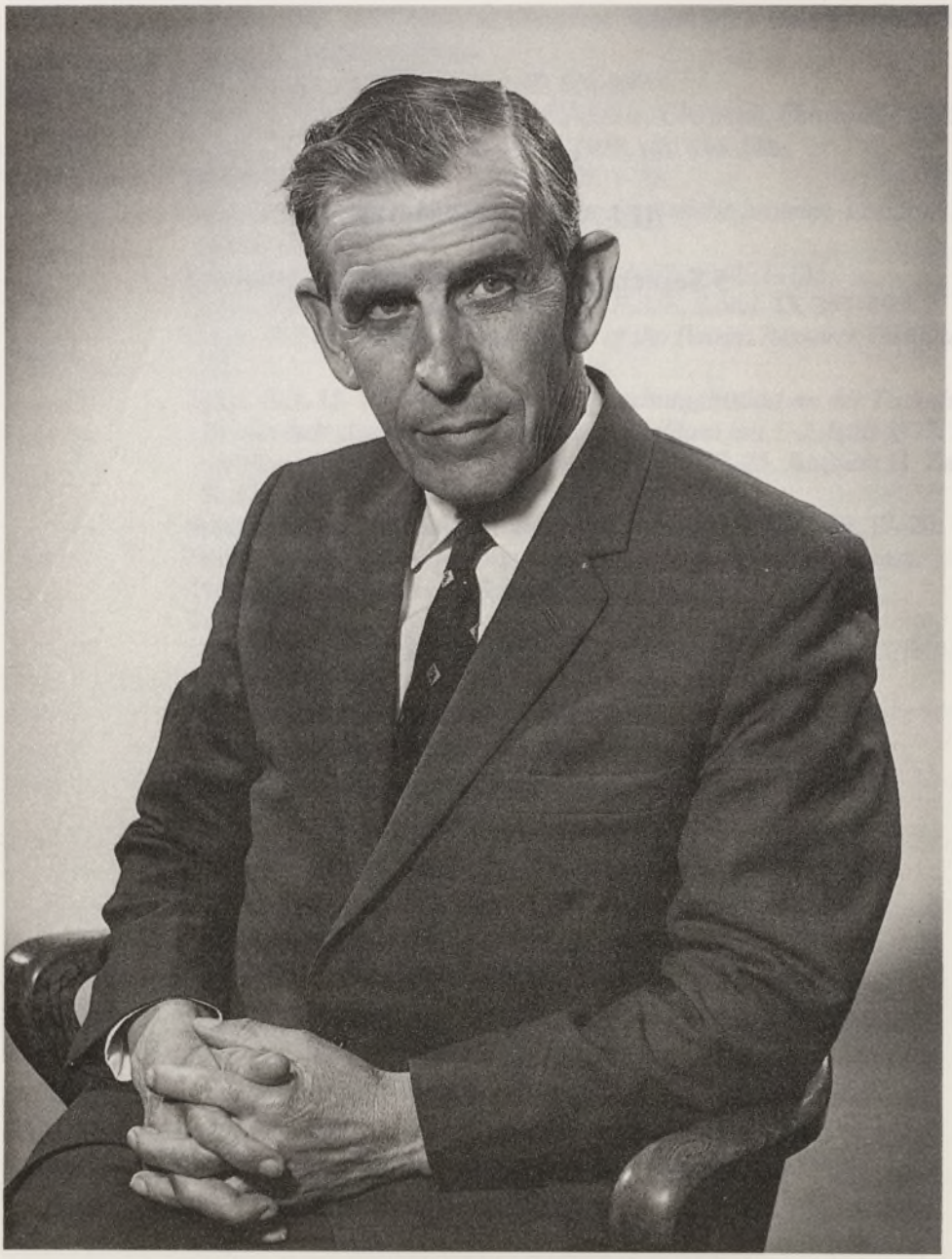
ALLAN WATT DOWNIE

5 September 1901—26 January 1988



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By D.A.J. TYRRELL, F.R.S. and K. MCCARTHY

ALLAN DOWNIE was born on 5 September 1901 and brought up on Mid Street in Rosehearty, Aberdeenshire, a village on the coast where his father, William, and grandfather had been fishermen. His mother, Margaret, was the daughter of a fisherman from Fife. He and his identical twin brother, Richard, were fifth in a family of eight boys and one girl. William John, the eldest brother of the twins, continued in the fishing tradition, sailing his own steam drifter till his retirement half way through this century. Allan recalled his childhood as being relatively happy and carefree, and, not surprisingly, many of his activities were linked up with the sea, such as sailing, fishing, swimming and exploring the rocky shoreline. He continued these interests through life and went bird-watching and fishing whenever he could. He was also a sportsman, representing Aberdeen University at football, water polo and golf, and played club football until middle age, tennis when opportunity offered and golf almost up to his death. Indeed he treasured the headline in a local newspaper when he left the University 'Noted local golfer retires'.

The twins were educated first at the local elementary school and their mother recognized their ability at an early stage. The dedicated headmaster gave them extra tuition in Latin and mathematics outside school hours. He also recognized the talent of Allan and his brother, and visited their parents to urge them to send them on to Frazerburgh Academy for secondary education. They were there from 1915 to 1918 and then went on to Aberdeen University Medical School. It is recorded that the two of them took many of the prizes for their year, Allan in Physiology, Obstetrics and Operative Surgery and his brother in Anatomy and Surgery, and in 1923 they both graduated with first class honours, but it is believed that they swept up other prizes as well. Indeed 34 years later the Public Orator presenting Allan for an honorary LLD went further. He said that at graduation in 1923, the Professor of Medicine, Sir Ashley MacKintosh, had revealed that he had added up the marks gained by each twin in their four professional examinations and had found the total to be identical. Furthermore, he said that their performances in the Final exam were also too close for him to discriminate as to which should be awarded the prize and that he had taken the unprecedented step of allowing the twins to make their own division of the academic spoils!

The astute Dr John Cruickshank who in 1923 was Head of Bacteriology at Marischal College Aberdeen, had taught and noted the twins. Immediately after Finals results

were announced he stole a march on other 'head hunters', sending a messenger into the Kirkgate Bar with the instructions 'Get me out one of the Downie twins'. Thus did Allan (nearest the pub door) hear of his first academic appointment, to start in the following October.

For four months Allan worked as an assistant in General Practice to Dr Pettigrew in Sheffield; to be succeeded, unnoticed it is said by the patients, by Richard who in due course became Principal in the practice. By a curious coincidence the wife of one of the authors was later trained in the practice by Richard.

ACADEMIC CAREER

Allan Downie maintained that his four years with Dr (later Professor) Cruickshank had a lasting formative effect on his bench work and particularly on his writing.

Research work in the Aberdeen Laboratory was all undertaken alongside the routine diagnostic work in one large laboratory which 'Cruickie' shared with his staff. Supervision, guidance, example, discussion and the flow of ideas was continuous. It was not long in such conditions before AWD wrote his first paper for publication; and thereafter followed a further lesson!

On presenting Cruickshank with his manuscript describing their joint work on 'The production of gall bladder cancer in guinea-pigs' Downie was disappointed to see it immediately thrust into a desk drawer where it remained for three months. Only then did Downie pluck up the courage to ask if it was satisfactory. Cruickshank feigned forgetfulness and thrust it back. 'You had better read it through again yourself first' he was told. He realized it was awful and Allan recalled later that he was glad that his first effort had gone unseen by his Chief. Version two appeared under joint authorship as Downie's first publication. Those who later wrote papers with Downie appreciated the precision, the accurate grammar and the elegant style the experience had taught him. Downie was too gentle a character to inflict such a discipline on his own juniors but his re-telling of the tale allowed Cruickshank's wisdom to filter through to the third generation.

In 1927 Downie moved to Manchester, first as lecturer in Pathology under Shaw Dunn and shortly afterwards in Bacteriology under H.B. Maitland. Maitland was a distinguished bacteriologist but was also one of the first to introduce the practice of organ fragment culture for the growth of viruses. Downie's first published paper on a virus infection (fowl paralysis) was with C.A. McGaughey (a vet who later moved to Ceylon for a Chair in Veterinary Pathology). It was published in 1931. By 1935 he had published his first pox virus paper, on mouse pox virus, marking the start of his lifelong interest in smallpox.

In the first quarter of the century a substantial amount of very important microbiological work was published from Germany and in German journals. To cope with this John Cruickshank held regular German-speaking evenings at his home. Downie ensured that his grasp of the language was sufficient for this challenge. Thus it was that in 1930 he found himself spending three months in the Hygienisches Institut, Breslau, under the Director, Carl Prausnitz. Soon after Prausnitz (best remembered for the Prausnitz–Kustner test for reagins) decided to leave Germany, to change his name to Giles and to adopt England as his home. Downie's brief stay in Germany

opened up many new friendships and contacts so that he was already acquiring international contacts, as well as fluency in the German tongue.

Downie's next appointment, in 1934, was to be Senior Freedom Fellow at the London Hospital Medical School. His appointment was however made conditional on his first spending nine months at the Rockefeller Institute for Medical Research, New York. It was a fortunate time for Downie to work at the Rockefeller Institute, for Avery was already on the track of the 'transforming principle', which he showed to be deoxyribonucleic acid (DNA), and finally reported in the classic paper by Avery, McLeod and McCarty.

On returning to Britain in 1936 he married Annie McHardy, who was born in Vancouver, Canada, but brought up by grandparents from 1920 when she was aged 10, in Tomintoul, Scotland, where her parents were born.

In 1939 Downie left the London Hospital to join the Medical Research Council Staff at the National Institute for Medical Research, Hampstead, but he was instead seconded by the Medical Research Council (MRC) (which was itself involved in setting up the Emergency Public Health Laboratory Service (EPHLS)), to a new emergency laboratory in Broxbourne, Herts, and then to succeed F. Griffith as head of the new EPHLS laboratory in Cambridge.

The EPHLS was set up to provide whatever public health laboratory services might be needed as a result of the war. These included the microbiological response to: the deliberate use of pathogenic microorganisms by the enemy; the disruption of water and sewerage services in the event of invasion; and any unusual infective outbreaks that might be imported as a consequence of troop movements from abroad. It was Downie's experience with mouse pox in Manchester and with cow pox in London that marked him out as the person to be responsible country-wide for the laboratory diagnosis of smallpox. Fortunately, the disease did not cause trouble in the UK until after the war.

The war was still on in 1943 when he was appointed to the Chair of Bacteriology in Liverpool where he remained until his formal retirement in 1966, and for several years his University Laboratory was responsible for this laboratory diagnostic service for the whole of the British Isles. It is interesting that a condition of his appointment was that he would *not* be Head of the diagnostic service for the teaching hospital, and so he divided his time between teaching and research, though as time went on he also became involved in University administration and was Dean of the Faculty of Medicine from 1951 to 1953 and Pro-Vice Chancellor from 1953 to 1957.

Work on smallpox

In due course several PHLS laboratories were also designated as smallpox diagnostic laboratories but Liverpool was the major seaport trading with India and Africa and with the industrial towns of the north west it frequently received imported cases. Often these gave rise to secondary cases before the disease was recognized by practitioners and Medical Officers of Health.

Downie was interested in the whole of the disease: source, strain, route of infection, infective dose, incubation period, period of infectivity, collection and transport of specimens, speed and accuracy of diagnosis, prognostic signs for recovery or death,

prophylaxis, treatment, new antiviral drugs, preventive vaccination and perhaps at the back of his mind, eradication.

He had read virtually everything that had been published on smallpox since Sydenham (1624–1689). He had abstracted all that he found believable and added his own observations on the epidemiologically determined periods of infectivity in every outbreak he studied. He compared these observations with laboratory findings of virus shedding.

From all these observations he was able to assign an exact period of risk to each focus of infection. It was these data that he conveyed to the World Health Organisation (WHO) Eradication Working Parties and which, ultimately, formed an essential basis for the strategy of the final worldwide Smallpox Eradication Programme.

That the WHO was able to assemble a knowledgeable team was again in part the result of Downie's worldwide reputation in the field. In the post-war years the Liverpool laboratory often received foreign visitors keen to assimilate Downie's methods and skills. They came from all five continents and left as firm and lasting friends.

Once the eradication plan was under way Downie went out to Madras in 1961 and 1963 to participate on the spot. With Henry Kempe in Madras he set up attempts to measure virus emission at the bedside of patients, as well as supervising the establishment of diagnostic facilities and in addition doing his own field work.

After retirement he was, from 1966–69 a visiting Professor in Henry Kempe's department at Colorado Medical School, Denver, Colorado. The post was closely linked with his work in the WHO Smallpox Eradication Programme, and there he set up a training course on smallpox diagnosis which he ran for 3 years. He worked in Liverpool from 1969 to 1972 on a further research programme concerned with a previously unknown pox virus infection (Tana pox) with a personal grant from the MRC.

For seven years after his 70th birthday he continued to work as a locum bacteriologist in the Sefton General Hospital, Liverpool.

WORK FOR THE WIDER COMMUNITY

He became a member of various scientific societies. In 1937 he became Secretary of the section of Comparative Medicine of the Royal Society of Medicine, and two years later in the section of Pathology. He was Honorary Secretary of the Pathological Society from 1954 to 1963 and editor of its journal from 1943 to 1946. He belonged to the British Society for Immunology and the Association of Clinical Pathologists and was admitted to the Medical Research Club of London and Harvey Society of New York.

He was a valued member of the Governing Boards of the Public Health Laboratory Service from 1961 to 1968; of the Microbiological Research Establishment, Porton Down, and of the Animal Virus Research Institute, Pirbright, from 1959 to 1966.

Probably his most significant roles in the wider community were with the WHO. He was one of their reference experts on virus diseases and was a member of the crucial Expert Committee on Smallpox, which wrote the technical report no. 283, and then

Chairman of the Scientific Group on Smallpox Eradication in 1968 which produced technical report no. 393 from which the subsequent eradication programme followed.

PERSONAL CHARACTERISTICS AND INFLUENCES

Alan Downie was of medium height and quite lightly built, but was always fit. His junior staff learnt this to their cost when accompanying him at a run along the street to a lecture; when they arrived he went straight to the front to speak, while they retired to the back to recover their wind. He believed that a secure home and family life were an essential basis for professional success, and he practised his belief. He took a keen interest in the individuals who passed through his department, and invited then to his home where his wife produced wonderful meals, while he would get his guests to help in the garden or join in party games of his own devising and, always intensely competitive, he tried to win himself. His wife dropped in to the department for tea from time to time when she had been shopping in town. He continued to keep in touch with members of the department for years and would want to hear of their work and successes in detail.

His junior staff remember him as 'fair and kind'. E.J.L. Lowbury paints this pen portrait of him at Cambridge during the war:

> A youthful 40-year-old with an attractive musical accent, an expression that was both serious and whimsical, a manner at once informal and commanding. He spoke quietly but incisively, wasting no words: his instructions were clear and unambiguous. I found him a most friendly and sympathetic boss and teacher ... at home Allan entertained us with many stories about bacteriologists he had known. His humour was infectious; he often referred to odd or amusing matters with a furrowed brow and a half smile ... .

An incident from his time in Liverpool illustrates both his rather mischievous iconoclasm and his concern for fairness. He persuaded six members of staff to sit down and write answers to a paper he had set the students and their answers were then transcribed by technicians to obscure the handwriting. The answers were then sent to six examiners with the story that the scripts were the six best in the class and had to be put in order as there was a prize for the best. No two examiners put the same paper first. M. McEntegart who tells the story and who was one of the 'examiners' records that he put Allan Downie's paper last and commented that the writer 'had little knowledge but the skill to spread it thinly'. He learnt what he had done when Downie presented the results at the Medical Sciences Club, and gave all concerned an unforgettable lesson in how subjective such judgements can be.

Others remember his ability to break down very difficult questions into a series of simple questions for which answers could be obtained. He had very broad knowledge of microbiology, and indeed classified himself as a 'pathologist' rather than anything more specialized. He took his interest and obtained his inspiration from broad medical problems, and indeed retained his clinical skills in examining and handling children and adults through the war and on to his studies of smallpox in Madras.

He was greatly admired as a laboratory worker. Throughout his life he performed his own experimental bench work. He is remembered going eagerly to the incubator in the morning to see what the new techniques tried the day before had yielded. He kept outstandingly good laboratory notebooks which included a record of every

procedure, volume, dilution for the day's task and a detailed note of the results. In later life he was contemptuous of publication of what he regarded as trivial observations, which he could show from his own notebook that he had made himself years before.

He encouraged his young research staff with a mixture of interest in their results, stimulating suggestions and friendly but trenchant criticism. If they were to give a paper it would be carefully rehearsed and timed with Downie in the back row of the theatre, checking audibility and slide quality. Then he would prepare the young speaker for the following discussion by some suitable 'devil's advocate' remarks.

Downie himself reckoned the academic year at the Rockefeller Institute and Hospital, New York, to be 'one of the happiest of my professional career'. He had been interested in streptococcal infections and written his M.D. on the subject, and went to work from 1934 to 1935 in the department of O.T. Avery on pneumococcal infections and pneumonia, on which he later wrote his D.Sc. He found 'the hospital was a friendly place in which to work and the research activities stimulating and exciting'. He became friends with many of the outstanding young bacteriologists and virologists in the department, most of whom had distinguished research careers in New York and elsewhere. They included Thomas Francis, Rene Dubos, Ken Goodner, Walther Goebel, Colin McLeod, Frank Horsfall and Rebecca Lancefield. The proximity of the Hospital also brought him the friendship of Alfred Cohn, Homer Swift, Donald van Slyke, Tom Rivers and Rivers's young assistants Joe Smadel and Tom McNair Scott.

Following the work in London of F. Griffith on the transformation of one pneumococcal capsular type into another by means of a specific soluble component in cell extracts, Avery realized that he could use this phenomenon to approach the chemistry of genetic specificity and thus discover the role of DNA.

His contacts with such scientists and such outstanding research must have been like a second academic apprenticeship. He learnt first-hand what excellent biological and clinical research is like: how it is directed and structured and then how the experiments are conceived, conducted and rigorously evaluated. This must have helped him to have such a creative career and to direct such an outstanding research department in the years that followed.

SCIENTIFIC WORK

For those interested in infections in the 1920s the streptococci were an important cause of disease and subject for research. So he studied laboratory infections and immunity against them under J. Cruickshank in Aberdeen (2)*. His MD thesis described studies on the inoculation of streptococci into rabbits (3, 4). The methodology was simple: inoculating animals, observing any illness that developed, culturing the blood for bacteria, and examining the tissues for pathological changes. As a result the basic facts about the type of cultures that would cause disease and the possible role of bacterial toxin began to emerge.

* Numbers given in this form refer to entries in the bibiography at the end of the text.

He did some basic work on the significance of the characteristic bile solubility of the pneumococcus (*Streptococcus pneumoniae*) but then took up the challenge of determining the role of bacterial infections in gastrointestinal tract disease in the area.

His short stay in Hamburg led to a paper in German proving the non-filterability of *M. tuberculosis*, a heresy then prevalent. Back in Manchester and under the influence of H.B. Maitland he began to study the latent pox virus of mice, namely extromelia. In those days experimental work with viruses was largely based on animal inoculation but he showed that ectromelia could be propagated in cultures of chopped tissue, one of the first instances of a virus being propagated in cells *in vitro*. He also showed that infection could be modified with immune serum (11, 12). He developed the theme of immunity to infection by trying to develop anti-staphylococcal vaccines for rabbits, again looking for evidence of the importance of toxin, and then, as mentioned above, as a result of his studies in New York he reported experiments on immunity against the pneumococcus and the importance of capsular polysaccharides (14–18), mainstream research work of the time.

He was stimulated by another clinical problem to return to the subject of a pox infection, this time the so-called cow-pox observed in cattle and the farm workers who looked after them. He cultured the viruses (19) and studied their effects in experimental infections (20). Because Jenner had used cow-pox for protection in the first vaccination against smallpox he decided to compare his newly isolated cow-pox virus with the vaccinia which was in general use for immunization at the time. He found they were antigenically related, but not identical. This was surprising at the time and raised the knotty problem of the origin and identity of vaccinia virus. It also showed his skill and ability as a careful biologist to determine the behaviour of the viruses in the laboratory and separate them from each other. Recent work by one of Downie's erstwhile trainees has revealed that cow-pox is primarily an infection of the domestic cat; a finding that Downie welcomed with wry amusement!

Faced with the practical problems of wartime Britain he approached these in a spirit of enquiry and published on neonatal diarrhoea (24), diptheric vaccination (25, 26), epidemiology in general in an RAF station (28–29), and in the operating theatre (30).

He was next stimulated by cases of smallpox among the soldiers returning home via Liverpool and sailors who came through as trade and business returned to the port. His resources were very simple, though normal for the time, consisting of a room with a few incubators, waterbaths and dishes, together with pipettes, a bench top centrifuge, and some test tube racks. Laboratory animals were housed on the bench or on the roof outside. For protection he used jars of Lysol disinfectant and a few cloths soaked in it, and repeated revaccination of all the staff. In such a laboratory he set out to perfect methods of detecting and characterizing variola and related viruses, using in particular the inoculation of the 'dropped' chorioallantoic membrane which had been first used before the war, (33–38, 41, 50, 51). He and his group then built up methods of detecting antibodies and serologically characterizing the various pox viruses (51, 44-46, 52). This immunological work also enabled them to detect smallpox virus antigen in the circulation of patients (56) as well as the virus itself (43). Only much later was it realized that in other virus infections, such as hepatitis B and AIDS, antigenaemia

can be of great diagnostic and prognostic significance. At this time his department was one of a handful in the UK in which active virus research was going on.

In the early 1950s his papers began to apply this earlier work to the problems of the spread and control of smallpox. For instance he showed that the virus of smallpox was not readily inactivated but that the infectivity of smallpox cases was not high (59). He also took part in a study of dried smallpox vaccines which showed they were stable and gave excellent 'take' rates when applied to humans and compared with conventional calf lymph vaccines (61): in addition he studied the antibody response of humans to smallpox and vaccinia virus infections (66-67) and the possibility of using antibody to protect against smallpox (64, 72). All this reflected his increasing involvement with the WHO, providing the scientific basis in the form of concepts and techniques which were required to develop the Smallpox Eradication Programme.

His work with smallpox in Madras is reflected in a further series of papers. He looked for virus – in mouth washings and from the air – in the environment of smallpox cases (73, 75, 86) and found rather little, confirming other evidence that it was not a highly communicable disease. He and colleagues monitored the frequency of antibody in the population after a vaccination programme (74) and showed that dried vaccine compared well with local traditional vaccinia vaccine lymph (76). He was also involved in a major trial of N-Methylisatin B-Thiosemicarbazone (Marboran), an antiviral drug developed by the Wellcome Foundation, for the prevention of smallpox in the contacts of cases of the disease in India (80, 91). The drug appeared to be effective but prone to cause vomiting and was never introduced generally. It was, however, the first example of a molecule being shown to have antiviral properties in the laboratory and then being shown to be effective in a clinical trial.

Interspersed with this he continued to be interested in vaccination and immunity against diptheria, pertussis, etc., and continued to write on the subject (26–27, 32, 58, 90).

He had a final burst of research productivity after he retired. With a small MRC grant he worked at the bench with a number of young collaborators and studied the characteristics and epidemiology of certain pox viruses which he himself first isolated from children in Africa. They were given the name of Tanapox viruses (101, 103, 105–106, 108–109) and appear to be enzootic in monkeys spreading to humans during flooding in the Tana valley. Studies of pox viruses of monkey have been important in the aftermath of smallpox eradication and his was a valuable contribution to the development of the subject.

From time to time he wrote major lectures and reviews of his field (48, 60, 77–78, 84). He also wrote interesting obituaries of outstanding medical microbiologists (23, 33, 88, 92, 100, 107, 110) and contributed valuable chapters to books and journals dealing with virus infections (42, 47, 53–55, 57, 68, 81–82, 84, 89, 97–99).

However, this brief survey of his publications does not do full justice to his scientific contributions, particularly at Liverpool. As mentioned earlier he was proud of his staff and of the fact that seven of them went on to University Chairs after leaving him. Those who worked in his laboratory would readily agree that he contributed significantly to the many research projects on which his name did not appear as coauthor; having helped to start a line of research, e.g. on chicken-pox virus (69–71) he let his

juniors have most of the credit. Had this not been so he would have had a much larger list of publications including work on rubella, poliomyelitis and toxoplasma. Throughout Downie's years as a professor (except when smallpox was on hand) teaching had first call on his time. He had a phenomenally good memory and could recall students' faces, names and performance in a way which always surprised them, especially after 10 or more years! Moreover he knew whither they had gone overseas. He always tried to keep in touch, if he could, on his overseas trips, seeking out old students as far away as Australia.

In the laboratory, however, Downie was most at home. He chose his assistants carefully and with evident success. Only one research fellow failed to come up to Downie's expectations. They agreed to part amicably after six weeks. Many of Downie's research students, Fellows and staff chose to work on pox viruses but Downie's own interests were very wide. When Kevin McCarthy joined him in 1946 it is probably true to say that Downie had read and abstracted every paper on a virus topic ever printed in English, German or French. He had in addition to smallpox a considerable interest in herpes viruses and encouraged diversity of research interest among his staff. Four o'clock tea was the time when all graduate staff gathered and discussed work, grammar, gardening, golf, fishing, football, future work, cars, family and any aspect of medicine.

When the spirit moved him, most of the figures, now legendary, whom Downie had either known or worked for were displayed before the staff in his dry humorous way. He combined penetrating character assessment with great charity and a wicked sense of the absurd.

In such an environment it is not surprising that ideas flowed freely. Often it was difficult in retrospect to discern who first suggested what. Everyone knew what the other groups were doing. Any new idea inevitably came up for discussion with others, including Downie, at tea.

He provided a sceptical 'devil's advocate' which ensured that new ideas had been thought through and properly evaluated before any scarce departmental resources were expended on their development. That he published only 110 papers reminds us that he was not a chief who would put his name on a paper if he had not himself sat at the bench and shared the work.

Conclusion

Allan Downie was a man who combined a great intellect with personal modesty. He will be remembered by his close associates and his students for his total honesty, his unfailing good humour, his personal kindness and his love of family. The wider world community may remember him as the man who made smallpox eradication a possibility.

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