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JAMES CRAIGIE

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BY SIR CHRISTOPHER ANDREWES, F.R.S.

James Craigie, who died in Edinburgh on 26 August 1978, was a microbiologist who will be remembered for the part he played in the development of his subject in Canada. It was there that he spent the most active 15 years of his life. When he went there from Scotland in 1931 virology was still in its infancy; he was one of those who helped to raise it to its present position as a discipline in the forefront of biological knowledge.

He was born in Arbroath, Angus, on 25 June 1899, the elder of two brothers. His grandfather, James, was a professional gardener, holding several appointments in large gardens in Scotland. His son, also James, the father of the microbiologist, was a librarian, having experience in several libraries in Scotland and Australia before settling in Perth in 1902 to become librarian to the Sandeman Library there. He was an elder of the church and an active and popular figure in local affairs. His brother, uncle of our Craigie, was Sir William Craigie, an outstanding lexicographer and philologist. He became co-editor of the *Oxford English Dictionary* and also wrote Scottish, American and Icelandic dictionaries. He was familiar, also, with Scandinavian, Anglo-Saxon, Frisian and Gaelic languages and literature.

Craigie's mother, Frances Stewart McHardy, came from a farming family at Inverey, near Braemar, and here he often spent much of his holidays. He early became interested in natural history, first in insects but soon, after being lent a microscope, in pond life. This interest he maintained, reading a paper on Ciliata (1) before the Perthshire Society of Natural Science. He was also interested in music, playing the organ and piano.

On leaving school he went to the University of St Andrew's, intending to take a combined medical/B.Sc. degree. On being called up during World War I, he was promptly sent back to complete his studies for a medical degree. From University College, Dundee (University of St Andrew's), he qualified M.B., Ch.B. in 1923. Later he took his Ph.D. and D.P.H. His first appointment was as assistant medical officer, Murray Royal, Perth. He was appointed in 1927 assistant in bacteriology under Professor W. J. Tulloch in Dundee. He early showed an interest in bacterial flagella (2, 3) and this led him on to a study of the serological reactions of the flagella of *B. typhosus* (now *Salmonella typhi*) (7). He also worked with Professor Tulloch and W. L. Burgess on a
‘variola—vaccinia flocculation test’, and with them was concerned in writing two Medical Research Council special monographs on the subject (4, 6).

Before we turn to the scientific side of his work, it will be convenient to sketch his early career, for his studies on vaccinia and typhoid were carried out on both sides of the Atlantic. In 1931 he emigrated to Canada to become a research assistant at the Connaught Laboratories in the University of Toronto. His status was advanced in successive stages; he became lecturer in epidemiology in 1924, associate Professor of Virus Infections in 1940 and, in 1946, Professor of Virus Infections. He remained in Canada for over 15 years, returning to Britain in 1947 to join the staff of the Imperial Cancer Research Fund. Over a period of 10 years (1935–45) he served as Secretary of the School of Hygiene in Toronto.

VACCINIA AND VARIOLA

Before the 1930s several workers, particularly M. H. Gordon, had described a ‘flocculation reaction’, seen when vaccine lymph or small-pox crusts were mixed with appropriate antisera. Such visible reactions with viral materials were unfamiliar and some claimed that they were non-specific, secondary bacterial invaders being concerned. In the first of the two M.R.C. reports with which Craigie was associated (4) evidence was produced that the reaction was specific, varicella crusts being negative. In the second report (6) the reaction was demonstrated with material free from secondary invaders and it was shown to be independent of the organ or species from which the lesions were derived.

Craigie continued his work on vaccinia after he came to Toronto. By that time it was generally recognized that the small particles generally known as elementary bodies were, in fact, infectious viral particles. Craigie added further evidence by means of an improved staining reaction (12) and by showing that purified elementary bodies elicited skin reactions in man similar to those induced by vaccine lymph (10). His main interest was, however, still in viral antigens and antibodies. He showed (8) that the ‘flocculation reaction’ was really a mixture of agglutination of elementary bodies and precipitation of an antigen which could be separated from the virus particles by filtration. That the same antibody was concerned in both reactions was revealed by absorption tests. These findings were paralleled by others using the complement-fixation test (15). Study of the heat-stability of vaccinia led to the conclusion (13) that the sera under study contained two antibodies directed respectively against a heat-labile (L) and a heat-stable (S) agglutinogen. The L-antigen was also more readily inactivated by some chemicals.

All these studies were finally brought together in three classical papers by Craigie and F. O. Wishart (22, 23, 24). It was shown that soluble precipitable substances, both the L and S antigens, were slowly released in vitro from suspensions of washed elementary bodies. Addition of either anti-L or anti-S sera to these suspensions precipitated both antigens and it was therefore concluded that they were components of a complex LS antigen. Both antigens
were present also in crude vaccine of dermal origin, whether coming from calf, rabbit or guinea pig. The LS antigen was able to stimulate the production of both L and S antibodies when used to immunize rabbits; the L-antigen, however, had its antigenicity destroyed by heating to 70 °C. A final paper in the field of pox-viruses described how the complement-fixation test using antivaccinial serum and variola crusts could be used in diagnosis; the test was eight to ten times more sensitive than the flocculation test and more convenient in practice (25).

**Typhoid**

The work that Craigie carried out while in Dundee was put together in a 95-page-long very involved paper (7). As a result of his studies of flagella and antibodies against them, he there put forward cogent criticism of the double receptor hypothesis of Weil and Felix; this had dealt with the relationships and importance of heat-labile and heat-stable antigens of certain enteric bacteria.

By the time he returned to the subject in Canada a few years later, Felix and his co-workers had described another, Vi (virulence), antigen present in freshly isolated typhoid bacilli but lost on sub-cultivation. Strains of the organism either had (V-forms) or had not (W-forms) the Vi-antigen. Craigie and Brandon (21) discovered a bacteriophage active only against V-forms. Such cultures, when treated with the phage, reverted to the W-form. Use of this phage proved of diagnostic value in identifying V-forms of *B. typhosus*; it was quicker in use than the agglutination test, giving positive results in six hours (19).

This work soon led on to what can probably be considered to be Craigie’s most important contribution to his subject. It was found that not all Vi-phages were alike. They could, in fact, be grouped into four types, differing in the size of plaques produced, in heat-stability and in the range of typhoid strains they could attack. Three of the strains would lyse any V-form of typhoid. Type 2, however, was different, showing activity only against certain typhoid strains. It proved, however, to be very adaptable; after passage on any strain it acquired the property of lysing that strain in, perhaps, a millionfold higher dilution than was found with a heterologous strain. It became possible on this basis to divide V-form typhoid bacilli into a number of groups according to their susceptibility or otherwise to various adapted strains of type 2 phage. These types proved to be stable. In the first study by Craigie and Yen (28), nearly 99% of strains could be placed in one or other of 6 types, but by 1947 24 types or subtypes had been identified.

The ability to type typhoid strains turned out to have great usefulness epidemiologically, for strains of common origin always belonged to the same type (29). Accordingly, when typhoid cultures were obtained and studied in the laboratory, one could decide which could have had a common origin and which could not. This was particularly useful when it came to blaming a particular typhoid carrier for spreading infection or absolving him.
There came to light some anomalies, necessitating the erection of sub-types; thus things became a little more complicated than in the above simplified account. In 1947 Craigie and Felix made suggestions for standardizing the test and maintaining reference reagents (39). The methods found so useful in typhoid were soon applied to Salmonella paratyphosus B and to other salmonellas.

**OTHER VIRUSES: TYPHUS**

During his 15 years in Canada Craigie concerned himself with a number of other viruses, particularly poliomyelitis, on which he wrote three papers (18, 27, 34). He became, in fact, an outstanding leader in the fields of virology and microbiology generally, in Canada. In 1946 he was elected President of the American Society of Bacteriologists and gave a presidential address entitled 'The significance of bacteriophage in bacteriological and virus research' (38). During World War II there were fears that the enemy might introduce rinderpest into America with disastrous results to the cattle industry. Craigie was a member of a joint U.S.-Canadian Commission on the matter (1942–46). Under its aegis a research station was set up on an island in the St Lawrence River, where the infection could be studied under conditions of rigorous isolation.

Another infection of importance in war-time is typhus. Craigie was closely involved in the preparation of vaccines against the disease. He, together with colleagues, wrote five memoranda on this subject for the National Research Council of Canada. His three published papers on typhus concerned an improved staining method for rickettsiae (35), a method of purifying rickettsiae from yolk-sac suspensions at an ether–water interface (36), and the serological relationships of epidemic and murine typhus (37). He described a heat-stable antigen common to both kinds of rickettsiae and a heat-labile specific one; the latter was more important in immunity. For all this work he was awarded a U.S. Typhus Commission medal (1946).

**CANCER**

Soon after the end of the war there came a complete change in Craigie’s interests. In 1946 W. E. Gye, then Director of the laboratories of the Imperial Cancer Research Fund in London, was touring laboratories in North America to learn of current progress; and Craigie joined him on the tour. Gye was much impressed by his ability and persuaded him to return to Britain to join the staff of the I.C.R.F. with a view to becoming Director in a few years’ time. Accordingly, in 1947, Craigie returned to Britain to work in the Fund’s laboratories at Mill Hill. These were next door to the National Institute for Medical Research, so that I saw a lot of him during the next few years.

Soon after his return, Craigie collaborated with Gye and others (42) in experiments which showed that tissues of several tumours of mice could survive either freezing or drying. It was felt to be unlikely that intact cells would
survive such treatment and that the findings indicated the probability that a virus was present as a continuing cause. It is likely that Craigie himself had reservations about such a conclusion, for in the next few years his work was directed largely to showing that, in fact, tumour cells could survive these treatments.

In the studies on freezing and drying Craigie showed evidence of his love of 'gadgetry'. He designed an improved method for rapid drying of tissues (41). He also described a tissue-mincer which would reduce tumour tissues almost to the state of single cells (40). He had made a 'fail-safe' freezing machine in which tissues were kept frozen in dry ice, but the whole was surrounded by an electric cooling system. There was thus insurance against either breakdown in the electricity supply or failure in supplies of dry ice. Intermittent use of the electrical system also resulted in considerable saving in the consumption of dry ice (48). To all this he brought his close knowledge of the physical principles involved.

There was an important result of this work. It had for many years been necessary for workers in cancer research to propagate transplantable tumours, especially in mice, by means of cell-grafts at fairly frequent intervals. This was expensive in time and labour and, moreover, the tumours could, and often did, change their properties in the course of transplantation. This safe method of preserving tissues in vitro over many years overcame these difficulties, and a 'tumour bank' was a consequence. This has proved outstandingly useful.

Two findings were particularly helpful. Many tumours injected intraperitoneally could be induced to grow as 'ascites tumours' with cells multiplying in the exudate they induced. Thus single-cell suspensions of tumour cells became available and quantitative work was correspondingly easier (47). Another finding was that in dextrose, tumour cells would survive particularly well at low temperatures (43), and this had important consequences, for microscopical studies, using phase contrast, showed that nuclei of surviving cells assumed a homogeneous vitreous appearance.

This led to the discovery that in tumour preparations, and especially in those of ascites tumours, survival was due to the presence of greater or smaller numbers of cells in an abnormal 'paramorphic' state (45, 46). These, when seen by phase contrast microscopy, were highly refractile; they were also resistant to hypertonic dextrose, glycerol, freezing and drying. When restored to more 'physiological' conditions they soon returned to normal and could start multiplying. The paramorphic state could not be recognized in fixed and stained preparations.

Craigie's last published work concerned Tyzzer's disease of mice and its causative organism, Bacillus piliformis. This has been a cause of outbreaks of disease which have ruined much laboratory work with mice. The organism grows intracellularly and had not been cultivable in bacteriological media. Craigie succeeded in propagating it serially in the yolk-sacs of fertile eggs. The vegetative form of the organism was difficult to preserve until it was found possible to do so by freezing tissue suspensions at −75 °C (51). Both
the parent strain and a non-sporing variant were pathogenic for mice. Infec-
tion was potentiated by cortisone but could be checked with penicillin (52).

**PERSONALITY**

Craigie was a remarkable man with the originality and curiosity necessary
for a good research worker. He was fascinated by gadgetry and techniques;
any new piece of apparatus had to be taken to pieces and reassembled so that
he thoroughly understood how it worked. He was meticulous in all he did.
His best work was done before World War II when he was working by him-
self or with one technician. At that time he was teaching in the Department
of Hygiene, University of Toronto. Dr R. J. Wilson writes that 'he will be
remembered by many students . . . as a magnificent teacher'.

It was when he was in charge of a department, first in Canada, later in
Mill Hill, that things became more difficult. He was essentially a kindly man
and troubles that arose stemmed from a difficulty in communication. In dis-
cussing a scientific problem he would start in the middle, assuming that his
hearers knew the background and, in particular, his own earlier writings.
Junior workers were too shy to admit that this left them all at sea. A number
of people have confessed that they were often baffled by a frustrating habit
he had; he would start to explain something, break off in the middle of a sen-
tence and look up with a smile, assuming one would know how the exposition
would end. As one commonly did not, one was none the wiser. Ensuing diffi-
culties would be overcome only by those with some sense of humour. He was
reluctant to delegate and too apt to devote himself to his own research rather
than to running the laboratory as a whole. Difficulties had gradually increased
from the time he was put in charge of the Mill Hill laboratories in 1949.
Accordingly it was suggested to him that he should step down from adminis-
trative charge of the laboratories, so that he could concentrate on his own
research. This he agreed to do and he was succeeded in 1957 as head of the
laboratories by Dr R. J. C. Harris. He was certainly happier and more effective
after this had come to pass, and thereafter junior colleagues actually found
him more helpful.

Craigie received a number of honours. In 1946 he received the O.B.E.
and was elected a Fellow of the Royal Society of Canada. In the following
year he was elected F.R.S., London, and was awarded the Medal of Freedom
of the U.S.A. He received the Stewart Prize of the British Medical Association
in 1950 and the LL.D. of St Andrew's in the same year.

On his return to Britain in 1947 he took a house at Christmas Common in
the Chilterns; there were ten acres of grounds. On his retirement in 1964
he found ample occupation in the many problems arising on this estate. He
was an enthusiastic gardener, raising many plants from seed and was partic-
ularly interested in breeding irises. Another resource derived from his lifelong
interest in apparatus, with many items to repair or construct. On his wife's
death he moved to Edinburgh, where one of his daughters lived.
I am very grateful for the help I have received from many sources: his two daughters, Mrs Margaret Ridehalgh, herself a microbiologist, and Miss Frances Craigie, Dr E. S. Anderson, Dr K. F. Brandon, Dr R. J. C. Harris, Dr G. Negroni, Dr R. J. Wilson, Professor R. Hare and Mrs J. Orr.

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James Craigie

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The work on cancer is also covered in annual reports of the Imperial Cancer Research Fund. Craigie was responsible for writing those of the years 1949–56.