

John Guyett Scadding's scepticism and pragmatism in addressing treatment uncertainties in clinical practice

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Introduction



John Guyett Scadding (1907–1999), my father, features quite prominently in the James Lind Library (JLL). The JLL includes reports of his controlled trials using alternate allocation and blinding to assess the effects of sulphonamides on gastrointestinal infections during 1944 and 1945;^{1–3} an article written by him for the JLL in 2002 reflecting on these studies⁴ and his comments in conversation with Iain Chalmers and Mike Clarke⁵ on the move from alternate allocation to concealed random allocation for the iconic Medical Research Council trial of streptomycin for pulmonary tuberculosis.⁶

Because clinical research done by my father covered a key moment in the history of controlled clinical trials, I was invited by the editors of the James Lind Library to provide some biographical information about him. My immediate reaction was that my father's life and achievements had already been covered by some excellent obituaries (see Appendix 1), for example, Citron's citation in Munk's Roll written for the Royal College of Physicians of London. Accordingly, this article focuses on information and

personal characteristics which I believe are of relevance to his clinical research in the 1940s. In addition to my own and my family's and colleagues' recollections of my father, I have drawn on published obituaries and a document entitled 'The Institute of Diseases of the Chest, 1946–1972: a personal history',⁷ from which I quote quite extensively.

Early life and school education

'Guy' Scadding was born at home in north London on 30 August 1907. His father was a headmaster of a local primary school which stood on the site where now stands an athletics track at the southern end of Parliament Hill Fields, adjacent to Gospel Oak. Guy attended this school before moving to the Mercers' School in the city of London.

He was academically precocious and had achieved all the necessary entry requirements for medical school at the age of 14! He spent much of his remaining years at school studying non-science subjects and winning virtually all the academic prizes available in every subject. Rather than awarding him each of these individual prizes, the school chose instead to present him with a microscope, which he used while at medical school and for the rest of his career until retirement in 1972.

He told me that an important inspiration and stimulus for him to consider medicine as a career were the visits of the family doctor, who arrived at the house with long cloak and top hat. It was only years later that he discovered that this doctor had been struck off the Medical Register because of his alcoholism.

Medical school and early career

Guy entered the Middlesex Hospital Medical School at the age of 17 and, at the age of 22, qualified in the Conjoint Examination in October 1929 and then MBBS in May 1930. He reflected on his

undergraduate education and early career in the personal history he wrote in 1993⁷:

My medical education at the Middlesex Hospital and its Medical School did little to qualify me for a career in academic medicine. It was probably rather old-fashioned even by then contemporary standards. There was virtually complete separation between the pre-clinical and clinical parts of the course. The pre-clinical was presumed to be scientific, while the clinical was regarded principally as a means of imparting knowledge of accepted views and practice and an opportunity for obtaining practical experience by apprenticeship.

There was no academic clinical unit, all teaching being in the hands of consultants devoting a few sessions weekly to their clinical work and teaching in the hospital. I think all were conscientious, but their ability as teachers was varied, and for most it was unashamedly didactic. Although there were active departments of bacteriology and biochemistry, morbid anatomy was still regarded as the principal scientific basis of medicine; aspiring physicians regarded a year spent as an assistant in the department of pathology doing post-mortems as good training for their prospective career.

Shortly before he qualified, Guy was invited to become junior resident anaesthetist at the Middlesex Hospital, an offer that he accepted. Six months later, he was unsuccessful in his application for the house physician post he really wanted at the hospital. Instead, he was appointed to the Connaught Hospital in Walthamstow, where he was responsible for 50 beds, without any support from registrars. There was a small pathology laboratory and a visiting pathologist, but Guy was expected to undertake post-mortem examinations when the pathologist was not available.

In the 9 months I spent in this appointment at the Connaught Hospital, I thus obtained wide experience in general medicine, paediatrics and medical pathology, with a useful mix of independence, with supervision, admittedly rather distant, from two able young physicians.

By today's standards, this post was rich in experience, exposure and commitment, with a light touch supervision that would simply not now be countenanced. Indeed, the post would be frowned upon and dismissed as being completely inappropriate as a training job.

Having, by this stage, decided that he would pursue a career in internal medicine, Guy looked

for posts at highly regarded London hospitals. He was interested in jobs at Brompton Hospital for chest diseases and the National Hospital for Nervous Diseases. Interviews for posts at Brompton Hospital came up first and he was appointed to one of them. As a result of this happenstance, my father became a respiratory physician rather than a neurologist (the specialty in which I trained 40 years later).

Following the post at Brompton Hospital he applied, again unsuccessfully, for a job at the Middlesex Hospital. Fortunately, he was invited to apply for a newly created Resident Physician post at Brompton Hospital, the main responsibility of which was running clinics for inducing artificial pneumothorax. This procedure was being used increasingly in managing pulmonary tuberculosis, despite the lack of evidence that it did more good than harm, as was later pointed out by the increasingly respected medical statistician, Austin Bradford Hill.⁸ Nevertheless, Guy accepted the post, as he remarked, 'pleased that someone wanted me!' It was while doing this job that he passed examinations both for Membership of the Royal College of Physicians and for the MD degree. As the highest scoring candidate in the latter, he was awarded London University's Gold Medal.

He then spent a year as a surgical resident at Brompton Hospital, where he was solely responsible for the pre- and postoperative care of patients under the care of two leading thoracic surgeons. He was appointed Resident Medical Officer at the Hospital in 1934.

At the Brompton, I obtained a very wide practical experience in all aspects, medical and surgical, of respiratory disease. Here again, learning was by apprenticeship; there was no provision for the education of residents, and the only laboratory was devoted to necessary routine clinical pathology. The residents had occasional discussions of clinical problems among ourselves in the evening after dinner under the informal chairmanship of the RMO, Geoffrey Todd; at these we learned of the varied policies of our chiefs, imparting to some of us a little scepticism about accepted views. We learnt how to read chest X-rays, and the useful trick of making decisions on limited evidence; perhaps it was only my sceptical turn of mind that saved me from relying on this, and becoming another didactic clinician.

British Postgraduate Medical School

As he later wrote, any tendency to become a 'didactic clinician' was discouraged when he moved to the new

Department of Medicine at Hammersmith Hospital in 1935.

Here there was the freest possible discussion between clinicians and laboratory colleagues in a wide range of related disciplines. I once remarked that at Hammersmith Staff Rounds even the most junior could safely say anything and disagree with anybody so long as what was said was not either stupid or libellous! But I realised that my lack of training in any laboratory discipline limited my contributions to those that could be made by a sceptical clinician.

He had moved to Hammersmith Hospital to take up one of the four Assistant Physician posts in an academic department of medicine (headed by Francis Fraser) which was being established by the British Postgraduate Medical School. The other three Assistant Physicians were Paul Wood, Geoffrey Jennings and JF Brock.

When he took up this appointment at Hammersmith Hospital, his junior colleagues at Brompton Hospital gave him a silver cigarette box, bearing the inscription: 'From the Residents Past and Present. Brompton Hospital, June 1935'. It now seems extraordinary that the leading chest hospital in Britain should choose such a gift, and it indicates the accepted normality of smoking at that time. It is a reminder that evidence linking smoking to pulmonary disease did not then exist. It was not until more than a decade later that epidemiological studies demonstrated a strong association.

I asked my father about his attitude to smoking and his own cigarette smoking habit in the 1930s. He recalled that he never actively enjoyed it, but smoked on social occasions. He switched to pipe smoking and continued this during the war, giving it up on his return to England in 1945. His reasons for stopping then were twofold: importantly, my mother did not like the 'stench' (her word) and dirt of the smoke; and my father thought that smoking might be exacerbating his longstanding intermittent nasal sinus symptoms.

In the new post at Hammersmith Hospital, although only 27 years old, he had consultant responsibility for 30 beds as well as outpatient clinics and provided specialist advice for respiratory problems throughout the hospital.

It was during his immersion in an atmosphere of questioning and scepticism at Hammersmith Hospital that he became familiar with Bradford Hill's work on the design of clinical trials,⁵ both from a course of lectures that Hill gave in the late 1930s and from reading Hill's book published in 1937.⁸

In 1939, Guy was appointed as an Assistant Physician at the Brompton Hospital, becoming part-time there and at Hammersmith Hospital. This arrangement continued, interrupted only by the war, until his appointment as the first Professor of Medicine at Brompton Hospital in 1962.

Controlled trials in the Egyptian desert

In the lead up to the Second World War, my father had volunteered for the newly formed Emergency Medical Service. A lull in the routine activity at Brompton Hospital, in anticipation of imminent air raids that did not arrive at that stage, was followed by gradual resumption of normal hospital activity. Guy still had responsibility for patients with artificial pneumothorax (AP) and commented:

We continued provision for the maintenance of AP clinics, and since it had become sketchy elsewhere, we had some very large clinics; one Saturday afternoon, we dealt with 100 patients.

By early 1940, feeling that he was not contributing much to the war effort, he volunteered and was accepted as a medical specialist in the Royal Army Medical Corps. He was called up in May 1940 and posted to Tidworth, a garrison town on the edge of Salisbury Plain. 'It is ironic', he commented later, 'that, having joined the Royal Army Medical Corps to see more action, I found myself in the safety of the Salisbury Plain when the London blitz started in September 1940'. The air raids did not prevent him marrying my mother (Mabel) in London during an air raid warning on his 33rd birthday.

Guy remained based at Tidworth until January 1941 when he was posted to Egypt as an Officer in Charge of the Medical Division of No. 19 General Hospital at Fayid, on the Great Bitter Lake (which forms part of the Suez Canal). In preparation for this posting, he attended a course on tropical diseases in Liverpool.⁴

The tented hospital at Fayid for which he had responsibility was probably the largest British military hospital in Egypt, with 1800 beds for British and allied troops and 1000 for German prisoners of war. Patients presented with a wide variety of problems.⁴

At one time or another we had to deal with nearly every acute infectious disease then known. The only notable exceptions were yellow fever and cholera, which did not occur in our area. Small-pox and plague appeared occasionally, as did outbreaks and sporadic cases of enteric fevers (typhoid and

paratyphoid) and diphtheria. Occasional outbreaks of the infectious diseases then prevalent in childhood in the West (measles, rubella, chicken pox, etc.) occurred among troops coming in from other areas, notably Ceylon.

Sited in the desert, miles away from Cairo, Alexandria or other large towns, Guy and his colleagues were left to get on with dealing with the medical problems of a large and changing population of troops from all over the world, with very little interference from 'higher-ups'. The doctors under his 'command' included many senior specialist trainees, including a young John Crofton,⁹ who was later to work with Guy at Brompton Hospital recruiting participants in 1947 and 1948 for the Medical Research Council's randomised trial of streptomycin for pulmonary tuberculosis.^{6,10}

In December 1943, Guy was summoned to Carthage to see Winston Churchill, who had become ill with pneumonia. By the time he arrived, Guy judged that the great man's pneumonia was indeed improving, and he resisted a suggestion that treatment with a sulphonamide should be changed to the new wonder drug, penicillin. Sure enough, Churchill continued to improve.¹¹ Guy was transported back to Cairo in Churchill's personal York aircraft, the distinctive aircraft being judged to be so recognisable as to give away Churchill's location.^{11,12}

It was during 1943 and 1944 that my father organised controlled trials to assess the effects of sulphonamides in treating mild bacillary dysentery. He reflected on these in an article later published in the James Lind Library,⁴ drawing on his quarterly reports of the Medical Division. He suggested that the trials provided a good illustration of the way in which introducing a treatment into clinical practice on the basis of theory, without testing the validity of the theory in clinical trials, can lead to entrenched 'clinical impressions' that are both wrong and difficult to displace.

When he arrived in Egypt, fluids alone were the standard treatment for patients with dysentery, but an official recommendation appeared stating that sulphaguanidine should be prescribed. This was because this sulphonamide was active against coliform organisms and was poorly absorbed, and so persisted in high concentration in the large gut:

...even those of us who retained our critical faculties but nevertheless followed instructions to use the drug tended, when we had prescribed sulphaguanidine for a man with severe dysentery, to attribute a

favourable course of the disease to the sulphaguanidine. And if the patient died, we wondered whether he might have recovered if the drug had been given earlier in the course of the disease. Accordingly, when sufficient supplies of sulphaguanidine became available, it became established as the standard, reputedly 'specific', drug for bacillary dysentery.

Several people are on record as having doubted this dogma, claiming that absorbable sulphonamides (sulphapyridine, sulphathiazole) and even the simple sulphanilamide (see references in Scadding 1944) were at least as effective as sulphaguanidine.

The controlled comparisons of different sulphonamides to address these uncertainties^{1,2} used alternate allocation to avoid allocation bias, blinding to avoid observer bias by using drugs supplied in indistinguishable suspensions, and statistical analysis.

The trials detected no evidence of the theoretical superiority of sulphaguanidine over other sulphonamides (sulphaguanidine, sulphanilamide, sulphapyridine, sulphadiazine and succinyl-sulphathiazole). The results of his research suggested not only that sulphadiazine was as well tolerated as sulphaguanidine, but that offered no advantage over rest and diet alone. These results raised questions about whether any of the drugs tested offered any advantage over supportive treatment without drugs.

This uncertainty led to collaboration with the local Infantry Training Depot to assess whether prophylactic use of sulphaguanidine for men presenting with simple diarrhoea might reduce the number who eventually required admission to hospital. Cases were allocated alternately either to the drug to a suspension of calcium carbonate. No advantage of the drug treatment was detected.³

In his article written for the James Lind Library, Guy recounts the difficulty he experienced in getting reports of these trials published. Six months passed before he learned that the editor of the *Journal of the Royal Army Medical Corps* had rejected both of them. One of the two rejected papers² was published in *The Lancet*; the manuscript of the other is available in the James Lind Library.³

It is worth repeating some of my father's reflections on these trials:⁴

Although I had never been involved in a controlled clinical trial before going to the Middle East, I now realise that very few people at that time ever had. However, I was fully aware of the principles because, before the war, I had attended Bradford Hill's course of lectures, which formed the basis for his book *Principles of Medical Statistics* (Hill, 1937). It was

really the application of these principles to clinical practice that was relatively new; the principles had been widely applied in some other biological fields. Looking back, I cannot help reflecting that it was the temporal and local circumstances that made my studies possible. As I have already noted, I was in an area where I had an astonishing degree of autonomy. I was able to take personal responsibility for the design of the studies; there was no requirement to submit everything to an ethics committee.

Although I had, and still have, no ethical qualms about any of them, and having had personal experience of two episodes of bacillary dysentery, would have been perfectly willing to have been included in any of them, I wonder what chance they would have had with a modern research ethics committee! I did not need to apply to anyone for financial support, since the studies were incorporated into the routine activities of the hospital; and, as I had no domestic responsibilities (to my great regret, having been posted abroad in 1941 a few months after my marriage!), I had no difficulty in finding time for the extra work entailed by the studies.

As regards my motivation in doing these studies, I think I can honestly say that it was simply to find out whether my hunches about the value of an advocated treatment, derived from critical clinical observation, were correct. At that time, I had not heard of Karl Popper – indeed his views on the logic of scientific discovery had been published only in German at that time, and I only much later became aware of them and discovered how consonant they are with my sceptical turn of mind. Now I suppose I might say that having doubts about accepted hypotheses about the value of sulphonamides, especially sulphaguanidine, in dysentery, I wanted to submit them to critical tests.

Another point that these studies illustrate is that in interpreting the practical implications of a controlled or comparative therapeutic trial it is important to remain aware of the criteria on which the type of case studied was defined. Unless unequivocal and precise aetiological definition is possible (which it hardly ever is), there is a danger that among the patients conforming to the definition there are subgroups with variations in causal factors relevant to outcome. In my studies there was suggestive evidence that response might vary with differences in bacterial type – a hypothesis which could be tested only by a very large and difficult-to-organise study, or by prompt action in an unusual and unpredictable epidemic of dysentery demonstrably caused by single bacillary type.

Membership of the MRC Streptomycin Trial Committee

In September 1945, after four and a half years in the Middle East and before he was officially demobilised, my father attended his first post-war meeting of Brompton Hospital's Medical Committee. He was surprised to find himself proposed and elected to become Dean of the Medical School, to become the Institute of Diseases of the Chest when a building dedicated for this purpose had been erected in the grounds of the hospital, in the difficult post-war environment, in 1949. As the main role of respiratory medicine at the time was the treatment of tuberculosis, it is unsurprising that the Institute would play an important role in the Medical Research Council's evaluation of streptomycin⁶ and other new treatments for tuberculosis. He believed he was invited to serve on the MRC Streptomycin Trial Committee because he was Dean of the Institute, not because he had organised controlled trials of sulphonamides for dysentery.⁴ Instigation of the streptomycin trials in 1947 also led to the appointment of John Crofton as a part-time registrar to coordinate Brompton Hospital's contribution to the streptomycin trial.¹⁰

Reflecting on his membership of the trial committee, my father noted:⁴

I suppose I was one member of that committee who did not need persuading of the importance of as objective a study as possible of the effects of a new drug before it slipped into routine use on the basis of laboratory studies and uncontrolled clinical impressions. The problem of avoiding bias was more difficult than in my studies. Allocation was freed from bias by reference to random sampling numbers. There was no way in which the study could be made 'blind' either to clinicians or to patients; but assessment of the radiographic and some other outcomes could be and were blinded to those making the observations.

A point that is now often not appreciated is that the streptomycin trial illustrates that ethical acceptability is dependent upon local and temporal social and epidemiological circumstances. The accepted management of the many patients with active tuberculosis in 1947 involved long periods of treatment in hospitals and sanatoria, which, in the UK, were part of a publicly financed anti-tuberculosis service. There were long waiting lists for admission to these. This made it possible to arrange that in selected centres, patients with a defined type of pulmonary tuberculosis, thought likely a priori to show

detectable change and not thought to be suitable for some accepted procedures, would be admitted without delay and be allocated by random sampling numbers to the best accepted treatment or to accepted treatment with the new drug in addition. All those coming into the trial had much earlier treatment. The supply of streptomycin was limited, and all was being used in the treatment of patients with disease of a kind thought likely to make an initial favourable response, though no-one knew whether, in the long term, this would be outweighed by unforeseen unwanted effects, or at what stage in the possibly long and unpredictable course of the disease it would prove best to use the new drug, whose effects seemed likely at that time to be of limited duration.

Fifty years after publication of the report of the MRC trial of streptomycin in the *British Medical Journal*, my father was one of the opening speakers at a conference convened by the Journal to mark the anniversary. He also contributed to a discussion of the reasons for the move from alternation to random allocation.¹³ When asked what advantage he felt random allocation offered compared with alternate allocation,⁵ he said that, because of its unpredictability, random allocation could provide better protection against allocation bias than alternation, particularly in trials in which people could not be blinded to the identity of the comparison groups. He had no recollection that statistical theory had been involved at all as a reason¹⁴ and could not remember being aware of Fisher's ideas. Indeed, he knew Fisher mainly as a consultant paid by the tobacco industry to challenge the findings of Doll and Hill's studies of the relationship between tobacco smoking and lung cancer.

The Institute of Diseases of the Chest and beyond

Having helped during the 1940s to usher in a golden age of Medical Research Council-controlled clinical trials,¹⁵ Guy Scadding's principal preoccupation became the development of the Institute of Diseases of the Chest. He regarded his role in the Institute's contribution to the development of academic respiratory medicine, and to respiratory medicine as a major medical specialty in the UK, as his proudest achievements. At the end of his personal history of the Institute,⁷ he looked back over his role in its development.

I think that the fact that I was regarded primarily as a clinician was an essential aid in the early days. Moran Campbell once remarked that I succeeded

because I could beat the clinicians at their own game! – a remark which I received with mixed feelings, since I liked to think that I was trying to obtain people's cooperation rather than competing with them. An important part of the problem was to persuade the staff of an established hospital with a deserved reputation for clinical expertise and accustomed to administrative arrangements that in effect enabled them to run their own show, to accept and cooperate in the establishment of a new-fangled academic associate likely to diminish their hitherto overriding influence. The fact that I appeared to be one of them was helpful; I understood their point of view, and realised that progress was bound to be slow, and learnt to be resigned to small steps forward, with occasional setbacks. Perhaps patient endurance was my greatest contribution in the early days. But as the numbers of members of the Hospital staff who were involved in the affairs of the Institute and of newly appointed academic staff of the Institute contributing to the clinical work of the Hospital increased, it became less difficult.

When I attended the opening of phase 1 of the new Royal Brompton Hospital by the Queen in February 1991, I was pleased to see once again the bas-relief stone carving depicting the Good Samaritan which had stood over the door of the Entrance Lodge of the old Brompton Hospital opening on to the Fulham Road. When the Lodge was demolished in 1966 at the time of the construction of the last phase of the extensions of the old Institute building to house the Paediatric Research Unit, the Good Samaritan had been removed and replaced next to the new entrance at the side of the building. It had now been moved again and placed in the entrance hall of the new Royal Brompton, to provide a link with the charitable motives of the Founders of the Brompton Hospital 150 years ago. I hope it will be a reminder to those now responsible for financing our hospitals that they too should be motivated by human kindness rather than driven by market forces. Instead of submitting slavishly to market forces, they should get things done in spite of them, as did our Founders.

These comments of a philosophical nature about the NHS, written in 1992, are just as true today in 2017. Those with political, administrative and managerial responsibility for the NHS and its inseparable link with academic medicine would do well to heed them.

The list of his publications in the Appendix provides an overview of his varied interests. A career-long interest in sarcoidosis led to many original publications and two editions of his book about the disease (1967, 1985). He described the clinical and histopathological features of pulmonary fibrosis,

introducing the term ‘diffuse fibrosing alveolitis’, explaining his reasons for doing so (Scadding and Hinson, 1967). He wrote lucidly about the definition of disease and medical terminology, not only in relation to broncho-pulmonary disease (Scadding, 1959; other refs) but also in mental illness (Scadding, 1975, 1978, 1979, 1980, 1990). The introduction of computers stimulated him to write about their applications and limitations in diagnosis (Scadding, 1967).

Although Guy retired in 1972, at the age of 65, he went without a break to spend seven months as a visiting professor with his old Hammersmith colleague and friend, Moran Campbell, at McMaster University in Canada – the birthplace of the Evidence-Based Medicine movement. Back in the UK, he continued to attend Hammersmith Hospital Grand Rounds almost every Wednesday morning and was frequently consulted on complex cases in the hospital well into his 80s. His last platform presentation was at a meeting of the Historical Resources Panel of the Royal College of Physicians, a few months before he died in 1999, aged 92.

Guy Scadding’s integrity and generosity of spirit led his friend Moran Campbell to dub him ‘the non-conformist conscience of British medicine’. My father abhorred arrogance and a lack of professional and personal modesty. He rarely saw things in black and white terms. When I was a schoolboy, and then later at medical school and beyond, he imbued in me the importance of honestly appreciating, accepting and confronting the limits of current evidence and learning to recognise uncertainty as the normal state of affairs in medical science.

From his school days and throughout his career, Guy Scadding’s approach to the world and to his responsibilities was characterised by careful judgements informed by the best evidence available to him. His pragmatic response to the uncertainties prompted by his sceptical reactions to opinions unsupported by reliable evidence was first clearly manifested in his pioneering use of controlled trials in the Egyptian desert in the 1940s.

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Appendix 1

Obituary

Citron KM, 2000. *John Guyett Scadding. Munk's Roll XI*: 501. Royal College of Physicians Publications

Publications

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Additional references relating to definition and terminology in relation to definition of disease and mental health**.*