Fighting resistance

Courtesy of Sir John Crofton

Sir John Crofton

Sir John Crofton received his medical education at Cambridge University and St Thomas's Hospital in London (United Kingdom), and qualified as a doctor in 1937. During the Second World War, he joined the Royal Army Medical Corps with service in France, Egypt, Eritrea, Greece, Malta and then Germany. In 1947, he became a lecturer at the Royal Postgraduate School of Medicine at Hammersmith Hospital and treated patients at Brompton Hospital, where he participated in groundbreaking tuberculosis studies. From 1952 to 1977, Crofton held the Chair of Respiratory Diseases in the University of Edinburgh, where he and his team developed the Edinburgh Method, which paid obsessive attention to supervision, involving district nurses to follow up patients at home, as well as the triple-drug approach. From 1984 until 1988, he was Chairman of the International Union against Tuberculosis and Lung Disease. He also worked extensively in tobacco control and is the author of over 170 scientific and other publications.

A pioneer in the early identification of drug resistance in tuberculosis patients, Sir John Crofton and his colleagues' seminal research into multidrug therapy for tuberculosis patients in the 1950s laid the groundwork for the WHO-recommended tuberculosis treatment today. This is one of the last interviews he gave before he passed away on 3 November at the age of 97, after a career that spanned three-quarters of a century.

Q: Why did you become interested in tuberculosis?

A: During the war I served under Lieutenant Colonel Guy Scadding, who had been a young consultant in London in a teaching hospital and had a particular interest in respiratory diseases. I was very stimulated by him, and we became great friends. When I came out of the army after the war, I worked under him at the Brompton Hospital in London. After a few months the new drug streptomycin became available and Scadding invited me to take part in the first classical controlled trial of streptomycin.

Q: When did you go to Edinburgh?

A: I was offered the vacant position of professor of tuberculosis at the University of Edinburgh in 1951. I accepted under the condition that it dealt with respiratory diseases in general. I went to Edinburgh [in 1952] and, from the tuberculosis point of view, it was grim. During the Second World War tuberculosis increased all over Europe, but after the war things got better nearly everywhere in Europe apart from Portugal and Scotland.

Q: Why was it grim in Edinburgh?

A: I inherited not only the 400 beds designated for tuberculosis at the hospital [there] but a waiting list of several hundred people. It was a grim situation not helped by the fact that there was one set of doctors handling outpatient diagnosis and another set dealing with the patients. I thought this was a bad thing from the point of view of continuity of care. There was also a problem with doctors in the hospital being able to pass patients they considered incurable back to the outpatient doctors. In other words they were able to get rid of their failures. I thought that if they had to keep their failures, they would make more of an effort not to have failures in the first place.

Q: What were the main challenges?

A: One was how to handle the epidemic itself. In 1954, there were 1000 new cases in a city of half a million. We divided [Edinburgh] into five areas, and drew up a scale reflecting clinical severity and social aspects, such as whether the patient was a child. Using this as a reference, and meeting on a weekly basis, we decided which patients were in most need of hospitalization, and then decided when patients in the wards had improved enough to go home and receive outpatient treatment. We thus got rid of our waiting list in a year. Our other main focus was the treatment effectiveness. We concentrated on the reasons for failure. We wanted to know why drugs that worked well in the test tube didn't work in all patients. We looked to see if they were absorbing the drug and if the drug was getting into the tubercle *bacilli*. We inherited patients who had been treated rather badly by the outpatient doctors, being given drugs alone or in ineffective combinations, and it became clear that the failures were due to drug resistance. Meanwhile we noted that with our own careful management of combination therapy – streptomycin and PAS (para-aminosalicyclic acid) – we were not creating resistance ourselves. But then in these first years, two of my colleagues each had a patient who showed resistance to the two drugs, even when properly administered. Now, the new rather magic drug isoniazid had just started to be used, and we had participated in Medical Research Council trials of the drug so we decided that the safest course of action would be to give all three drugs together. To our astonishment we found that we were curing everyone.

Q: And that became known as the "Edinburgh Method". How was this received?

A: My colleagues accepted the results because they had been involved in the research, but practically nobody else believed us apart from two bacteriologists from the Pasteur Institute (in France). Others even accused us of fiddling our figures.

Q: What effect did the new triple therapy have?

A: We were curing nearly everyone we treated. For the first time 100% cure was a reasonable goal; in the past it had only been 50%. New cases dropped by 59% in the three years from 1954. Treatment was effective, but it was still a challenge to get patients to take the drugs. Patients took all three drugs

when they were terrified of the disease, but as soon as they showed improvement they stopped. We did urine tests on patients whose sputum had been declared negative and who had been discharged home with instructions to continue chemotherapy. Of 100 sampled, 25 patients showed no trace of having taken the drugs. So we initiated a routine of regular urine testing and follow-up with patients who were not taking the drugs.

Q: When did the medical establishment accept the Edinburgh Method?

A: We initiated a trial in some 23 countries, choosing influential centres where if they got good results other people would take up the treatment. Due to scepticism about our method, we called it "a study of the causes of disease in far advanced pulmonary tuberculosis". We specified in the protocol that the cases could be moribund, very advanced and very bad, and that all the patients would have all three drugs. It worked out as we had hoped. While one or two moribund patients died a week or two after they came into the trial, all the other treatment failures were because the doctors had failed to adhere to the protocol. So at last we had acceptance.

Q: When did you start working with the World Health Organization (WHO)?

A: In 1993, I was invited to [attend a meeting of the WHO Coordination and Advisory Review Group, CARG]. I was impressed by the team WHO had put together but noted that at the first meeting there had been no mention of drug resistance. [Norwegian tuberculosis expert, Dr] Knut Øvreberg and I wrote in a memo that it would be useful to find out the drug resistance situation in any particular country before developing a national control programme. WHO agreed and produced a good survey of drug resistance [published in 1997]. Then, in 1995, I was asked by WHO to help develop guidelines on the treatment of multidrug-resistance tuberculosis (MDR-TB), the first such guidelines focused on the clinical treatment of patients with these resistant strains.

Q: DOTS[1] is often associated with the work of Dr Karel Styblo in Africa. How did the Edinburgh Method influence his work?

A: I first met Styblo in 1960 in Czechoslovakia. He was fairly junior then. The government had initiated detailed X-raying of the population in one part of the country, and Styblo was in charge. As a result of that visit, they completely changed their approach to treatment, following what we had pioneered in Edinburgh. Later on we worked together closely at the International Union against Tuberculosis and Lung Disease. He was a quiet man, but wonderfully persistent and an enormous worker. Several east African countries had asked for help with tuberculosis and Styblo was sent there. He proved to have a genius for persuading governments that tuberculosis was a major economic problem as well as a public health concern. He was also able to convince them that they could handle diagnosis and treatment through their routine health services, without special tuberculosis clinics and services. Above all he stressed the importance of monitoring patients throughout the course of treatment, as he had seen done in Edinburgh.

Q: Why was it difficult to introduce "directly observed treatment" – i.e. close supervision that tuberculosis patients are taking their medicine – in some countries?

A: To make directly observed treatment work as part of a programme the relevant professionals and the general population in the country must feel they own it. I first saw this achieved in Algeria in 1958, where a French doctor and an Algerian doctor ran an extremely good programme, which included national and regional meetings with doctors and politicians – so that everyone owned it. The other challenge with directly observed treatment relates to the supervision of the individual patients and their treatment. How effective this can be varies from country to country and culture to culture. In some countries a family member can supervise treatment. In others, that doesn't work. Then there is the issue of private practice and its influence [on tuberculosis control]. Even when you have a good government programme, you can still have private practitioners using the wrong drug combination and creating resistance.

Q: How do you see future prospects of tuberculosis control?

A: The situation is more hopeful now than 20 years ago. Many years ago when I was on the Medical Research Council committee, we went to all the big pharmaceutical companies and asked them if they were doing research on new tuberculosis drugs. Because it was mostly a third-world problem at that time none of them were doing anything. Now with the tremendous priority that politicians have placed on the problem internationally – that is on tuberculosis, HIV and malaria – far more money is going into new drugs to cope with resistant strains.

Q: So can we expect to control tuberculosis in the future?

A: I'm cautiously optimistic that in the long run we will control tuberculosis, but it's going to be a tremendous challenge and results will depend as much on political stability as technical progress.

Q: Is there anything you would like to add?

A: I worked very closely with both senior and junior colleagues, who made at least as much of a contribution as I did. In my old age I have been flattered to receive a good deal of credit for my work in tuberculosis and I feel that I have had too much credit and some of my colleagues not enough. ■

[1] DOTS originally stood for Directly Observed Treatment, Short course. Now the acronym refers to the five-element treatment strategy that is recommended by WHO and that is the core of the Stop TB strategy.