Personal and Historical Perspectives

Sir Horace Smirk
Pioneer in Drug Treatment of Hypertension

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Sir Horace Smirk deserves much of the credit for establishing the benefits of reducing blood pressure. He was one of the main early proponents of the idea that it was the raised intra-arterial pressure itself that caused many of the cardiac and vascular complications of hypertension. His training in both pharmacology and internal medicine enabled him to devise practical methods for successful treatment of hypertension with ganglion blocking drugs such as hexamethonium. The major clinical benefits that followed such drug treatment proved a great stimulus to the development of drugs with fewer disadvantages and to widespread acceptance of the beneficial effects of antihypertensive drug treatment. (Hypertension 1991;17:247–250)

Sir Horace Smirk was born in Lancashire, England, in 1902 and graduated with distinction in medicine from the University of Manchester in 1926. After resident appointments, he was awarded a traveling research scholarship that enabled him to study in Vienna. He was subsequently awarded a Beit Memorial Fellowship, one of the few paid research appointments available in the 1930s. Smirk took up the appointment at University College Hospital, London, where T.R. Elliot was establishing one of the very few departments in which clinical and laboratory research were encouraged. Sir Thomas Lewis was a major figure in the department, and other young graduates such as Pickering, Wayne, and McMichael, who all later became professors of medicine, were also in this department.

Smirk was obviously greatly influenced by his experiences in this department. He greatly admired Thomas Lewis and often spoke of his considerable accomplishments. There was considerable competition among the graduate students in this environment, which no doubt was partly related to the fact that at that time there were few senior appointments in England and Scotland to which they could hope to be appointed. Although most of his peers succeeded to chairs of medicine in the United Kingdom, Smirk made the rather unusual transfer in 1935 to the chair of pharmacology in Cairo, where he succeeded Gaddum, who returned to Edinburgh. Smirk remained in Cairo for 7 years; while there he began a systematic search for new drugs, particularly those that might reduce or raise blood pressure or affect cardiac rhythm. He continued his developed interest in the physiology of hypertension and in particular the question of the factors influencing variability of blood pressure. With Alam, he described the reflex effects of ischemic skeletal muscle on blood pressure and found that the responses were greater in hypertensive than in normotensive persons. They also developed the concept of casual and basal blood pressures and advanced the hypothesis that a large rise of blood pressure in response to either physical or mental stimuli might be an important precursor of both hypertension and secondary hypertrophy of arterioles leading to persistent elevation of blood pressure.

In 1942, Smirk was appointed to the chair of medicine at the University of Otago, Dunedin, New Zealand. His was the first appointment of a full-time professor of medicine in this school. Previous incumbents had been part-time physicians with major interests in clinical medicine but little interest in research. In later years, Smirk described how, at the time of his appointment, the only laboratory facilities available consisted of a solitary Bunsen burner. After appointment to the chair of medicine, Smirk also assumed responsibility for the teaching of pharmacology, a strategy that provided his department with laboratory facilities and a budget for apparatus for practical classes with which he was able to continue his laboratory research. He was able to recruit F.N. Fastier, with whom he continued studies on drugs that he had begun to develop in Cairo. One of these was amarin, which Fastier and Smirk showed could induce idioventricular rhythm in conjunction with epinephrine. It was during the course of these animal experiments that Smirk first noted the premonitory interruption of the T wave by ectopic R waves, leading to ventricular tachycardia and fibrillation.

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subsequently noted the same phenomenon clinically and showed that this was an electrocardiographic harbinger of subsequent sudden death due presumably to ventricular fibrillation, an observation that was widely confirmed when coronary care units were established some 15 years later.

While in Dunedin, Smirk attempted to reproduce the kind of research-based clinical department in which he had worked with Sir Thomas Lewis. He continued with his work on basal blood pressure and with younger colleagues was able to define the importance of the basal level of blood pressure as a guide to prognosis. He also began experiments in rats, including attempts to induce hypertension by exposing them to intermittent loud noise produced with motor horns. This work later led to the development, by selective inbreeding, of a group of Wistar rats with spontaneous hypertension.

At this time, attempts to treat hypertension were sporadic. It was generally believed that the rise in blood pressure was in some way necessary to maintain the perfusion of vital organs such as the heart, brain, and kidney, and it was widely supposed that attempts to reduce blood pressure without removing the underlying cause of the hypertension would lead to widespread ischemia of these organs. This later led to the development, by selective inbreeding, of a group of Wistar rats with spontaneous hypertension.

Smithwick also commented that falls of blood pressure of significant degree lasting 1–5 years occurred in about 50% of patients.

In the late 1940s, a second method of treating severe hypertension, namely, the rice diet, was developed by Kempner. This diet consisted solely of rice boiled in distilled water with the addition of fruit juices and provided a daily intake of less than 10–20 meq sodium. In some cases of malignant hypertension, improvement was dramatic. Blood pressure fell, the enlarged heart was reduced in size, and manifestations of heart failure disappeared, and some patients with malignant hypertension survived for several years. The major role played by the reduction in blood pressure was again overlooked in favor of ideas about the pathogenetic mechanisms that sodium restriction might be counteracting.

It is reasonable to conclude that during 1948–1950, there was little general enthusiasm for the likely role of blood pressure reduction per se as a therapeutic measure in hypertension. Smirk had formulated a view about the pathogenesis of essential hypertension, which was published in 1949. The concept held that although the initiation of the rise in blood pressure may be of composite origin, the rise in blood pressure itself leads to a number of pathological changes that serve to maintain and further to elevate the blood pressure. Smirk also postulated that it was the elevated blood pressure itself that was responsible for most of the clinical manifestations of hypertension, which as he pointed out were the same irrespective of the underlying pathology. In a later paper, Smirk summarized his views as follows:

Essential hypertension is both a syndrome and a disease. It is a syndrome in that its characteristic clinical and pathological features form part of all protracted high-blood-pressure cases, whatever the primary cause. It is a disease in that the clinical entity we call essential hypertension the syndrome is the whole disorder. In nephritis, cortical hyperadrenalism, and many other conditions associated with blood-pressure elevation, the syndrome of essential hypertension is only part of the disease.

Thus Smirk had the conviction that reducing blood pressure was likely to be an effective way of improving the clinical state of hypertensive patients; additionally, he had the requisite training in pharmacology that was
to prove so important in developing the techniques to use ganglion blocking drugs successfully.

Although the pharmacology of the quaternary ammonium bases had been known since 1868, it was not until 1915 that Burn and Dale showed that tetraethylammonium chloride (TEAC) could block autonomic ganglia without any nicotinelike initial stimulation. TEAC gained some popularity as a test substance to establish whether it would induce a fall in blood pressure in patients being considered for surgical sympathectomy, but it does not seem to have been used definitively to treat hypertension. In 1948, Barlow and Ing synthesized a new series of quaternary ammonium compounds in which two quaternary ammonium groups were separated by a chain of CH₃ groups. These workers were mainly interested in the curarelike actions of the C10 compound decamethonium, which had 10 separating CH₃ groups. However, the C5 and C6 members of this series, pentamethonium and hexamethonium (halides), were reported by Paton and Zaimis to be powerful blockers of autonomic ganglia, and later in 1949, two groups of British workers reported that intravenous or intramuscular injections of hexamethonium or pentamethonium in human subjects produced a fall of blood pressure that was more marked when the subjects were standing than when they were lying down. The idea that these drugs, by producing a "medical sympathectomy," might be able to reproduce the success of the surgical treatment pioneered by Smithwick was attractive, and during the latter half of 1949, the manufacturers, May and Baker, approached a number of clinicians to request clinical trials of hexamethonium and pentamethonium. Readers in 1991 will perhaps note with envy that the time taken from synthesis to clinical use was between 1 and 2 years; no drug regulatory approval was sought since no regulatory agencies existed at that time. It is certainly difficult to imagine that the ganglion blocking drugs, if introduced now, would have a smooth passage through the drug licensing agencies. The drug was made available to a number of researchers in Britain. Among these was Horace Smirk, who was spending a period of study leave at the Postgraduate Medical School in London and who was able to return to New Zealand with a supply of both hexamethonium and pentamethonium salts. During 1949 and 1950 some preliminary reports were published on the use of methonium compounds in hypertension. Arnold and Rosenheim confirmed that the drug produced marked falls of blood pressure and concluded that although pentamethonium was of value in the investigation of hypertension, postural hypertension would limit its use in routine treatment. They thought it would prove of value in the control of hypertension crises. Turner reported three cases in detail in a paper that emphasized the difficulties that he had experienced in using oral doses of hexamethonium. He concluded that the methonium drugs had as yet no place in the routine management of patients, although they might prove useful in the treatment of resistant symptoms related to hypertension. Saville reported using the drug in five patients; she thought that methonium drugs might be useful and emphasized that in all five cases symptoms had been relieved and progress of the disease had apparently been halted. Campbell and Robertson described eight cases of severe hypertension treated with hexamethonium with marked lowering of blood pressure and relief of symptoms. They believed, on the basis of this experience, that hexamethonium seemed likely to provide a useful method of reducing blood pressure with relative freedom from toxicity.

In 1950, Restall and Smirk described their initial results in treatment of hypertension with methonium compounds, and these results were summarized by Smirk in a letter to the Lancet. In 26 patients with severe hypertension, hexamethonium or pentamethonium compounds were given by subcutaneous injection with very small initial doses and use of the postural effect to maximize the falls of blood pressure produced by these minimal doses. Smirk stressed the need for individualization of treatment, emphasizing that each patient had different dose requirements, that tolerance slowly developed, and that the antihypertensive effects of these drugs were greatly enhanced by low sodium intake, by diuretics, and by fever. Smirk emphasized that because dose requirements were so precise in individual patients, oral treatment was not safe because the drug absorption was extremely variable, even in the same patient at different times. Smirk also stressed that by using the postural effect and small doses to maximize reduction of blood pressure, the severity of the side effects due to parasympathetic ganglion block, such as dry mouth, constipation, and blurred vision, could be minimized. In a summary to an article describing practical details of treatment, Smirk commented that "substances which in overdoses can reduce the casual systolic blood pressure from 260 to under 60 mm of mercury require knowledgeable handling."

Two or three subcutaneous injections of hexamethonium daily caused a dramatic clinical improvement with disappearance of papilledema, retinal hemorrhages and exudates, resolution of congestive heart failure with reduction in pulmonary congestion and heart size, and disappearance of hypertensive headache. Patients were taught to administer their own injections and were also taught that as in diabetes, accurate control of dosage was critically important to achieving good results in hypertension.

I arrived in New Zealand to work with Smirk at the beginning of 1952. Having been working in a traditional way in a British hospital, I was amazed at the confident and routine way that these difficult drugs were being used. Smirk had anticipated by some 15 years the use of nurses to administer drugs and to observe results. Patients would arrive at the clinic at about 8:30 AM, have blood pressures recorded while seated and standing, and be given a dose of hexamethonium subcutaneously by the nurse. Blood pressures were then recorded in both postures at 30-
minute intervals throughout the day. At about 12:30
PM Smirk would visit the clinic, look at the data, and
order the appropriate afternoon doses. Patients
would attend daily until the correct dose had been
attained and would then be allowed to leave, having
been supplied with tuberculin syringes, needles, and
multidose containers of the drug, which they had
been trained to use. Incidentally, drugs in the multi-
dose containers had been made up in the Depart-
ment of Pharmacology at the university by dissolving
bulk supplies obtained from May and Baker in the
United Kingdom. It was 1–2 years before prepacked
multidose vials were supplied by the manufacturers.
In retrospect, it is not surprising that it took a long
time for other centers to be in a position to repro-
duce these results. Even by 1954, when I returned to
London, there were few specialized hypertension
clinics and none with the expertise that had been
developed in Dunedin.

Some centers in the United States were quick to
appreciate the significance of Smirk’s observation.
Freis and his colleagues25 in 1952 confirmed most of
Smirk’s findings and, in addition, emphasized the
value of combining hexamethonium with the recently
described drug hydralazine.29 Schroeder28 also re-
ported favorably on the combined use of hydralazine
and hexamethonium (hyphex). Subsequently, the in-
roduction to Western medicine of Rauwolfia serpen-
tina (reserpine)29 and the demonstration of the effi-
cacy of a combination of reserpine and the ganglion
blockers30 ultimately led to the concept of the use of
several drugs to control hypertension.

In many ways, although the drugs have changed,
the concepts established in the early 1950s have
remained the basis for drug treatment of hyperten-
sion until the present day. Sir Horace Smirk played a
major role in the development of these concepts and
has earned a lasting and honored place in the history of
hypertension.

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KEY WORDS • historical article • antihypertensive agents
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Hypertension. 1991;17:247-250
doi: 10.1161/01.HYP.17.2.247

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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