to suicide. Because of its sedative effect, it was thought to be the drug of choice for the 'mild labile hypertensive patient with anxiety neurosis'.

'Where does hypertension begin?'

Most ordinary physicians were reluctant to use these drugs unless the blood pressure was inordinately high. In an editorial in 1957 entitled 'Where does hypertension begin?', the *Lancet* pointed out that, 'although many write as though hypertensives formed a clear-cut group like paraplegics,' several studies of large groups of normals had shown that, as with glucose tolerance, there was no natural cut-off between normal and abnormal (Lancet, 1957). The conclusion was that:

> *'At present blood pressure can only be lowered at the cost, not only of constant medical supervision, but also of various unpleasant effects. Before he exposes* [symptomless] *hypertensives to the perils of mecamylamine ileus, veratrine emesis, reserpine psychosis, or hydrallazine lupus, a manometric Procrustes[1] should be sure of his ground.'*

1. Procrustes was a Greek tyrant who only had one bed for his guests. If they were too short for it, he stretched them, and if they were too long, he cut bits off.

Major advances

The most important advance was the synthesis of the diuretics chlorothiazide, in 1957, and hydrochlorothiazide, in 1958 (Beyer, 1977). The reason this was such a breakthrough was that lower doses of the other agents could be used with a reduction in side effects. Also, in contrast to other drugs available at the time, they were pleasant to take, and they soon gained a large share of the market. In 1961, 30 million prescriptions were issued in the USA. Unfortunately, they also turned out to be diabetogenic, at least in people with a strong family history or 'subclinical diabetes'. A minority of patients with established diabetes were liable to be destabilised by a thiazide, but when it was stopped the *status quo ante* was usually restored (Goldner et al, 1960).

A new benzothiadiazine, diazoxide, was introduced in 1962 and turned out to be very strongly diabetogenic. The first two patients, aged 30 and 60, treated with it at the Hammersmith Hospital in London developed diabetes acutely after 4 weeks with fasting blood sugars of 21.1 and 32.5 mmol/l. Both had normal glucose tolerance 17 days after the drug was withdrawn (Dollery et al, 1962). Diazoxide was later used with modest success in the treatment of insulinomas. Two more drugs were introduced in 1960, alpha-methyldopa and guanethidine. The latter had many side effects, including flushing, postural hypotension, diarrhoea and failure of ejaculation, while methyldopa was promoted as a 'patient-friendly' drug, although most who took it never felt really well.

Now that physicians had a choice of half a dozen or more effective blood pressure-lowering drugs, the question was who to give them to.

Who should receive antihypertensive drugs?

The issue was debated in an American context in a 1966 book, *Controversies in Internal Medicine* (Ingelfinger et al, 1966). The view of the 'therapeutic nihilists' was that the only justification for antihypertensive drugs was if cardiac, cerebral, renal and retinal vascular disease could be proved to be a direct consequence of raised blood pressure. To them it seemed quite possible, or even probable, that vascular disease might cause hypertension or that the two might be independent – similar arguments were put forward at the same time about the relation between hyperglycaemia and diabetic complications. Their conclusion was that, 'after about 15 years of data collecting, the alleged usefulness of antihypertensive drugs rests on conclusions drawn from notoriously uncertain statistical complications compounded by equally uncertain estimates of morbidity and mortality in the natural history of a disease of highly unpredictable course.' Their argument was bolstered by a 1960 trial in which 58 patients with complicated hypertension (diabetes was specifically excluded) were divided into two groups, one left untreated and the others given a variety of available treatments. After follow-up of 5 years, 16 in each group had died (Perera, 1960).

Those who believed the treatment of hypertension to be beneficial pointed to the dramatic way in which drugs had changed the course of malignant hypertension while accepting that there had been no adequate trials in ordinary hypertension. In his editorial comment in *Controversies in Internal Medicine*, Arnold Relman suggested that the reason there had not been any trials was that:

> *'Physicians find it difficult to withold for very long any highly touted form of therapy that appears relatively safe and simple to us, even though its ultimate value has yet to be clearly established. The achievement of lower levels of blood pressure, which is usually possible with drugs, seems like such a tangible and immediate benefit that most patients, and many physicians, never bother to wonder whether this will in the long run prove to be helpful.'*

Diabetes specialists, who were of course general physicians, were well aware that many of their patients had high blood pressure but it was not something which seems to have interested them very much. In the English textbook of Oakley, Pyke and Taylor (1968), two pages were devoted to a discussion about whether hypertension was more common in people with diabetes than the general population (surprisingly the answer was 'no') and a half-page was devoted to treatment. In the American textbook of Ellenberg and Rifkin (1970) it merited only one paragraph, which concluded that it became more common with increasing duration of diabetes. Both books advised that it should be treated in the same way as hypertension in people without diabetes. In 1973 in a review of diabetes and hypertension, Richard Christlieb of the Joslin Clinic could not find a single trial of antihypertensive therapy in diabetes but he did point out that the Framingham study showed a higher mortality and morbidity from heart attacks and strokes in the person with diabetes and hypertension than his or her normoglycaemic brother or sister (Christlieb, 1973). Whether treatment would prevent such outcomes was unknown but Christlieb relied on the 1967 results of the Veterans Administration studies in people without diabetes or hypertension to suggest that treatment would be equally, if not more, effective in those with diabetes (Veterans Administration Cooperative Study, 1967).

As I remember it from 1970, my bosses were unconvinced of the benefit of treatment in common or garden hypertension and were also reluctant to burden their patients who had diabetes with yet another lot of tablets and potential side effects. The change which took place over the next 30 years was truly remarkable and will form the third article in this trilogy.

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