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How does a Drug become Medicine? Hexamethonium and the Treatment of High Blood Pressure, 1940s-1950s

Carsten Timmermann

Popular accounts of drug discovery usually start with a disease in search of a cure. This may well be an adequate approach to the history of therapeutic substances such as salvarsan, the sulfonamides, or penicillin, even streptomycin, but for other medicines the case is less clear cut. Rein Vos suggested in his 1991 book that the process for some drugs can be characterized as ‘Drugs Looking for Diseases’.¹ His case studies are the beta blockers and the calcium antagonists, which both came into widespread use for the treatment of high blood pressure, or hypertension, a disorder that, as we understand it today, is neither life threatening nor has immediate symptoms, but increases the risk of suffering cardiovascular complications later in life.² However, these substances were not the first drugs that were used for the treatment of hypertension. By the time the beta blockers and the calcium antagonists were ‘looking for diseases’, hypertension was considered treatable. It became a treatable disease, as I will demonstrate in this paper, through the construction of a standardized treatment package, a set of routinized clinical practices associated with an earlier drug: hexamethonium, a substance that became known as a so-called ganglion blocker. I will look at developments in the late 1940s, at the UK National Institute for Medical Research (NIMR) and the Headquarters of the Medical Research Council (MRC) in London, several hospitals in Britain and a teaching hospital in Dunedin, New Zealand, tracing how a substance that had long been known as a physiological research tool, turned into medicine. MRC officials acted as boosters and matchmakers in this story, between pharmaceutical industry, laboratory researchers and clinicians. My argument is, first, that clinical routines associated with the management of the drug and its side effects were crucial to this process, and, second, that ‘treatability’ (and the disciplining that was incorporated in the treatment protocols) changed the nature of the disease that was treated, both in terms of meanings and of incidence, as the disease became ‘manageable’ and the malignant form of hypertension disappeared from the industrialized world. The availability in the MRC archives of treatment manuals developed in Dunedin, along with correspondence with the MRC headquarters, allows us to understand this process. But let us first look at the drugs at the centre of this story.

1 A longer paper based on this material has been published as ‘Hexamethonium, Hypertension and Pharmaceutical Innovation: The transformation of an experimental drug in post-war Britain’, in C. Timmermann and J. Anderson (eds), *Devices and Designs: Medical Technologies in Historical Perspective*, Houndmills: Palgrave Macmillan, 2006, pp. 156-74.

R. Vos, *Drugs Looking for Diseases: Innovative Drug Research and the Development of the Beta Blockers and the Calcium Antagonists*, Dordrecht/Boston/London: Kluwer, 1991. On beta blockers, see also V. Quirke, ‘Putting Theory into Practice: James Black, Receptor Theory and the Development of the Beta-Blockers at ICI, 1958-1978,’ *Medical History*, 50 (2006), 69-92.

2 On hypertension and its treatment see also C. Timmermann, ‘A Matter of Degree: The Normalisation of Hypertension, circa 1940–2000’, in: W. Ernst (ed.), *Histories of the Normal and the Abnormal: Social and cultural histories of norms and normativity*, London: Routledge, 2006, pp. 245-261; idem, ‘To Treat or Not to Treat: Drug Research and the Changing Nature of Essential Hypertension’, in T. Schlich and U. Tröhler (eds), *The Risks of Medical Innovation: Risk Perception and Assessment in Historical Context*, London: Routledge, 2006, pp. 133-147.

Quaternary ammonium salts

The quaternary ammonium salts that later became known as ganglion blockers were well known by the 1940s, but not used for clinical purposes. They had been tools for physiological research for decades. Pharmacologists and physiologists, notably the members of the Cambridge school, had been interested in these substances because some of their effects on experimental animals resembled those of the nerve poison curare. Their main focus of interest was not the clinical application of these drugs; they were studying the molecular mechanisms of the nervous system. The blood pressure lowering effect of some of these compounds, especially Tetraethylammonium (TEA) had been noted on a few occasions but never seen as particularly significant.³

The name that came to be used to describe these compounds, ganglion blocking drugs, was a product of academic research on TEA by two young physiologists, George Acheson and Gordon Moe at Harvard Medical School in 1945 and 1946. To explain some of the effects of the drugs in animal experiments, Moe suggested that the TEA ion blocked the ganglia of the autonomic nervous system. What distinguished Acheson and Moe from the researchers that had previously investigated the effects of quaternary ammonium compounds was that they found it worthwhile to explore possible clinical applications for TEA. They initiated clinical tests for TEA, but these were not very successful. The effects of the drug did not last long enough and, while the tests established the notion of ganglion blockade as a possibility, TEA was not the drug that could move smoothly from bench to bedside. The first ganglion blockers that were to prove clinically useful were the methonium compounds, and for this part of the story we are now looking to Britain, to the MRC's National Institute for Medical Research in Hampstead.

As was the case for TEA, the observation that methonium compounds had an effect on blood pressure was partly a serendipitous discovery, a by-product of work within the framework of a certain physiological-pharmacological tradition combined with a heightened sensitivity for cardiovascular effects in the post-war years. The physiologist William Paton came across the methonium compounds, when his laboratory at the NIMR – not for the first time – took on some work for the Institute's Division of Biological Standards. Paton and his colleagues were asked to look at the toxicity of a promising antibiotic substance, licheniformin, that a member of the Chemotherapy Division, R.K. Callow, had isolated from microbe cultures. They injected the licheniformin into a cat under chloralose and found that nothing happened for about 25 seconds, when an abrupt and transient fall in blood pressure could be measured. The effect impressed Paton and colleagues because 'it was such an interesting and clean response'.⁴ Callow told them more about the chemical structure of licheniformin, and Paton obtained a range of substances with related chemical groups, in many of whom they found that they triggered a similar 'delayed repressor response'. The series of compounds they tested also contained two derivatives of the methonium series, C8 and C16 (the figure represents the number of atoms in the carbon chain

3 G. H. Acheson, 'Tetraethylammonium, Ganglionic Blocking Agents, and the Development of Antihypertensive Therapy', *Perspectives in Biology and Medicine*, 19 (1975): 136-148.

4 W. D. M. Paton, 'Hexamethonium', *British Journal of Clinical Pharmacology*, 13 (1982): 7-14, pp. 7-8. See also Paton Laboratory Notebooks, Wellcome Library, PP/WDP/C/1/2. The excitement over clean and pure responses seems to be a typical sentiment for pharmacologists, and it comes up again and again, not only in Paton's writings. For other examples, see Vos, *Drugs Looking for Diseases*.

between the two quaternary ammonium groups). C8 produced a somewhat different, but also remarkably clean response. It proved to be a potent neuromuscular blocking agent, a drug that led to temporary paralysis, with potential applications for anaesthesia and surgery.

The decision to further pursue work on this group of substances was informed by the growing interest in developing synthetic drugs with curare-like action, to treat convulsions and as muscle relaxants for surgery. Colleagues in the institute had long been researching the active principle of curare, and Paton, together with a new colleague, Eleanor Zaimis, decided to undertake a study of the whole series of methonium compounds and their effects, with carbon chain lengths from C2 to C12. When they started this work, Paton and Zaimis discovered that Ing and Barlow at Oxford were studying the same compounds, in a more systematic way and as one among a number of other homologous series, in an attempt to explain the structure-action relationships of neuromuscular block.⁵ In 1948, both groups arranged a simultaneous publication (as Letters to the Editor) in the journal *Nature*. It is worth noting that effects on blood pressure were mentioned in neither paper.⁶ Such effects had been observed, though. Paton and Zaimis injected the drug into a number of laboratory animals, which revealed that C5 and C6, the compounds most active in anaesthetised cats, had significant effects on the animals' blood pressures.⁷

There was some interest in possible uses as anti-hypertensives, mostly due to Acheson and Moe's series of articles two years earlier on TEA and its effect on blood pressure and to an increasingly lively debate over the aetiology and treatment of hypertension in the medical journals.⁸ At the time, however, the methonium compounds to Paton and Zaimis were above all interesting pharmacological research tools. Only in a further letter to *Nature* in November 1948 they suggested – in one brief sentence at the end of the paper – that C6 'offers possibilities of clinical usefulness in such fields as hypertension and vascular disease, whenever tetraethylammonium iodide has too brief or slight an action'. In the following section I will follow the MRC's attempts to establish the methonium compounds in the clinic.

Clinical trials and invisible industrialists

In order to explore possible clinical uses of the methonium drugs, the MRC launched an informal committee, chaired by Paton.⁹ Paton and Zaimis heroically tested the effects of several methonium compounds on themselves at Westminster Hospital, assisted by the anaesthetist Geoffrey Organe.¹⁰ A very short time later the MRC initiated the first clinical study of

5 Paton noted later that 'Barlow and Ing have never at any time either looked for or been interested in the ganglionic actions of this series'. Paton to Green, 19.7.1950, UK National Archives, FD1/1172.

6 R. B. Barlow, H. R. Ing, 'Curare-like Action of Polymethylene bis-Quaternary Ammonium Salts', *Nature* 161 (1948): 718. W. D. M. Paton, E. J. Zaimis, 'Curare-like Action of Polymethylene bis-Quaternary Ammonium Salts', *Nature* 161 (1948): 718-719.

7 Paton Laboratory notebooks.

8 C. Timmermann, 'A Matter of Degree: The Normalisation of Hypertension, circa 1940–2000', in W. Ernst (ed.), *Histories of the Normal and the Abnormal: Social and cultural histories of norms and normativity*, London: Routledge, 2006, pp. 245-261.

9 UK National Archives, FD1/1172.

10 G. Organe, W. D. M. Paton, E. J. Zaimis, 'Preliminary Trials of Bismethylammonium Decane and Pentane Diiodide (C10 and C5) in Man', *Lancet*, 253 (1949): 21.

pentamethonium for the treatment of hypertension. The *Lancet* published the results in August 1948.¹¹ The investigation was carried out by P. Arnold and Max Rosenberg in the Medical Unit at University College Hospital, where Rosenberg had succeeded Thomas R. Elliott on the first, MRC-funded, full-time chair for clinical research in Britain.¹² Arnold and Rosenberg reported that ‘pentamethonium iodide has an action similar to that of tetraethylammonium chloride, but it is effective in smaller doses’ and that ‘an excessive fall in blood-pressure has been the only serious toxic effect so far observed’.¹³ Anaesthetists experimented with hexamethonium as an antidote to the muscle relaxant decamethonium and viewed blood pressure reduction as an undesired side effect: ‘In the very first case it seemed that the ensuing hypotension might be severe enough to be fatal.’¹⁴ It is not obvious from these early publications that soon the lowering of blood pressure would be discussed as the main beneficial effect rather than a dangerous side effect of ganglion blockers. During an MRC Conference on Clinical Tests of Methonium Drugs on 22 June 1950, hypertension was only one among several possible indications.¹⁵

The initial responses to the methonium compounds and the suggestion that they might provide a useful treatment option for high blood pressure were cautious. Increasingly, though, they were cautiously optimistic. A series of articles reporting results of studies were published in the *Lancet* in 1950. So were reports on other antihypertensive treatments, all relatively new, such as the Kempner Rice Diet or a variety of surgical procedures. Some authors characterized the effect of hexamethonium as ‘medical sympathectomy’.¹⁶ One of these early, cautiously positive responses is that by Stephanie Saville. Saville reported the results of a study undertaken at St Martin’s Hospital, Bath, in a well-established clinic for hypertension. The customary treatment over years in this clinic had been rest in bed, sedation, and regular venesection, to which ‘many patients failed to respond significantly or to maintain initial improvement’. Five cases of malignant hypertension were experimentally treated with pentamethonium, starting in December 1949, initially in the hospital and later also as outpatients. The aim was to lower the blood pressure enough to relieve symptoms without provoking others due to hypotension. While Saville was reluctant to predict the final outcome, she observed that ‘none of the five cases sufficiently treated to date has failed to obtain relief from symptoms’. Saville’s conclusion: ‘The results in 5 patients suggest that pentamethonium bromide may be useful in the treatment of at

11 P. Arnold, M.L. Rosenheim, ‘Effect of Pentamethonium Iodide on Normal and Hypertensive Persons’, *Lancet*, 254 (1949): 321-323.

12 Ibid.

13 Ibid.

14 A.R. Hunter, ‘Hexamethonium Bromide’, *Lancet*, 255 (1950): 251-252, p. 252.

15 Conference on Clinical Tests of Methonium Drugs, 22.6.1950, Minutes of the Meeting, UK National Archives, FD1/1172.

16 R. Turner, “Medical Sympathectomy” in Hypertension: a clinical study of methonium compounds’, *Lancet*, 256 (1950): 353-358. See also M.L. Rosenheim, ‘Lability of Blood Pressure’, *Lectures on the Scientific Basis of Medicine*, 1951-1952, 1 (1953): 96-115. On the rice diet, see ‘Diet in Hypertension [editorial]’, *Lancet*, 255 (1950): 549-560; ‘Rice Diet in Hypertension [editorial]’, *Lancet*, 256 (1950): 529-530. The MRC organized a study of the effects of the rice diet: D.R. Cameron, D.M. Dunlop, R. Platt, M.L. Rosenheim, E.P. Sharpey-Schaffer, ‘The Rice Diet in the Treatment of Hypertension: A report to the Medical Research Council’, *Lancet*, 256 (1950): 509-13. On surgery: R. Platt, S.W. Stanbury, ‘Sympathectomy in Hypertension’, *Lancet*, 255 (1950): 659-659; ‘Sympathectomy in Hypertension [editorial]’, *Lancet*, 255 (1950): 768-769.

least some forms of hypertension.¹⁷ Allan Campbell and Eric Robertson at the Royal Alexandra Infirmary, Paisley found (in a study with 8 patients) that ‘hexamethonium seems to provide a useful method of reducing the blood pressure in severe hypertension with ready administration and relative freedom from toxicity’.¹⁸ The main problem was finding the right dosage, and some of the side effects were quite drastic, too. R. Turner in Edinburgh suggested that ‘methonium drugs have as yet no place in the routine management of patients, though they may prove useful in the treatment of resistant symptoms related to hypertension. We need more information about their precise action, and for the present it will be most profitable to study, in detail, patients who might otherwise be treated by sympathectomy.’¹⁹

Several of the early studies with methonium compounds, which – like those undertaken at UCH, in Bath or Glasgow – involved rather small numbers of patients for today’s standards, were initiated and supported by the MRC.²⁰ There appeared to be no formal protocol for such testing procedures, and the programme was organised relying on connections within an informal network of researchers associated with the MRC. The Council also mediated between the clinical researchers and the British pharmaceutical companies that provided the drugs, which included Wellcome Burroughs, Allen & Hanbury’s, and more often than the others, May & Baker. Like TEA, the methonium compounds were not patent protected, and the drugs from different producers were different only with regard to preparation and sometimes purity.

Drug companies played a remarkably small and subordinate part in the transformation of the ganglion blockers, quite different from the pro-active role in the development of new drugs that forms part of the image of this industry today. The ganglion blockers provide us with an example for a major pharmaceutical innovation that had its origins in the public sector. Austin Doyle in an article published in 1991, projecting current patterns of drug development on the past, assumed that May & Baker approached clinicians with the request to test the methonium compounds in the clinic.²¹ The files in the National Archives tell a different story, one where the MRC pulled the strings in the crucial period between 1948 and 1952, with Paton as an inofficial patron of the ganglion blockers, supported and backed by Frank Green, the MRC’s Principal Medical Officer.

The MRC acted as a booster for the methonium drugs and a ‘matchmaker’ between clinical researchers and drug manufacturers, who assumed, it seems, that it was improper for them to approach the researchers directly. A memo by Green in 1950 illustrates the mechanics of this interaction and the central role of the Council:

I telephoned to Dr Forgan [of May & Baker] to ask him to send supplies of pentamethonium and hexamethonium for trial by the mouth in cases of hypertension. Forgan said he would be glad to do so. He asked whether it would be in order for him to invite Rosenheim to express an opinion on the relative effects of these two substances, as May & Baker have the

17 S. Saville, ‘Pentamethonium in Hypertension’, *Lancet*, 256 (1950): 358-60.

18 A. Campbell, E. Robertson, ‘Treatment of Severe Hypertension with Hexamethonium Bromide’, *British Medical Journal*, 256 (1950): 804-806.

19 R. Turner, “‘Medical Sympathectomy’ in Hypertension: a clinical study of methonium compounds’, *Lancet*, 256 (1950): 353-358.

20 Minutes of a meeting on clinical tests of methonium drugs held on 19 July 1950, UK National Archives, FD1/1172.

21 A.E. Doyle, ‘Sir Horace Smirk: Pioneer in Drug Treatment of Hypertension’, *Hypertension*, 17 (1991): 247-250, p. 249.

impression that hexamethonium is so much more useful than pentamethonium that the latter may be on its way out. I said that there would be no objection whatever from our point of view to his asking Rosenheim this or any other question which occurred to him. (Note: May & Bakers still seem to be under the erroneous impression that the Council, when they arrange clinical trials, prohibit the manufacturers from communicating directly with the investigator; this arrangement applied in the early days of the Therapeutic Trials Committee, but it has long since been abandoned as both unpopular and inefficient.)²²

In the same memo, Green noted that he had suggested to Forgan that May & Baker should look into the possible uses of the methonium drugs in ulcerative colitis, and proposed to contact a number of suitable clinical investigators for such questions and to organise a conference, with Paton as secretary. On a different occasion Green wrote to Paton that

[W]e should certainly not regard it as improper for the firm of Geigy – or, indeed, any other firm – to approach Kay and Smith directly on a scientific question such as you mention. Of course, there is no obligation on Kay and Smith to assist Geigy with advice unless they like to do so.²³

The power relationships, it seems, were distinctly different from those that Nick Rasmussen has described for the United States, where he finds patterns of company-funded clinical research very similar to today's as early as the inter-war period.²⁴

Therapeutic enthusiasm

MRC officials were keen to promote the ganglion blockers, but the initial responses from clinicians were cautious. In order to understand the transformation of methonium compounds from experimental drugs to routine treatment for malignant hypertension, in this section I will look at the role of clinicians such as Frederick Horace Smirk at the University of Otago Medical School at Dunedin, New Zealand, who we might want to call a 'therapeutic enthusiast'.²⁵ Smirk may appear to be a somewhat marginal figure at the first glance. When looking a bit more carefully, though, it becomes clear that his department at Dunedin was closely modelled on the MRC-funded units run by T.R. Elliot and Thomas Lewis at University College Hospital (UCH) London, where Smirk trained in the interwar years. 'The clinic', Smirk stated in a report on his hypertension clinic in Dunedin, 'has served both research and routine requirements and often there has been no distinction between these requirements'.²⁶ A product of the work at Dunedin was, besides a routine method of treating hypertension with drugs, a major textbook on *High*

22 Memo, probably by Green, 27.9.50, UK National Archives, FD1/1172.

23 Green to Paton, 4.10.1950, UK National Archives, FD1/1172.

24 N. Rasmussen, 'The Drug Industry and Clinical Research in Interwar America: Three Types of Physician Collaborator', *Bulletin of the History of Medicine*, 79 (2005), 50-80; idem, 'The Moral Economy of the Drug Company-Medical Scientist Collaboration in Interwar America', *Social Studies of Science*, 34 (2004), 161-185.

25 Another therapeutic enthusiast was Edward Freis in the US, who later organised the large-scale treatment trials for hypertension with the Veterans Association Hospitals.

26 F.H. Smirk, 'Organisation of a Hypertensive Clinic, More Particularly For Patients On Methonium Treatment', October 1951, typescript, p. 4, UK National Archives, FD1/1172.

Arterial Pressure.²⁷ Dunedin became a satellite of clinical research in the British metropolis, and in this was not so different from British provincial universities.

Smirk, the son of a Lancashire schoolmaster, had attended Manchester University in the early 1920s, graduating MB, ChB with first class honors in 1925. He acquired his MD in 1927. After junior posts at Manchester Royal Infirmary, a Dickenson Travelling Scholarship from the MRC allowed him to go to Vienna and a Beit Memorial Medical Research Fellowship to join T.R. Elliot's unit at UCH. As Smirk's Dunedin colleague F.N. Fastier put it, UCH 'was an almost inevitable choice for tenure of the Beit Fellowship. No other British medical school could have provided during the 1930s a more stimulating environment for those "new men" who were intent on fusing the skills of the laboratory and the clinic.'²⁸ The 'new men' who joined the research staff at UCH with Beit fellowships in the interwar period included George Pickering or John McMichael, who would shape post-war British clinical science.²⁹

While many of his contemporaries found positions in Britain, often full-time posts in the new research units established by the MRC, Smirk's next move after teaching appointments in the departments of pharmacology and medicine at UCH was to the chair of pharmacology at Cairo University in 1935. He stayed in Cairo for four years, during which he turned to the search for drugs that had an effect on blood pressure, screening nearly 1,500 commercially available chemicals in stray dogs, with little success. In 1940 he was appointed to the first full-time chair of medicine at Otago, replacing the part-time professors of systematic and clinical medicine who had retired the previous year. The move towards full-time professors who were expected to be research active paralleled contemporary developments in Britain. Later Smirk was able to link Dunedin to the metropolis in other ways. He was a scientific entrepreneur who managed to secure funding for his work from a variety of sources, including pharmaceutical companies. This success was undoubtedly due to his great enthusiasm for pharmaceutical solutions and his success in turning the ganglion blockers into routine drugs. He is also associated with breeding a strain of spontaneously hypertensive rats for laboratory experiments. The greatest coup of his career as research administrator was to secure £120,000 from the Wellcome Trust for a completely new clinical research institute in Dunedin in 1960, then among the biggest grants the Trust had ever committed. This was undoubtedly helped by the fact that McMichael by then was a Wellcome Trustee and Green the Trust's medical secretary.

Initially, however, the war years did not make it easy to establish a functioning laboratory in Dunedin. There was hardly any equipment and much had to be improvised, supplies were unreliable, and there was not much space for Smirk and his staff. Furthermore, Smirk was faced with a heavy teaching and administrative load. During the war, Smirk turned to typical war-time research, such as the study of nitrogen mustards and the search for a pharmaceutical treatment

27 F.H. Smirk, *High Arterial Pressure*, Oxford: Blackwell, 1957.

28 F.N. Fastier, 'Biography: Sir Horace Smirk: Professor Emeritus', *New Zealand Medical Journal*, 67 (1968), 258-265, p. 258.

29 On clinical science in Britain, see C.C. Booth, 'Clinical Research', in W.F. Bynum and R. Porter (eds), *Companion Encyclopedia of the History of Medicine*, London & New York: Routledge, 1993, pp. 205-229; idem, 'From Art to Science: The story of clinical research', in *A Physician Reflects: Herman Boerhaave and other Essays*, London: Wellcome Trust Centre for the History of Medicine at UCL, 2003, pp. 79-101.

for shock. After 1945 he returned to the search for antihypertensive drugs. This search received a boost when in 1949 he spent a sabbatical at the Postgraduate Medical School at Hammersmith Hospital in London, where McMichael was director and professor of medicine. This was the year when Paton, Zaimis and Organe, and later, more importantly, Arnold and Rosenheim, Elliot's successor at UCH, published the first results of their experiments with pentamethonium and hexamethonium in humans.³⁰ Smirk, who received supplies of the drugs from May & Baker when he returned to New Zealand, it seems, had found the compounds he was looking for.³¹

The debate over the question if hypertension was a disease in itself or only a symptom of an underlying disorder continued well into the 1960s. If the latter was the case, was symptomatic treatment indicated? The therapeutic enthusiasts argued that such etiological questions did not matter, as long as lowering the blood pressure appeared to be beneficial. Edward Freis in the US, like Smirk initially simply assumed such benefits for patients with severe hypertension. Furthermore, Smirk designed a detailed treatment regime, including quick and simple fixes for the most obvious shortcomings and side effects of ganglion blocker therapy, enabling it to become routine.

An important problem of the methonium compounds was their low solubility in water and the resulting low (and unreliable) rate with which the drugs were absorbed into the bloodstream when taken by mouth. Smirk overcame this by devising a regime of subcutaneous injection, a management solution very similar to the administration of insulin to diabetics. Patients had to be 'titrated', the right dose found for each individual patient, and this dose adjusted as patient bodies got used to the drug. As the Hull physician Edmond Murphy observed (who, incidentally, characterised Smirk's attitude towards hexamethonium as 'enthusiastic'), 'Smirk and Alstad [one of Smirk's co-workers in Dunedin] claimed that with adequate parenteral doses – *each patient being a law unto himself* – a lowered tension can be maintained indefinitely'.³² This went along with a strict monitoring regime. Austin Doyle, who joined Smirk's department in 1952, remembers:

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. ... 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.³³

30 Organe et al., 'Preliminary Trials'; Arnold and Rosenheim, 'Effect of Pentamethonium Iodide'.

31 Cf Doyle, 'Sir Horace Smirk'. Doyle joined Smirk's department in 1952.

32 E.A. Murphy, 'Treatment of Hypertension with Hexamethonium Bromide', *Lancet*, 258 (1951), 899-901. My emphasis.

33 Doyle, 'Sir Horace Smirk', pp. 249-250

The multidose containers had been prepared at the university's pharmacology department by dissolving bulk supplies provided by May and Baker. Some years later, such multidose vials were available pre-packed, directly from the drug producers.

Drugs and discipline

Hexamethonium, it seems, disciplined doctors, patients, carers, and technicians alike. 'It is most important', Smirk states in his account of the practices in the hypertension clinic with a view to the three-hour daily trials, 'that the patient should understand something of the working of the drug, and in our experience the technician is invaluable in educating patients, and any special points she cannot answer can be dealt with when the doctor comes round'.³⁴ A passage referring to these women is capitalised in his report:

There is one essential without which our clinic could not function effectively, and this is the presence of reliable technicians interested in their work and with sufficient stability, friendliness and poise to be trusted by the patients. With intelligent girls who are keen to learn we have experienced no difficulty whatsoever in obtaining from them accurate pressure readings and comments on corresponding symptoms, if any.³⁵

Smirk devised a treatment manual for patients and carers that explained the reasons for the treatment, suggested ways of dealing with the possible side effects of the drugs, which would disappear soon if patients co-operated and played active parts in the therapy, and warned of the possible consequences of non-compliance or interruption of the treatment.³⁶ Smirk explained patients that '[t]he object of treatment is to decrease the risk of complications of high blood pressure such as heart failure and stroke, and secondly to relieve symptoms such as headache and breathlessness in cases where these are due to high blood pressure'.³⁷ Patients were encouraged to perform simple tests on themselves, which relied on them developing an awareness of the effects of the drug on their bodies. The 'standing test' took advantage of one of the most common side effects of hexamethonium, postural hypotension, a sudden lowering of the blood pressure when patients stood up, which led to dizziness. 'Almost all of our well-trained patients can tell the doctor from their own subjective sensations whether a given dose is producing a considerable fall of the blood pressure', Smirk reported. 'Intelligent and co-operative patients have been entrusted with the fine adjustment of their dose'.³⁸ The ways in which Smirk's practices dealt with postural hypotension and made use of this side effect indicate that even a difficult drug could be managed.

Smirk blamed the bad results that other clinical researchers reported with the methonium drugs, as Green wrote in a letter to Paton, on "'faulty technique", namely lack of proper ancillary

34 Smirk, 'Organisation of a Hypertensive Clinic', p. 5.

35 Ibid., p. 4.

36 F.H. Smirk, 'Instructions for Patients on C6 Injections', October 1951, typescript, UK National Archives, FD1/1172. On compliance, see J. Greene, 'Therapeutic Infidelities: "Noncompliance" Enters the Medical Literature, 1955-1975', *Social History of Medicine*, 17 (2004), 327-343.

37 Smirk, 'Instructions for Patients on C6 Injections', p. 1.

38 Smirk, 'Organisation of a Hypertensive Clinic', p. 7.

care of the patients'.³⁹ Smirk's practices involved patients as well as technicians and nurses in active and responsible roles. The psychology of the patients also needed tending to: 'It is well to remember that nervous tension, worry, quarrels, excitement and adverse emotion lead to elevation of the blood pressure', Smirk wrote. 'It is a part of treatment to lessen such troubles.'⁴⁰ How was this done? 'Reassurance by doctor and technician that the milder side effects are in no sense dangerous and will probably disappear anyhow usually leads to a happier frame of mind.'⁴¹ As important, it seems, was the company of other patients. Patients would sit together in groups of four while undergoing their lengthy tests, exchanging experiences, and there was 'something of the atmosphere of a club about the clinic'.⁴² Not all were happy, though: 'It is well to realise ... that a drug which, in a proportion of patients, causes side effects will get the blame for all sorts of incidental illness.'⁴³ Frank Green, after his visit in New Zealand, reported to Paton:

I talked to some of his patients under treatment in the wards, and I think it is fair to say that I got the impression that their enthusiasm for hexamethonium therapy is not quite so great as his. Not unnaturally, they dislike the side effects. If, however, as Smirk says, it is possible to keep patients with malignant hypertension alive and reasonably comfortable for periods at least of several years, then that does represent an important advance in therapy.⁴⁴

Conclusion

The unhappy patients who Green met in Smirk's clinic were most likely new arrivals, who had not yet been 'trained'. A *Lancet* editorial in 1953 supports Green's conclusions regarding the potential of the drugs, stating that 'Early reports leave no doubt that the methonium compounds are the most powerful hypotensive agents yet developed.'⁴⁵ By the end of the 1950s, hypertension had been transformed into a treatable disease. Malignant hypertension was no longer life threatening. The ganglion blockers, along with the routines designed by Smirk and his colleagues, had come to form a relatively standardized package that circulated easily and that paved the way for new, more specific antihypertensive drugs. Green and Paton felt that the MRC had done what it could do for the methonium compounds in 1952, when they thought that these drugs no longer needed boosting.⁴⁶ The Council's emphasis was clearly on research rather than commercial exploitation. Commercial exploitation followed, however, with several drug companies developing their own, patent-protected ganglion blockers on the back of the success with the methonium compounds. Examples are May and Baker's Gaplegin, or Pendiomide, which was developed and marketed by both Ciba and ICI more or less simultaneously. The new ganglion blockers were not necessarily better antihypertensives than hexamethonium, but they were more easily absorbed by the gut

39 Green to Paton, 25.4.1952, UK National Archives, FD1/1172.

40 Smirk, 'Organisation of a Hypertensive Clinic', p. 9.

41 Ibid.

42 Ibid.

43 Ibid.

44 Green to Paton, 25.4.1952.

45 Methonium and Hypertension [editorial], *Lancet*, February 1951, 395-396, p. 395.

46 Paton to Green, 28.4.1952, UK National Archives, FD1/1172.

and therefore more reliable when taken by mouth.⁴⁷ For several producers, the ganglion blockers provided a stepping stone into the new field of pharmaceuticals for blood pressure control.⁴⁸

47 F.H. Smirk, 'Hypotensive Actions of Hexamethonium Bromide and some of its Homologues: Their Use in High Blood-Pressure', *Lancet*, 260 (1952), 1002-1005.

48 See V. Quirke, 'From Evidence to Market: Alfred Spinks's 1953 survey of fields for pharmacological research, and the origins of ICI's cardiovascular programme', in V. Berridge and K. Loughlin (eds), *Producing Health: Medicine, the market and the mass media in the twentieth century*, London: Routledge, 2005, 144-169; K. H. Beyer, 'Chlorothiazide', *British Journal of Clinical Pharmacology*, 13 (1982), 15-24.

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