

The origins of the Common Cold Unit

DAVID TYRRELL, MD, FRCP, FRCPath, FRS

Director, *MRC Common Cold Unit, Salisbury, Wiltshire*

ABSTRACT – In 1941 Harvard University and the American Red Cross provided an epidemiological team and an infectious diseases hospital for Britain. Since 1946 the buildings have been occupied by the Common Cold Unit where research has been carried out into many aspects of the causative viruses and their role in the disease, and also into methods of preventing it. The establishment is to be closed down this year.

The fiftieth anniversary of the outbreak of the Second World War has just passed and it seems to be an appropriate time to recall the fact that individual Americans and certain institutions in the USA provided medical support to Britain, even though their country was, at that time, neutral and therefore could not be seen to support our war effort.

Harvard University and the American Red Cross

In 1939 Dr Conant, the president of Harvard University, wanted to organise a volunteer unit that would fill a real need in Britain. It was agreed with the Ministry of Health that their particular concern was the possible spread of infectious diseases. Detailed proposals were worked out by a group including Dr Gordon of the school of public health at Harvard. In 1940 it was decided to send out a tripartite unit consisting of a team equipped to do field studies, a laboratory and an infectious diseases hospital of 125 beds to serve civilians and the services. The funds were raised from individual donors and foundations. The university team felt that they themselves were not the right group to set up a hospital and recruit nursing staff. They therefore approached the American Red Cross who responded willingly. The plan was to ship to the UK a prepackaged hospital and the staff to run it. The hospital was planned and its buildings and equipment were ordered 'off the shelf' in Washington. The Ministry of Health provided and prepared a site, near Salisbury, and helped with the erection of the buildings which were wooden huts made from modular components so that their internal layout could be flexible. In many respects the specifications were high: they all had oil-fired central heating and the floors were of oak-veneered nine-ply panels. Some huts were to be wards, others staff quarters, and others laboratories,

stores and offices. There were many difficulties on the way. Dr Gordon arrived in London just as the bombing was beginning. It was difficult to obtain space in ships, and one carrying building materials and staff was sunk by enemy action: six nurses were lost while others narrowly escaped with their lives. These losses were made good and in 1941 the whole establishment was in place and functioning.

By all accounts the unit was much appreciated by the British, not only for the practical medical help it gave but also for its symbolic significance — the staff had volunteered to help at a time when Britain was threatened and in need of friends. The unit aimed to augment what was being done by the emergency medical service and the laboratory services. Not only did the hospital provide care for local people with infectious diseases but any outbreaks of infectious disease in the region were also investigated. On one occasion, when members of a research team in premises on Salisbury Plain, working to develop a typhus vaccine, accidentally infected themselves with the organism, it was arranged for them to be cared for in the wards in isolation.

When the USA entered the war, following the Japanese attack on Pearl Harbour, there was thus already an American medical team in operation in southern England. In 1942 it was decided to offer the unit to the US Army on the understanding that when the war was over it would be passed to the Ministry of Health. Most of the officials and medical and nursing staff agreed to enlist and run the hospital as part of the US Army. The formal letter at the time of transfer gives a good picture of what had been achieved by then:

The unit has a staff of eighty-five physicians, nurses and technicians. It consists of an epidemiological field unit, a well equipped laboratory and a hospital of 125 beds carefully planned and built with the cooperation of the British Ministry of Health for the care and study of communicable disease. The three divisions of the unit have been in successful operation for approximately a year and the hospital is equipped to give expert aid and consultation in epidemic diseases. The American Red Cross and Harvard University are desirous of extending maximum assistance to our armed forces in the British Isles and we have not only welcomed the opportunity but are pleased that we have been able, with the collaboration of the British Ministry of Health, to offer to the United States Army an already established and complete epidemiological unit which appears to be so admirably suited to meet the needs of our armed forces

Address for correspondence: Dr David Tyrrell, MRC Common Cold Unit, Harvard Hospital, Coombe Road, Salisbury SP2 8BW.

in the field of preventive medicine. It is significant that the unit as of the time of transfer to the army represents a total investment in excess of one million dollars.

The Harvard medical school also staffed the fifth American general hospital which was set up on the downs nearby at Odstock. The buildings have been in use ever since and the site is being redeveloped to provide a new district general hospital for Salisbury. The Harvard hospital served as a pathology laboratory and the laboratory facilities were extended.

The United States Army

Dr John Wallace recalls that from 1942 he was working at the army blood supply department in Bristol. At that time, when blood transfusion was a new technique, he established a close collaboration with an American, a Captain (later Lieutenant-Colonel) R. G. Haslin, and together they trained 200 US medical officers. It was decided to set up a blood bank in the UK ready for the invasion of Europe; the Harvard hospital was chosen as the site and Dr Haslin started to equip it in February 1944. Up to 60 truck drivers were trained to transport refrigerated blood, the laboratories were set up to provide serotyping and cross-matching services, and there were storage and shipping sections and a record section. Between May 1944 and 1945 a total of 118,143 donations of blood were distributed to medical units of the US Army, including 104 ships of the invasion fleet. Dr Wallace, who became director of blood transfusion services in the west of Scotland, renewed his acquaintance with the site when he became the clinical observer in volunteer trials at the Common Cold Unit.

Some outstanding individuals passed through the unit. Dr Paul Beeson, the physician in chief at the original hospital, later returned to England as Regius Professor of Medicine at Oxford. Dr Muckenfuss, who had documented the pathology of pandemic influenza, and Dr J. Smadel, well known later for his work on rickettsial diseases and influenza, and as director of the Walter Reed Institute in Washington, were on the staff of the pathology laboratory.

Many of the medical and nursing staff were quite young; although they worked hard, there was time for socialising and courting, and a good many marriages followed. Some of the survivors have made sentimental journeys to visit the place which they still remember with pleasure; a party of 16 made their final farewell visit in October 1989.

After 1944 and the D-Day landings the war front moved too far away from Salisbury, so the laboratory was transferred to France and for a while the Salisbury site was in the care of the Pioneer Corps of the British Army.

Apparently, when the question of what should happen to the buildings 'after the war' was raised in the very first discussions about the project, it was suggested that they might be used for research of some kind, though nothing final or definite was done about it.

Despite huge post-war problems in returning the country to a peacetime footing, rebuilding the economy and repairing the damaged and neglected housing stock, as early as 1946 the initiative was taken to establish on the site the Common Cold Research Unit; this has maintained an active programme of investigations up to the present.

The Medical Research Council and the Ministry of Health

The seeds of the Common Cold Unit had already been sown in the early 1930s. In the preceding decades many investigators had tried to show that colds were due to infection with bacteria or viruses. Most of the results had been inconclusive or unrepeatable but Dochez, working at the Rockefeller Institute in New York, showed that there were no consistent changes in the bacterial flora of people with colds and that he could repeat earlier experiments in which colds were produced by the intranasal inoculation of filtered nasal washings from patients who had colds. His studies were convincing because of the care with which he proved that the filters retained bacteria, and the care with which he prevented other sources of infection from reaching the chimpanzees and the humans that he used as 'guinea pigs' (all lower species proving insusceptible). Dr (later Sir) Christopher Andrewes had visited New York and knew about the work; he was also interested to repeat experiments in which Dochez's group claimed they could propagate the cold virus in cultures of chick embryo tissue. Andrewes was working for the Medical Research Council at the National Institute for Medical Research, Mill Hill. He appealed to students at his old medical school, St Bartholomew's, to offer themselves as volunteers and tried to repeat the New York experiment, even to the extent of carrying material back from Dochez's laboratory and persuading a steward on the Queen Mary to keep it in a refrigerator during the voyage. He could not get any evidence that the virus was growing in tissue cultures; he had problems with the clinical trials since he could not isolate his volunteers as Dochez had done (virtually imprisoning them) and there was a possibility that they might pick up colds as they moved about London. The research was not followed up since Andrewes was at first involved in pursuing the discovery of the influenza virus, and later, at the outbreak of war, he was helping to establish the emergency public health service.

The war was scarcely over when Andrewes heard that the site at Salisbury might be available. His friend Dr W. Bradley helped to persuade the Ministry of Health that here was an ideal site at which sufficient numbers of human volunteers could be isolated. Early in 1946 the Medical Research Council was approached for funds to set up and run a research laboratory in the buildings, to tackle the questions of how colds were caused and how they spread. It is greatly to the credit of the people involved and the way decisions were taken that staff were appointed, the buildings

were refurbished and the laboratory was equipped so that the first intake of volunteers could arrive in July of that year. It is also remarkable that the methods for isolating and housing the volunteers, the duration of the trials and the recording of clinical observations, which were planned by the clinician Dr Chalmers in the first weeks, remained essentially unchanged from that day to our last trial in 1989.

Research with volunteers

At the time the unit was set up probably no one would have foreseen its long history. There is a story, no doubt apocryphal, to the effect that Andrewes at one stage suggested that they might occupy one hut for six weeks for their experiments, though a more credible report is that he expected to culture the virus and make a vaccine to it within a few years. In fact research has continued without a break for a total of 44 years. There have been numerous changes in the staff, and one research topic after another has been taken up as knowledge has advanced, but the great strength of the unit throughout has been the availability of substantial numbers of volunteers and the facilities for housing, inoculating and observing them in a highly effective and reproducible manner. Although it was recognised that progress would be slow until laboratory methods could be developed to replace experiments in man, eg the detection of viruses, it was a tremendous advantage to have a method, namely the production of colds by inoculating strictly isolated volunteers, whereby it could be sensitively shown that experimental material (perhaps a nasal washing or a tissue culture fluid) contained a virus that could cause a common cold. Later on, when the causative viruses were well known and could be readily cultivated and detected *in vitro*, it was important to inoculate volunteers in order to study the role of immunity in resistance and recovery, and to study pathogenesis and detect whether various possible drugs, antivirals, anti-inflammatory drugs or immune enhancers prevented or even treated colds.

Some research results

This is not the place for a detailed review of the scientific output of the unit, but one or two high points may be mentioned. In the early 1950s work began on growing cold viruses in tissue cultures, and by 1960 we had a method for detecting viruses in about a quarter of the patients who had colds. These viruses were shown to belong to multiple serotypes and they were finally recognised as belonging to a new family, the rhinoviruses; in the succeeding decades the serotypes have been studied and defined on an international basis.

In 1965 we introduced a form of organ culture of human respiratory epithelium which would propagate still more rhinoviruses, and also a distinct group of viruses, previously unrecognised, for which we suggested the now agreed name of coronaviruses.

In recent years diagnostic methods based on new technologies have been developed, such as ELISA tests

for detecting specific antibodies in sera and secretions, and molecular hybridisation methods for identifying viruses in clinical specimens, although these have not yet been widely adopted.

Working with various collaborators, A. S. Beare spent years studying how to reduce the virulence of influenza viruses by manipulation in the laboratory. This and succeeding work led not only to international co-operation but also to candidate live influenza vaccines, as yet not widely taken up; it also enhanced our understanding of influenza virus virulence and mechanisms of immunity. In recent years members of the unit have studied immunity to rhinovirus and coronavirus colds down to the molecular level, though this has not yet resulted in the production of a vaccine. However, studies on *ts* mutants as vaccines against respiratory syncytial virus were in progress up to the last months of clinical trials.

Since vaccines proved inappropriate we have retained an interest in antiviral prevention and treatment, even though for much of the time influential opinion regarded it as impossible. In the end we showed that intranasal sprays of interferon would prevent colds due to rhinoviruses and other viruses, and the parameters of this effect were explored over a number of years. Studies of synthetic antivirals in volunteers for decades yielded meagre results but in the last years a series of increasingly active antirhinovirus compounds, synthesised by a number of different pharmaceutical companies, were evaluated. After many trials one of them, R61837 made by Janssen, was shown to have clinical effectiveness similar to that of the interferons in preventing colds due to a sensitive rhinovirus (type 9). This clearly opens the way towards the management of colds and more serious disease with other antivirals.

Occasional studies revealed that psychological factors such as personality or life stress apparently alter susceptibility to colds. In the last four years comprehensive data have been collected to confirm and refine these findings. After the unit is closed the data will be subjected to detailed analysis in collaboration with our psychologist colleague Dr Sheldon Cohen of the Carnegie-Mellon University, Pittsburgh. The way in which virus infections affect the performance of volunteers has also been studied, using a variety of methods of psychometric testing. Thus we have been able to take the opportunity offered by antiviral and other trials to use the unit to explore the effect of the mind on a model organic disease, namely a cold, and the effect of that infection on human skills. These are matters that every clinician knows to be of interest and importance but only rarely can they be studied rigorously or analytically in clinical practice.

Thanks to the volunteers

As Table 1 shows, the unit has been very well supported by the public; indeed I have frequently been told that only in Britain could one get such substantial and continuous support from members of the public when

Table 1. Number of visits made by volunteers to the Common Cold Unit.

Number of separate visits	Men	Women	Total	Total number of visits
1	3,609	5,221	8,830	8,830
2	686	1,076	1,762	3,524
3	247	367	614	1,842
4	130	206	336	1,344
5	66	123	189	945
6	39	54	93	558
7	43	62	105	735
8	19	29	48	384
9	8	22	30	270
10	12	8	20	200
11	9	12	21	231
12	6	6	12	144
13	2	7	9	117
14	1	6	7	98
15	3	7	10	150
16	1	4	5	80
17	1	3	4	68
18	—	1	1	18
19	1	1	2	38
20	—	2	2	40
21	1	2	3	63
22	1	4	5	110
23	—	1	1	23
24	1	1	2	48
25	1	—	1	25
26	1	—	1	26
<i>Total</i>	<i>4,888</i>	<i>7,225</i>	<i>12,113</i>	<i>19,911</i>

so little inducement was offered. Many of the volunteers came to help the cause of medicine, in which they believed, others to escape from telephones and demanding relatives or to have a free 'holiday'. Whatever their reasons, they have been excellent collaborators during the decades of the unit's existence, and without them the unit could not have made its unique contribution to research on respiratory tract infections — work recorded in many hundreds of published scientific papers. However, in July 1989 the last trial was concluded and in 1990 the establishment will be closed. The Medical Research Council has decided not to continue the work elsewhere but we all hope that there will be some appropriate reminder of a unique example of US-British collaboration in medical care and research.

The Most Reverend Dr Secker

Thomas Secker was born in 1693 at Sibthorpe, Notts, into a dissenting family and at first proposed to enter that ministry. At the age of 23 he changed to medicine, studied in London and Paris, and 27 gained the MD of Leyden. He then went up to Exeter College, Oxford, and changed back to the Church. His ecclesiastical career was uniformly successful. After parochial livings he became in turn Bishop of Bristol, Bishop of Oxford, Dean of St Paul's and Archbishop of Canterbury, the only medical man to have held that office.

ALEC COOKE FRCP