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VIDEO INTERVIEW TRANSCRIPT

Nunn, Andrew: transcript of a video interview (09-Aug-2016)

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Nunn, Andrew: transcript of a video interview (09-Aug-2016)*

Biography: Professor Andrew Nunn (b. 1943) has been working in clinical trials and epidemiological research since 1966, when he joined the Medical Research Council (MRC) Tuberculosis & Chest Diseases Unit as a Statistician, becoming Senior Statistician in 1972. Until 1986 he was directly involved in the design, conduct and analysis of the programme of trials conducted under the leadership of Professors Wallace Fox and Denny Mitchison in East Africa, Hong Kong and Singapore, which led to the worldwide adoption of short-course chemotherapy for tuberculosis (TB). Following the closure of that Unit he joined the MRC's Uganda AIDS Programme which researched the dynamics of the human immunodeficiency virus (HIV) epidemic in a rural African environment. On his return to the UK, he became Head of the Division Without Portfolio within the newly formed MRC Clinical Trials Unit with responsibility for developing trials in neglected areas. He was Senior Statistician on the recently completed REMoxTB and RIFAQUIN trials. Currently, he is an Investigator and Senior Statistician on three international phase 3 trials of TB treatment, one of which, STREAM, he is Co-Chief Investigator, the first phase 3 trial in multidrug-resistant TB (MDR-TB).

[1]. BECOMING A MEDICAL STATISTICIAN

I studied at the University of Sussex, and my first degree was in maths and physics. In the maths degree I had the opportunity to do a little bit on statistics, and I really enjoyed that, and decided that it would be good to do a Master's in statistics. So I stayed at Sussex for another year, enjoyed the master's course, and towards the end of the course was asked by the Careers Department of the University to go and see them to discuss what I was likely to be doing when I left university. Now I had already had some job applications to the civil service, and indeed had some job offers. I wasn't terribly excited by what was being suggested, and so I went along to the careers people, and told them this, said I wasn't entirely clear what I wanted to do yet, and right out of the blue they mentioned something that I knew nothing about before, and that was the possibility of using statistics in medical research. It sounded interesting, but what really was interesting was they suggested that I should go and see somebody, but the somebody they suggested was Sir Richard Doll. Richard Doll at that time was the Director of the MRC Statistics and Services Unit in Gower Street. It sounded a great idea, so I went up to London and met him. Now Richard Doll had been involved and was still involved in that mammoth study of all the GPs [General Practitioners] in the UK, and looking at their smoking habits in relation to the onset of lung cancer. I can't really remember much of our conversation, but I know I came away thinking 'This is it, this is what I would really like to do.' As it happened, there was a vacancy coming up in his Unit in the near future. I applied for that, unsuccessfully, but shortly after that another MRC Unit had a vacancy, and that was the Tuberculosis & Chest Diseases Unit. I applied for the job there, and got the job as Junior Statistician.

[2]. MRC TUBERCULOSIS & CHEST DISEASES UNIT

The MRC's Tuberculosis & Chest Disease Unit dated back to 1948, which was the year of the publication of the streptomycin trial; streptomycin being the very first drug found to be effective in the treatment of TB, and the Unit had gone on to do further work in the development of treatment regimens for TB and

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 09 August 2016, in the School of History, Queen Mary University of London. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Mrs Sarah Beanland.

new regimens. The Unit was based originally in Holly Hill, but then moved subsequently to the Brompton, and I joined it just before the move to the Brompton Hospital. It was a very interesting Unit, because a lot of the work that was being done was in the developing world. We did some studies in the UK, but most of them were in East Africa, Hong Kong and Singapore, looking to find effective and not too expensive treatments for patients in the developing world. We had a very effective regimen in the UK, but the problem was it was too expensive to use in the developing world. There was an alternative drug, there wasn't a lot to choose from, but there was an alternative drug called "thiacetazone" which was much cheaper, although there were some concerns of its toxicity. So we did some studies of its efficacy, and, indeed, a worldwide study of some 4,000 patients, looking at its safety. And this was my first exposure to work in this particular area. Obviously, this was completely new to me - I hadn't really much knowledge of TB at all, let alone its treatment, when I was a student. So this was a fast learning curve, but it was a great place to work because Wallace Fox was clearly one of the world leaders in this particular area.

[3]. HIGHLIGHTS OF AN MRC CAREER: TB, AIDS, AND TB AGAIN

Looking back over the almost 50 years since I joined the MRC, there have been one or two real highlights for me. I think the first of those was the study that we started in 1970 looking for a much shorter but effective treatment for TB. Up until that point in time everybody had to be treated for at least 18 months, and it was very difficult getting patients to take their treatment. But with the advent of a new drug, rifampicin, which became available in the early 1960s, we were able to actually show that six months' treatment was sufficient in this patient population. And this was the first of quite a large series of studies which went on to be the development of particular treatment worldwide. Following the 20 years that I spent in the TB Unit, in the late 1980s I went to Uganda to work on the Uganda AIDS programme, another MRC-funded programme. This was very interesting work because in fact, at that point in time, very little was known about the HIV epidemic in the developing country. Most of the research was actually being done in the western world. And we showed very clearly what an enormous impact HIV was having on the population, even in areas where the prevalence was relatively low compared to some parts of Africa, and the proportion of patients who were dying from HIV compared to dying from any other cause was remarkably high. These findings were recognized as being really important in having a good understanding of what was happening to the epidemic in Africa. It was encouraging to see in Uganda, in the years that followed, a real change as the HIV infection rates dropped steadily. More recently, I've got involved again in the work on TB research. And there is one area in TB which has been very badly neglected over the years, and that is research in multidrug-resistant disease. For drug-sensitive disease we have a lot of research, and there's a very solid basis for the treatments that we give. But the recommendations made by WHO [the World Health Organization] with respect to multidrug-resistant disease - that's resistance to the two key drugs, isoniazid and rifampicin - are actually very poor, because they are based not on clinical trials, but really on expert opinion and a limited number of cohort studies. Currently, I'm Chief Investigator of a study which is looking at a new regimen which hopefully will be much more acceptable to patients, and more effective than the current recommended treatment, which goes on for almost two years, whereas this treatment is just for nine months. Recently that study has also been expanded to bring a new drug, the first new drug for TB for just about 50 years, since rifampicin, which should enable us not only to give a more effective treatment, but a safer treatment, because we're hoping to be able to drop the injectable part, which causes a lot of problems for many patients.

[4]. DEVELOPMENT OF SHORT-COURSE CHEMOTHERAPY FOR TB

When we did the first studies of short-course chemotherapies that came to be known in East Africa, we did them under very tightly controlled conditions. Although it wasn't necessary to keep the patients in hospital, we kept them in hospital for the duration of their six months' treatment, in order to be really sure they'd taken it, so that if, at the end of the day, the treatment failed, it wasn't because they hadn't taken their treatment. When we showed those treatments worked, we were in a position to be able to go into settings where perhaps it was less likely that the patient would always be taking their treatment as carefully and as thoroughly as they might do. And the most interesting of those studies was one we conducted in Algeria. In fact, it was in the Algerian Sahara. We had an interesting population; it was a mixed population of people

who were living in the towns, but also an equal number of patients who were nomads, who were moving around the desert with their flocks of sheep or goats, and also picking dates, the season of the dates. A lot of these patients had TB, and quite bad TB as well, so this was going to be a real test of the regimen. The patients in that study were randomized to a standard longer regimen or the six-month short regimen. And remarkably for the nomads, the results were just as good as those patients who were settled patients, who were living in a particular town, who stayed there, as the nomads who were moving around and had to collect their drugs in different places, and had nobody to really supervise the taking of their treatment. This was an exciting development: that really this treatment could be used in a variety of settings beyond the rather tightly controlled setting that we'd originally used when we started the studies.

[5]. HIV AND UGANDA

In the late 1980s, many people tended to think of Uganda as a place where the HIV epidemic was worse than anywhere else. It's quite interesting - the National Geographic magazine had an issue at that time which was called *Uganda: land beyond sorrows*, which described the extent of the HIV epidemic. As a very interesting background to the HIV situation in Uganda was the story which the President told at the opening of one of the Africa AIDS conferences. Somewhere in the mid 1980s he met up with Fidel Castro at a non-aligned summit, and Fidel Castro said to him 'You've got a problem in your country.' Museveni said 'What's that?' He said, 'You know those soldiers you sent to us for training, we sent them off for testing for HIV and about one-third of them were infected.' Museveni's immediate reaction was 'Well, that's not possible, HIV is not an African disease, it's a disease for the west.' 'Well,' he said 'that's a fact, we did.' So Museveni went back to his country, back to Uganda, and asked his Ministry of Health how many ELISA [enzyme-linked immunosorbent assay] machines they had for testing for HIV, and they said there were only two in the country, one in one Government hospital and one in a mission hospital. So he straightaway asked them to buy some more, but he also wrote to both the British Government and the American Government and asked if they could come and research the disease in that country. The other thing that was striking about this is that he didn't hide the problem. Quite a number of African countries were very eager to make sure that other people didn't know they had an HIV problem, whereas in Uganda they made it very clear they had a problem, did everything they could to try to bring it down. Consequently, Uganda was the only country which for many years saw any real change in the prevalence rates of HIV, which was really encouraging.

[6]. CLOSURE OF THE MRC TB UNIT

The MRC closed the TB Unit, which had been running since 1948, in 1986, on the retirement of the Director Wallace Fox. Now what happens when the Director of a Unit retires is the Unit is reviewed with a view to saying whether or not the work should continue. The MRC, in its wisdom, felt that, having developed short-course chemotherapy, and the treatment was now accepted worldwide, there wasn't really too much more to be done. Well, sadly that's not the case, and what they didn't realise was two things. One was the advent of the HIV epidemic, which just about that time was really beginning to hit Africa quite badly, and in the years that followed the notification rates in many countries went up to four to five times higher than they had been prior to HIV. So in Zambia, for example, the rate had been 100 per 100,000 in the population; it went up to 500 per 100,000, and that presented a whole new problem which needed to be addressed. This was unfortunate, of course, but we can look back with hindsight and say that's what the MRC should have done, they should have kept the Unit going in order to address the problem of HIV, but they didn't know the problem was there really to that extent. The second issue which hadn't really raised its head, in 1986, was the problem of multidrug resistance. Now it's a problem which does concern those who are treating TB, and indeed we are still looking for the right solution for that. But right then resistance to rifampicin, the new drug, was only really on a very low level, so not a very major problem.

[7]. LOOKING BACK: STATISTICIANS, MEDICAL RESEARCH AND CLINICAL TRIALS

Looking back there have been a lot of changes over time. One of them is in fact that statisticians seem to be much more involved these days. Many more statisticians are involved in medical research than there were forty or fifty years ago. And, indeed, the way that we do our work as well has changed. In those days, we

hardly ever used computers; most of the data was recorded on cards that had to be analysed by sorting into groups by hand. But even then, there were other important differences too; the way that patients were enrolled into studies. Nowadays a lot of care is given to the way that patients are given the opportunity to ask questions and to enquire about what's going on in the study, to make quite sure that they are getting properly informed consent. The regulation of trials has changed a lot over the last fifty years. Many things are for the better, not least the way that patients are consented in the way that there was very little attention given to that in the past. I think they were almost told to join a trial by their doctor, back in the 1950s and 1960s. Nowadays patients are given a very long informed consent form to look at and to decide whether or not they want to join the study. And that's good, although in fact getting the balance right is difficult, because sometimes I think we give them too much information, so much so that they suffer from information overload, and are not really quite sure they know what's involved in joining the study. One of the other changes that's taken place is the role of the data monitoring committee. That's particularly important from a patient perspective to know that there is a totally independent committee which is overseeing the safety of the patients on a regular basis. Even when there are data monitoring committees sometimes mistakes are made, and certainly must make an enormous difference to have such a committee which can regulate, review the data in an un-blinded fashion, knowing just what's going on, and if necessary modify the design of the study and even stop them in some cases, simply because it's not safe to continue. So there have been a lot of changes, both technical and in the way that things are conducted, mostly for the good, I think, but we have to be careful that we don't overdo some of the regulations.

[8]. LOOKING BACK: INFLUENCES AND OPPORTUNITIES

Looking back over the last fifty years, I think I've been extremely fortunate. It doesn't work out for everybody quite so well. Obviously I was very fortunate in the way that the careers people pointed me to Richard Doll, and otherwise I might never have ended up in medical research at all. But then working with Wallace Fox and Denny Mitchison was a great privilege because they were two of the leading researchers in the field of TB, not just in this country, but worldwide. Then when that all came to an end the opportunity came to go to Uganda, at, again, a rather critical point in the understanding of the HIV epidemic. It was a real privilege to be part of that team, and work with Dan Mulder and others in determining the dynamics of HIV infection in a rural Ugandan setting. And then more recently being able to come back to the UK and, for the last 18 years or so, to be part of the Clinical Trials Unit; first of all, developing trials in neglected areas, and then again finally returning to TB, and one of its unsolved problems, the treatment of multidrug-resistant disease. Overall, I've got a great deal to be thankful for, and things have turned out very well.

[9]. LOOKING FORWARD: TB TREATMENT

Looking to the future, it's interesting to speculate as to what might happen, and, indeed, to think what one would like to happen in the future. Particularly with TB; it's been one of the diseases that's been round for the longest period of time. We know that there's evidence of it if we go back thousands of years. It would be nice to think that in this century, or perhaps even quicker than that, we might be able to eliminate it. Certainly WHO have it as an objective. Whether it can really be done in the next thirty years or so, that's a real challenge, I believe. Right now we're not very good at being able to identify all the cases, and about one-third of the cases at least go untreated, simply because they're never discovered in the first place. But with new diagnostics, I think we do have the possibility of identifying cases more quickly. And that will make a big difference because with the old technologies we often had to wait a long time before we could really be sure somebody had the disease, by which time many of the patients got fed up and stopped coming. Hopefully if we can get a rapid response and know very quickly that a patient has got TB, then in fact treating them will be much easier. And, of course, we need drugs which can treat them for much shorter periods than six months. Six months is a lot better than 18 months, but six weeks or even less than six weeks would be a big advance. And I hope that day is not too far off.

[END OF TRANSCRIPT]

Further related resources:

1. Christie D A, Tansey E M (eds) (2005) *Short-Course Chemotherapy for Tuberculosis*. Wellcome Witnesses to Twentieth Century Medicine, vol. 24. London: Wellcome Trust Centre for the History of Medicine at UCL.
2. Overy C, Tansey E M (eds) (2017) *Historical Perspectives on Rural Medicine. The Proceedings of Two Witness Seminars*. Wellcome Witnesses to Contemporary Medicine, vol. 61. London: Queen Mary University of London.
3. Reynolds L A, Tansey E M (eds) (2001) *British Contributions to Medical Research and Education in Africa after the Second World War*. Wellcome Witnesses to Twentieth Century Medicine, vol. 10. London: Wellcome Trust Centre for the History of Medicine at UCL.
4. Tansey E M (intvr); Tansey E M, Beanland S (eds) (2016) *Moore-Gillon, John: transcript of an audio interview (29-Apr-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016126. London: Queen Mary University of London.
5. Tansey E M (intvr); Tansey E M, Beanland S (eds) (2016) *Moore-Gillon, John: transcript of a video interview (29-Apr-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016127. London: Queen Mary University of London.
6. Tansey E M (intvr); Tansey E M, Beanland S (eds) (2017) *Nunn, Andrew: transcript of an audio interview (09-Aug-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2017056. London: Queen Mary University of London.
7. Tansey E M (intvr); Tansey E M, Yabsley A (eds) (2017) *Parry, Eldryd: transcript of an audio interview (12-Jul-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2017067. London: Queen Mary University of London.
8. Tansey E M (intvr); Tansey E M, Yabsley A (eds) (2017) *Parry, Eldryd: transcript of a video interview (12-Jul-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2017068. London: Queen Mary University of London.