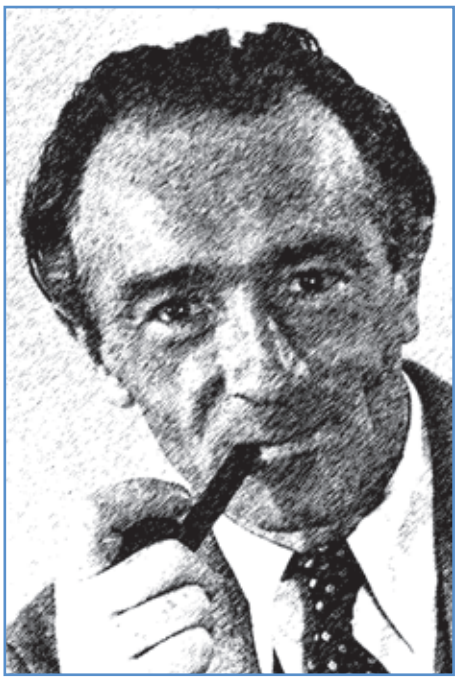
Archie's beautiful adventure



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ABSTRACT

Archibald "Archie" Cochrane is the brilliant creator of the evidence-based medicine (EBM). His book "Effectiveness and Efficiency: random reflections on health services" is one of the fundamental texts of Medicine today. For his influence on the progress of medicine, Cochrane may be considered one of the greater physicians of all time. He gave an exceptional boost to the improvement of medical practice worldwide. Cochrane's vision of medicine and his great scientific achievements are still alive through the Cochrane Collaboration, an organization which provides valuable impulses to improving the quality of medical care. Also he was a great epidemiologist, very proud of his epidemiological work, and his life is interesting for adventurous events and extraordinary examples of righteousness and generosity.

Key words: Evidence Based Medicine; Public Health; Epidemiology

Archibald Leman Cochrane was born in Galashiels, Scotland, on January 12th, 1909, into a wealthy Scottish family. He was the first son of Walter Francis and Emma Mabel, Cochrane. Archie was not lucky during his youth. In his early years, his father was killed in the Battle of Gaza. When Archie was just 8 years old, one of his brothers, aged 2 years, died of pneumonia. His other brother, Robert, 22 years old, died in a motorcycle accident. Therefore, the relationship with his sister, Helen, became very close and affectionate and lasted throughout Archie's life. Helen was admitted to a psychiatric hospital when she was diagnosed, probably with superficiality, dementia: Archie did not accept this diagnosis and he claimed that further investigation showed that he and Helen suffered from porphyria. Archie suspected the same diagnosis in other family members, so he convinced many of them to do a control about porphyria. 152 relatives were affected without knowing it [1]!

This anecdote sums up the essence of Archie's spirit: he was always ready to challenge the medical authorities and to demand the proof of evidence of the effectiveness of an intervention. Although he had an interest mainly epidemiological towards welfare community, he was also deeply concerned about the health of a single individual. As evidenced by the survey carried out with his relatives, he was particularly appreciated in order to achieve very high rates of participation and follow-up in his studies.

After attending schools in Rhos-on-Sea, in Wales, in 1922, Archie Cochrane won a scholarship to study at Uppingham (England). He became a perfect student and a valued member of the local football team. In 1927 he won a scholarship to the prestigious King's College, Cambridge, where he graduated in 1927. An inheritance allowed him to continue his studies and in 1931 he worked in the Strangeways Laboratory in Cambridge, carrying out research on tissue culture. Soon, however, he was tired of this experimental work, because even concerned about his health, and he went to the Kaiser Wilhelm Institute in Berlin, where his health problems were taken with great seriousness and he was welcomed with great warmth. Between 1931 and 1934 he was in psychoanalysis by a disciple of Freud, Theodor Reik (1888-1969), first in Berlin and then in Vienna and The Hague, when they fled from racial persecution. Therefore, Archie performed some medical studies in Vienna and Leiden. In those years Archie studied and learned perfectly many foreign languages. This period (the early 30s) was extremely important in developing his skeptical thinking towards all those theories (including psychoanalysis) not validated by experiments. The direct knowledge of a totalitarian ideology instilled in him not only a strong hate towards fascism, but also a skeptical attitude towards a blind faith in dogmas.

After returning to Britain in 1934, Archie enrolled as a student of clinical medicine at University College London (UCH), but he abandoned his studies two years later to join as a volunteer in the Spanish Civil War, on the Aragon front. Archie met in London, in August 8th, 1936, a group of doctors, medical students and nurses assessing the ability to send medical aid to Republicans fighting in the Spanish Civil War. A committee for medical aid to Spain was constituted. Cochrane volunteered to be an active member of this team and set off for Spain. Archie was one of those young British doctors who had been strongly excited by the succession of events in the mid 30s and who had voluntarily joined the Spanish Medical Aid Committee. "It was the time of the Hunger March, Mosley's Blackshirts, and a round of anti-fascist meetings. Then came the Popular Fronts in France and Spain, and a stream of refugees. Finally, in the summer of 1936, Franco and his Moors invaded Spain and the pot boiled over. My friends and I feared that if Spain went fascist and joined with Hitler and Mussolini, France and the UK were doomed; but we were admittedly ignorant of the complexities of Spanish politics. We were incensed by the UK's commitment to a non-intervention pact, especially when it became clear that Germany, Italy, and Portugal were openly flouting such a policy" [2].

Cochrane was framed, with Reginald Saxton and Alex Tudor-Hart, in the 35th Division Medical Unit connected to the French battalion of the XIV International Brigade. He participated at the Battle of Jaramain, in February 1937, collaborating in the creation of a field hospital in a country club, at Villarejo de Salvanés, using a bar as the operating room and operating on three table-tops. Archie remembered those years in his autobiography, *One Man's Medicine* [3]: "On my flight back to the UK I tried to sum things up. I was glad I had gone to Spain; glad that I had not given up in despair at Grañén. Given my limited abilities, I had made a reasonable contribution to the anti-fascist cause, rather than merely talking about it. I had also learned a lot. Although I had come to hate war, I now knew that fascism would have to be fought and that pacifism was impossible. I had, too, become increasingly suspicious of the communists. There had been valuable opportunities to discuss political theories

with knowledgeable people of different persuasions - anarchists and Trotskyites; Russian, German, French, and American communists; British socialists and communists; and a few British liberals. I realised that no one knew how to run a country or a revolution... Overall I had a general feeling of satisfaction that I had risked my life for a cause I believed in" [2].

At UCH, in 1937, Cochrane resumed his studies and became a doctor in 1938. Until the outbreak of the Second World War, he worked, at first, in West London Hospital, then as a research assistant at UCH Medical Unit. He served his country as a captain in the Royal Army Medical Corps, first in Egypt and then in Layforce battalion. The only military action in which he participated personally was a disaster: he was captured in June 1941, in Crete. Archie was a medical officer in a series of prisoner of war camps, including Salonika, Hildburghausen, Elsterhorst and Wittenberg. His health conditions improved when he arrived in Nazi Germany. "German rations at about 2 500 calories a day and regular Red Cross parcels, which took us over the 3 000 calorie mark, were heaven on earth. This transformed me. I lost my edema and jaundice, put on weight, and became, I hope, a more useful doctor and more reasonable human being" [3].

During his experience as a medical officer prisoner of war, he reinforced his interest to verify effectiveness of different medical treatments. In fact, while he was prisoner, he made his first randomized clinical trial. This study evaluated the utility of a yeast supplement to cure edema related to malnutrition in prisoners of war camp in Thessaloniki. Cochrane was so demanding on himself, in fact, he didn't describe his study as "randomized" because the randomization in the prison camp had been carried out alternately and not by truly random assignment.

"I remember then that reading one of those ads propaganda deemed suitable for prisoners of war physicians on the clinical freedom and democracy, I found them impossible to understand. I had some freedom to choose therapy: my problem was that I did not know which one to use and when. I would gladly have sacrificed my freedom for a piece of knowledge. I had never heard of Randomized Clinical Trials, but I was aware that there was a very real evidence that anything we offered had any effect on tuberculosis. I was afraid to even shorten the life of some of my friends, using unnecessary interventions" [3].

At this juncture, he received a medal for his services. During his imprisonment he wrote poetry, published in 1954 as *Poems from Prison*.

COCHRANE AND EPIDEMIOLOGY

After leaving the army at the end of the war, Archie Cochrane obtained a Rockefeller scholarship in Preventive Medicine. He began to attend the diploma course in Public Health at the London School of Hygiene and Tropical Medicine, where he was greatly influenced by Austin Bradford Hill [4], who taught epidemiology and randomized clinical trials. In 1947, Archie went to Philadelphia at the Henry Phipps Clinic, where he took an interest in the X-ray studies in tuberculosis, deepening the knowledge of inter-and intra-observer error.

After returning in UK, in 1948, Archie Cochrane worked, for about twenty years, in the field of epidemiology of lung diseases, particularly tuberculosis and pneumoconiosis. His critical spirit and his contribution to the methodology of the studies of prevalence and follow-up were really extraordinary.

Archie reached highest response rates in his studies (98% of responses) and he well described the characteristics of non-respondents and the relationship between order of response and social factors. He believed that doing research with population studies meant to do something **for** the people rather than do something **with** people [5].

Archie began a member of the scientific staff recently trained at the Medical

Research Council's Pneumoconiosis Research Unit in Penarth, near Cardiff (Wales) and he conducted comparative studies on the levels of dust in the coal mines of South Wales. Two years later, he launched the Aberdare Rhondda Fach Velley, a diagram used to investigate the etiology of progressive massive fibrosis. Archie worked for Pneumoconiosis Research Unit for more than 10 years on radiological classification of pneumoconiosis of coal workers and on the difference between radiographic features, exposure to dust and disability. His interest in this field lasted throughout his life, as evidenced by the completion of follow-up studies on the population in which his speech is originally applied.

The research results of Archie reached very high standards for epidemiological studies at the time, due to his persistence in achieving high response rates in the surveys and follow-up studies and his meticulous controls about the reproducibility of the measurements carried out. The excellent quality of his work got a great deal for groups of disabled miners of which he took care. As a result of his success, he was offered the leadership of the new Epidemiology Unit in Cardiff. He accepted this appointment in 1960, assuming at the same time, also, the Chair of Tuberculosis and Thoracic Diseases at the Welsh National School of Medicine, kept until 1969. Under his direction, the Epidemiology Unit of Cardiff reached a remarkable international reputation for the quality of investigations, to perform natural history studies and to investigate the etiology of a wide range of common diseases, such as anemia, glaucoma, asthma and cholecystitis. The valley of Glamorgan, where Archie worked, quickly became the best-studied area of Britain, from an epidemiological point of view. These studies led to Archie, also, be interested in the validation of screening strategies within the National Health Service.

FROM CLINICAL TRIALS TO EBM

Archie Cochrane, in the mid-thirties, was favor of setting up a national health system, but he was very concerned to clarify that treatments had to be not only free but also effective: "All effective treatments must be free" [5] was, in fact, one of his first slogan.

Cochrane believed that the assessment of effectiveness was necessary to prove that an intervention produces more benefits than harm and this should be a top priority for health systems and workers of a public health perspective.

According to Sir Richard Doll, his colleague and close friend for over 50 years, the name of Cochrane is inextricably linked to randomized clinical trials and evaluations of effectiveness of health interventions. His unit coordinated a great variety of trials, evaluating the effectiveness of pharmacological, surgical and public health interventions. These pioneering studies were first investigations establishing that aspirin could reduce the incidence of cardiovascular disease.

Archie was witty and unpredictable also in presentations. Together with Gordon Mather, a cardiologist of Bristol, he decided to perform a randomized study to evaluate the effectiveness of coronary care units compared to home treatment: after a few months of study drafted an interim report referred his own words are worth remembering: "The results of that stage showed a slight advantage for those who had been treated at home. But I wrote nastily two reports: in the second one I reversed the numbers of deaths in the two groups. Before entering the committee's room I showed cardiologists the reversed results and they immediately became aggressive: "Archie we've always thought that the study was not ethical. Now you have to stop the study". After having made them vent for a while, I apologized and gave him the true results, challenging them with equal vehemence to say that coronary care units had to be closed. There was a dead silence, and I felt bad because they were, after all, my colleagues."

Cochrane worked very assiduously to the earliest randomized clinical trials on cardiovascular diseases prevention with low-dose aspirin. After much discussion, Archie, Peter Elwood and Jimmy Graham agreed to a study: "low-dose aspirin (300 mg) versus placebo". At those times, the dosage of aspirin as antiplatelet agent was still not coded: the mode of presentation of the results that are still relevant today. The available studies showed reductions in mortality at around 25%, with a mortality of 10%, but in most of these studies this difference was not statistically significant [5].

Cochrane worked on the presentation of the available studies, but Richard Peto quantified in 2% the real benefit with a formal meta-analysis: aspirin reduced mortality after myocardial infarction from 10% to 8%. In fact, Cochrane said that these two different ways of expressing results can be defined respectively the "clinic vision" (reduction in mortality of 25% relative) and the "true vision" (survival increasing from 88% to 90%). These are still the cornerstones of a good presentation of results.

Archie Cochrane had many formidable insights: protective effects of alcohol on cardiovascular disease (or French paradox), the displacement of gravity center of our care systems from hospital to community medicine or primary care, the use of unselected populations (not only patients in the hospital) to reduce measurement bias, as well as the crucial role of independent research which leading him to encourage the use of randomized trials as a tool to reduce potential bias of the British health care system. He was deeply convinced that a reliable health planning and health management would benefit greatly from an epidemiological evaluating expertise; Archie tried also to reduce interventionism and the medicalisation without evidence of benefit, from screening to treatment. He believed firmly in applied research as a priority of a health system compared to basic research, and he considered that both researches should have equal dignity. He pronounced freedom of choice saying: "When I was working as a doctor in a war prisoners camp I had a considerable freedom of therapies choice. My problem was that I did not know which treatment to use and when. I would gladly have sacrificed my freedom for a bit of knowledge."

The randomized studies have now undoubted importance orienting decisions on the use of resources in the health service. Archie developed this theme in a invitation to give a lecture in 1971, addressing as nobody had ever managed to do. The result was a book, *Effectiveness and Efficiency: Random Reflections on Health Service*, that quickly became a bestseller. The book was very readable and covered important topics of general interest, such as the need to use the randomized studies to identify health interventions more beneficial, and the importance of evaluating the costs of the available options before including in the English Health Service. The book was soon translated into many languages.

In the same year, 1972, when the book was published, Archie Cochrane became the first President of the new School of Community Medicine (later known as Faculty of Public Health). The following year, he received an honorary doctorate from the University of York.

Archie Cochrane also favored social sciences approaches in medicine and he encouraged sociologists. As a humanist and lover of arts, he didn't appreciate scientific English "thorough, meticulous and almost free from bias (neutral), but not able to reveal the biases of the researchers. But the main defect is that it is almost illegible". He thought, finally, that the main job of the directors, managers and programmers was to make choices between alternatives to produce data of benefits and costs of alternatives.

Archie was a unique, perfect set of methodological rigor and candor, not devoid of that pinch of aggressiveness, proper to those who question dogmas.

Nowadays, in a medical-scientific world very vulnerable and pervaded by conflicts of interest, these attitudes are increasingly rare [5].

Archie Cochrane was, also, an expert gardener (his stone garden won an award given by the Royal Horticulture Society) and a keen patron of art and modern sculpture. He died in 1988 after a long battle with cancer. A few years after his death, in 1993, the New York Academy of Sciences organized a big conference in his memory: "Doing more good than harm". That event was the groundwork for the development of Cochrane Collaboration. In fact, in October 1993, 77 researchers from nine countries founded, in Oxford, the Cochrane Collaboration, an international non-profit organization to the purpose to prepare, maintain and disseminate systematic reviews on effectiveness of health assistance. Now this non-profit organization counts over 15 000 people, mostly volunteers, in several countries and specialties.

He described himself in his obituary, appeared in the BMJ, in this manner: "He lived and died, a man who smoked too much, without the consolation of a wife, a religious belief or a merit award. But he didn't do so badly"[6].

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