

## Crofton J. Reginald Bignall (1913-2000)

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**Author contact details:** John Crofton, 13 Spylaw Bank Road, Colinton, Edinburgh EH13 0JW.  
Email: [ElizabethAnn.Pretty@btinternet.com](mailto:ElizabethAnn.Pretty@btinternet.com)

Reginald Bignall made important contributions to early chemotherapy research in tuberculosis. He established a research sub-committee to carry out unbiased trials of drugs on behalf of, but independently, of the pharmaceutical industry. And he played a key role internationally through the International Union Against Tuberculosis and Lung Disease. I feel Reg Bignall has been undeservedly forgotten, so I was pleased to be invited to record my memories of his work for publication in *The James Lind Library*.



### Early work at the Brompton Hospital

Reg Bignall's medical career started before World War 2, in general practice in Arundel, Sussex. However, after serving in the Royal Army Medical Corps in North Africa and Italy and writing an MD thesis on sandfly fever, he decided to pursue a career in clinical research. He went to see Guy Scadding at the Brompton Hospital, London, who had also served in North Africa ([Scadding 2002](#)), who was then in charge of research and teaching at the Institute of Diseases of the Chest, where Reg was subsequently appointed as a Lecturer.

It was at about that time that I became a half-time member of the Medical Research Council's Tuberculosis Research Unit, with responsibility for coordinating the Brompton Hospital's contribution to the controlled trial of the then new drug, streptomycin, in pulmonary tuberculosis ([MRC 1948](#); [Crofton 2006](#)); and that is how I came to know and work closely with Reg.

We recorded and investigated side effects of streptomycin, such as giddiness (Bignall et al. 1951). One of the side effects was vomiting, which occurred in some patients about six weeks after starting the drug. This may have been due to impurities in the early supplies of the drug because we did not see it with later supplies. We thought the vomiting might be a hypersensitivity effect because of the timing of its onset, so we investigated whether an antihistamine drug would suppress it. Our double blind crossover trial confirmed the success we had hoped for ([Bignall and Crofton 1949](#)). Noting our experience, others went on to show that antihistamines were helpful in reducing seasickness ([Glaser and Hervey 1951](#)).

In 1950, after I had left the MRC Tuberculosis Research Unit and begun to spend more time at the Postgraduate Medical School, Reg assumed increased responsibility for the next phase of the MRC tuberculosis trials. These compared streptomycin with the new drug PAS ([Swedish National Association against Tuberculosis 1950](#)), as well as with a combination of both drugs. Compared to either drug given alone, the combined treatment greatly reduced the incidence of resistance and increased the rate of subsequent cure.

### Later work at the Brompton Hospital

I moved to Edinburgh in 1952, so I had less day-to-day knowledge of Reg's work and research at the Brompton Hospital; but we remained good friends and I formed a high opinion of his organising skills.

In the mid-1950s, Philip d'Arcy Hart ([Tansey 2004](#)), director of the MRC Tuberculosis Research Unit, complained

to me that the then editor of the well-established journal *Tubercle* had little grasp of recent advances, particularly in chemotherapy. We agreed that Reg would be a good choice as a new editor. If I remember correctly, I was the chair of the editorial committee; at any rate Philip D'Arcy Hart clearly expected me to take the initiative. It was all rather awkward, the current editor also being a member of the committee. But after consulting other members of the committee, I proposed formally that Reg should become editor. Unsurprisingly the current editor was surprised and shocked, but Reg subsequently did a splendid job in raising the standard of the journal, which he continued to edit until 1978.

Later, I was asked to chair the Research Committee of the British Tuberculosis Association (which later became the British Thoracic Society), and Reg was a member of this committee. One of his notable contributions was his suggestion of how to handle the many requests made by pharmaceutical companies to physicians who they wanted to carry out research on new products. At the time, companies would usually design the trials, provide expenses to one or more clinical units, and control or even write the subsequent reports. This system gave rise to suspicion of commercial bias - negative results were less likely to be reported.

Reg's suggestion was that the British Tuberculosis Association's Research Committee should appoint a sub-committee to deal with research requests from industry. The subcommittee was instituted in the early or mid-1960s, with Reg in the chair. If a company wanted a drug tested clinically, it would submit details of animal studies and known side effects, and if the sub-committee thought the drug was worth testing they would suggest this to the main committee. If the recommendation was endorsed, the sub-committee would then design the trial and invite various clinical units to participate. Because the MRC tuberculosis trials had usually involved multicentre collaboration, many units had become used to such cooperative research. The results were analysed and published by the sub-committee. The company had no control over this, whatever the result. All the expenses would be paid to the subcommittee, which would then allocate each participating centre its share. Later it was decided that the main research committee should take responsibility for deciding which industry trials to pursue, and then appoint sub-committees to carry forward each project. Over the years such projects were carried out in a number of fields, and the latest has been published recently in the *British Medical Journal* (Campbell et al. 2007).

## International work

Reg made his debut on the international scene by highly efficient coordination of an early example of successful international collaboration in clinical research (International Union Against Tuberculosis 1964). This study came about as follows.

When I moved to Edinburgh in January 1952 my colleagues and I collaborated in the MRC's multicentre trials testing the new drug isoniazid, alone and in combination with streptomycin or PAS, both of which had become generally available. There was a major tuberculosis epidemic in Scotland at that time, a great shortage of hospital beds, poor treatment of patients treated as outpatients, and a high rate of treatment failures. We carried out detailed examinations of apparent treatment failures, recording patients' successive patterns of treatment (length, drugs alone or in combination), and compared the fluctuations of their disease (clinical, X-ray or bacteriological) with the corresponding drug resistance tests on their tubercle bacilli. We soon concluded that treatment failures were almost uniformly due to drug resistance, however slight, rather than severity of disease or failure to absorb the drugs ([Crofton 2006](#)).

Then we had an unpleasant surprise. The MRC trials had demonstrated that a two-drug combination was the best treatment schedule available, but two of our colleagues (Norman Home and Ian Grant) each had treated a new patient with this regimen, but both patients were subsequently shown to have already been infected with tubercle bacilli that were already resistant to one of the two drugs they had been given. This was a grim new phenomenon which came to be known as "primary resistance". Sadly, renewed testing of specimens taken at 6 weeks showed that the patient's tubercle bacilli had also become resistant to the second drug. As isoniazid had recently become available, we decided to start all new patients on three drugs, at least until pre-treatment tests showed that the patient's tubercle bacilli were fully sensitive to all three.

To our astonishment we found, in patients who had tubercle bacilli initially sensitive to at least two of the drugs, we were curing all new patients who had pulmonary tuberculosis (a condition which had had a pre-chemotherapy mortality of about 50%). Most centres in the UK and abroad continued to have substantial treatment failure rates, and they simply did not believe our results. Indeed we were accused of fiddling our figures, especially perhaps because there was an appreciable failure rate in the two-drug MRC trials.

The only research workers who believed us were two bacteriologists from the Pasteur Institute in Paris, Noel Rist and Georges Canetti. At the time Rist chaired the Bacteriology Scientific Committee of the International Union against Tuberculosis and I chaired the Chemotherapy Committee. Rist said to me "They won't ever believe you until they see it in their own patients". So we decided to organise an international study of the causes of failure in the treatment of advanced pulmonary tuberculosis, which would involve an influential centre in each of 23

countries giving our 3-drug regimen. We hoped that a ripple effect on practice would occur if the Edinburgh experience was replicated.

Reg Bignall was one of the people who did not believe the Edinburgh results (he had described a talk I had given at an international meeting in Canada as "good propaganda"). That scepticism, combined with his organising ability and skill in handling senior colleagues, made him an ideal choice as coordinator of the study. He did the job brilliantly, and it worked out as we had hoped. Although there were a few early deaths in moribund patients, virtually all the other failures were patients in whom the doctors had failed to adhere to the treatment protocols (International Union Against Tuberculosis 1964). The study achieved the 'ripple effect' we had hoped for, albeit at variable speeds.

As a result of his successful coordination of this study Reg became very well known internationally, and was later appointed Coordinator of the Scientific Committees of the International Union against Tuberculosis and Lung Disease (1968-74). He was awarded the Carlo Forlani Gold Medal in Rome in 1974.

## Later years

Reg was awarded the Weber Parkes Prize by the Royal College of Physicians in 1975. As the importance of tuberculosis declined in developed countries, so the importance of lung cancer increased. Reg edited a book on the disease (Bignall 1958) and published a number of papers about it in *The Lancet* (Kupar and Bignall 1966; Lancet 1967; Lancet 1972). He served as dean of the Institute of Diseases of the Chest between 1960 and 1968, and was a consultant physician at the Brompton Hospital until 1979

I have the impression that Reg was eventually eased out of his academic position at the Institute by new professors who were more interested in laboratory than clinical research, and that he must also have been persuaded to transfer his clinical duties from the Brompton Hospital to Frimley Hospital. Frimley Hospital had been the Brompton Hospital's sanatorium, but it later became a convalescent hospital for the Brompton Hospital's patients. Reg subsequently wrote "an affectionate study" of the hospital (Bignall 1979). He retired to South Wales, where his son John was a GP at that time, and died there on 15 November 2000.

## Acknowledgements

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