BIOGRAPHICAL MEMOIRS OF FELLOWS OF THE ROYAL SOCIETY

Cyril Leslie Oakley. 20 June 1907 -- 27 March 1975

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CYRIL LESLIE OAKLEY

20 June 1907 — 27 March 1975

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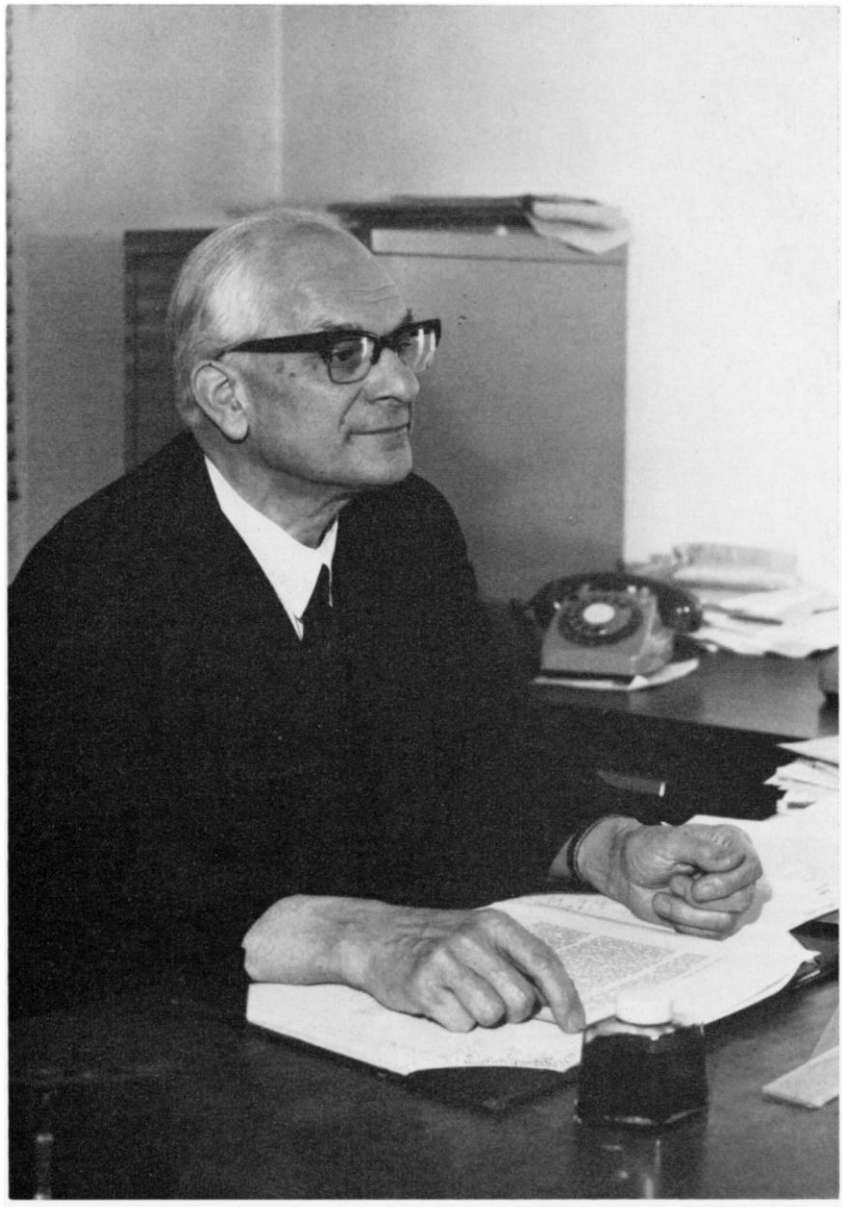
Cyril Leslie Oakley was an eminent immunologist with an international reputation that had been built up at the Wellcome Research Laboratories, Beckenham, by his work on the analysis of the filtrable antigenic factors produced by pathogenic bacteria of the genus *Clostridium*. Although medically qualified, Oakley never became deeply involved in medical practice, but maintained throughout his life a great fondness for experimental laboratory work, which he always performed with meticulous care and rigorous attention to accuracy.

Early years

Oakley was born in Lambeth on 20 June 1907, the elder of two children; his sister, Mabel, was two years younger. His father, George Oakley, was a first class petty officer in the merchant navy. Shortly after the birth of his son, the family moved to Portsmouth and here young Oakley attended the local Church of England school which he enjoyed and kept in touch with in later life. It is probable that the interest which he later developed in ecclesiastical architecture was initiated during these early days as a result of a visit with his father to Reculver in Kent to see the ruins of an ancient monastic church—a visit which Oakley often recalled with great pleasure.

In 1916 when Oakley was nine years old his father died in the submarine service of the Royal Navy and his mother, Henrietta Ellen, who had little money apart from a small naval pension, was forced to take up jobs such as teaching, tailoring and service to support her family. Oakley was left very much on his own during this period and occupied his time reading widely—mostly books bought on his frequent visits to second-hand book shops. It was about this time that he began to show signs of academic ability and this was noticed particularly by his grandmother (on his mother's side) who was then about 72 years old. Oakley had a strong affection for his grandmother and spent a great deal of time with her. It was she who in 1918 brought the family to Balham in South London and arranged for Oakley to sit for a London County Council Scholarship which he was duly awarded. He then went to Westminster City School in Palace Street, where he remained for seven years. Here he worked hard, played no games, read avidly and learnt by heart much prose and poetry. His memory was phenomenal



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and throughout his life he could recite long passages from *Lycidas* which he had committed to memory when a schoolboy. As there were no facilities at Westminster City School at that time for teaching zoology, Oakley joined the Chelsea Polytechnic for evening classes where, he always maintained, he received an excellent grounding in the subject from W. H. Leigh-Sharpe. Furthermore, it was Leigh-Sharpe who predicted a great future for Oakley and advised him to take up medicine. He developed during this period an interest in parasitic copepoda (fish lice) and his first scientific publication when he was 19 years old was on this topic. The interest in copepoda remained with him throughout his life as was evident in 1962 when, at a meeting in London of the Society of General Microbiology, instead of giving his paper which appeared on the programme, on clostridial antigens, he announced to his audience that he would rather tell them about copepoda; this he proceeded to do, much to everyone's enjoyment.

In addition to his early interest in science, particularly zoology, he developed in his schooldays a strong feeling for foreign languages. He knew Latin, Greek and Hebrew intimately and could speak French and German with ease, often lecturing in these languages when abroad. In the last 15 years of his life he learnt Chinese and was influential in establishing a Department of Chinese Studies in the University of Leeds before he retired.

At the end of his period at Westminster City School, Oakley was awarded a Kitchener Memorial Scholarship to go to University College London to study medicine. In 1930, he obtained his M.B., B.S., along with a first class honours B.Sc. in zoology, and was awarded a Graham Research Scholarship in experimental pathology to work at University College Hospital Medical School under A. E. Boycott on the physiology of the circulation. It was here that Oakley met G. R. Cameron, who was also in Boycott's department; they became firm friends and worked together on the pathology of the liver. Oakley obtained his M.D. in 1933 and then spent four months in Aschoff's laboratory in Freiburg, Germany.

Wellcome Laboratories

In 1934 Oakley was appointed as experimental pathologist to the staff of the Wellcome Research Laboratories at Beckenham where he stayed for 19 years and eventually became head of both the Departments of Experimental Pathology and Immunology. This period at Beckenham he always regarded as the most valuable in his scientific life, for not only were there outstanding facilities and opportunities available for his immunological researches enabling him to produce his most important contributions, but also many stimulating colleagues from whom he obtained considerable cooperation. There were, to mention just a few, G. Harriet Warrack who worked very closely with him in the laboratory, A. T. Glenny who, with his constant interest and criticism, was an exceptional stimulus, R. G. Macfarlane, W. E. van Heyningen, H. J. Parish, C. G. Pope, Irene Batty, Mollie Barr, B. C. J. G. Knight, Ethel Bidwell, Patricia H. Clarke and Helen E. Ross.

Initially, the commercial aspects of the new position at the Wellcome Laboratories occupied much of Oakley's time; he had taken on heavy responsibilities associated with the pathological control of safety and efficacy of pharmaceutical products and there was little time for research work. He did, however, become interested for a short time in the immunology of viral diseases and carried out an investigation of the antibody response in mice infected with influenza virus. In 1941 the exciting observations on the association between the alpha toxin and the lecithinase of *Cl. welchii* type A attracted his attention and he began work with R. G. Macfarlane on this subject. This was the actual beginning of his researches on the clostridial antigens which proved so profitable over the following 15 years and lead to his election to the Fellowship of the Royal Society in 1957. Before coming to the end of his period at Beckenham he was made a Fellow of University College London (1951), became President of the Section of Comparative Medicine of the Royal Society of Medicine (1952), was awarded his D.Sc. (1953) and gave the Holme Memorial Lecture at University College Hospital Medical School (1950).

University of Leeds

In 1953 Oakley was appointed to the Brotherton Chair of Microbiology at the University of Leeds on the retirement of J. W. McLeod who had held the chair for many years. This new position brought Oakley much pleasure for he was now able to enjoy the academic atmosphere of the University, which was in marked contrast to the heavy commercial responsibilities he had carried throughout his Beckenham period. The move brought about a big change in Oakley's activities; whereas at Beckenham research had been his main interest, at Leeds this was replaced by teaching. There was no difficulty in this transformation, for he was certainly a born teacher with a facility for imparting knowledge in an understandable and interesting form, and with the considerable advantage of his first hand knowledge of the practical aspects of immunology as a result of his 19 years' experience at Beckenham. His lectures to medical and science students were prepared with great care and beautifully illustrated, often ingeniously. This ability to express himself with clarity was also of substantial help in his work for the *Journal of pathology and bacteriology* of which he became chief editor in 1955. He continued as chief editor in 1968 when the journal was divided into the *Journal of pathology* and the *Journal of medical microbiology* and fulfilled this double responsibility with distinction until 1973 shortly after he had retired from the University. It is well known that many papers submitted to these journals were often rewritten by him to bring them up to the high standard he set himself; otherwise they would have remained unpublished. He also played a major rôle in the business of the University, being a member of many committees to which he always brought a tolerant, non-partisan and sometimes amusing counsel.

In addition to his academic and scientific work Oakley had many other interests to which he gave much time and thought. It is said that perhaps he dissipated his energies too widely and might have been an even more outstanding

scientist had he not; on the other hand, he would probably have been a less attractive personality. The outside interest to which he gave his most sustained enthusiasm was ecclesiastical architecture, in which he amassed an enormous knowledge. This had begun when he was a boy and was cultivated during his student days, when he shared lodgings with G. R. Rigby a research student at Imperial College; Oakley and Rigby became firm friends and together visited as many churches and cathedrals as possible up and down the country during weekends and holidays. This interest further developed when Oakley moved to Leeds and met an old wartime friend, W. H. Plommer, who had similar enthusiasms. Oakley's knowledge of the subject secured for him a considerable following at the annual course of lectures he gave at the Swarthmore Adult Education Centre in Leeds and on the weekend excursions he organized to the numerous churches in Yorkshire, as well as at the courses he gave with Plommer at Grantley Hall. Another activity during his years at Leeds was in connection with the Georgian Theatre in Richmond, Yorkshire, a unique building which was being resurrected and used for its original purpose. Lady Craythorne and later Baroness Elliott were responsible for this venture, and had enlisted the help of many, among them Oakley, who contributed greatly in time and energy towards shaping the theatre into the lively organization it is today.

Scientific work

Extensive work under the direction of A. T. Glenny had been carried out for a number of years at the Wellcome Laboratories on the multiplicity of toxic antigenic factors present in the culture filtrates of various bacteria. The techniques employed were further developed by Oakley and, as a result he was able to unravel the antigenic complexity of the toxic filtrates of many of the clostridia important in human and veterinary pathology and moreover opened up the way for similar methods to be applied to other organisms.

The basis for the procedures he adopted was as follows. The demonstration in a bacterial culture filtrate of one activity is no proof that only one active substance is present and, conversely, the presence of many activities is not evidence of multiple active substances. For example, a filtrate may show four different activities, such as two different haemolysins as well as lethal and dermo-necrotic activities, but only two substances might be responsible, the lethal and dermo-necrotic activities being caused by one of the haemolysins and not the other. It may be possible by dilution methods to separate out the various factors of such a filtrate, but there is no guarantee that the results would always be reliable. Antigenic analysis is more satisfactory and this requires a number of avid antisera prepared against filtrates from the same strain of organism at different periods of growth and also against filtrates of different strains of the same organism, so that the antisera will contain as large a variation as possible in the proportions of antibodies to the different factors. One antiserum is selected as a standard of reference and assigned an arbitrary unitage for its antibody level against each activity and the other antisera are assayed in terms of this standard. If the antisera show consistent relative abilities to neutralize a

number of different activities it can be concluded that all the activities are probably due to one and the same antigen. If discrepancies occur in antibody values then antigenic complexity is evident.

A simple example is seen in the following table:

Antisera	Number of units required to neutralize		
	haemolysin	lethal toxin	necrotic toxin
Standard	100	100	100
A	150	50	50
B	10	550	550
C	700	120	120
D	100	600	600
E	20	300	300

from which it can be concluded that the lethal and dermo-necrotic activities are due to one and the same antigen and the haemolytic activity to a separate antigen. Further examination can be made by blocking out one of the activities with selected monospecific antisera or by chemical and physical methods in which one or other of the activities of a filtrate may be inhibited and the values of the neutralizing potencies against the original filtrate compared with those against the modified filtrate.

Using these procedures, Oakley and his colleagues from 1941 onwards made a number of important discoveries. The alpha toxin of *Cl. welchii* was shown to have haemolytic, lecithinase, lethal and dermo-necrotic activities and to be antigenically distinct from another haemolysin (theta) which was oxygen labile. Furthermore, the *in vitro* effects of the alpha toxin were shown to be activated by Ca ions. These observations were followed up in 1943 by what is now regarded as a classical comprehensive review of the toxins of *Cl. welchii* appearing in the *Bulletin of hygiene* in which their properties were described and the relationship between four types of *Cl. welchii* and their toxic composition clearly outlined. In 1945, R. G. Macfarlane and J. D. Maclennan showed that *Cl. welchii* type A filtrates contained a collagenase which disintegrated human or rabbit muscle. Oakley devised an *in vitro* test to study this activity, as well as its neutralization by antisera, using as indicator collagen 'paper' prepared from horse tendon. He showed that the collagenase activity (kappa toxin) was immunologically distinct from the lethal lecithinase (alpha toxin), the oxygen-labile haemolysin (theta toxin) and the hyaluronidase. Similar investigations followed with other clostridia such as *Cl. oedematiens* in which six separate antigenic components were identified in toxic filtrates, *Cl. histolyticum* which gave four antigenic components and *Cl. haemolyticum* (*Cl. oedematiens* type D) which gave two components. During this period Oakley made the discovery of a new type of *Cl. welchii*—which he called type F—associated with human enteritis necroticans which was one of the hazards of severely undernourished people in some parts of Germany immediately after the war. This discovery was based on the results obtained from the examination of the antigenic factors produced by the organism in culture filtrates; it was clear that the pattern of factors did not fit with those produced by any of

the other known types of *Cl. welchii*. Also he collaborated with Betty C. Hobbs of the Central Public Health Laboratory, Colindale, in establishing the importance of heat-resistant *Cl. welchii* strains in food poisoning.

As a result of Oakley's work on the antigenic analysis of bacterial culture filtrate, many workers in the field of bacterial classification tended to hold the view that certain bacteria could be classified on the basis of their soluble antigens. Oakley was very much against this approach as he regarded the identification of soluble antigens rather as an adjunct to the usual means of classification based on morphological, cultural and biochemical features. He was of the opinion that to be widely useful in classification a character must be easy to demonstrate, consistent and present over a wide range of organisms, and that the production of a particular soluble antigen was by no means satisfactory in any of these three criteria, since it could be inconsistent in a particular species, complex immunological methods were needed for its true identification and insufficient was known about its distribution. He wrote in one of his reviews, 'Any attempt to use bacterial antigens in classification is limited by our ignorance, as well as by the regrettable habit bacteria have of ceasing to produce antigens that are regarded as characteristic of them, or of producing them only in circumstances that are very complex and difficult to repeat'.

In 1949, Oakley became interested in the localization of antibody production and together with G. Harriet Warrack and Irene Batty carried out some elegant research on the subject. At that time it was generally supposed that antibody production occurred in the reticulo-endothelial system and many experiments were reported on the depression of antibody production by reticulo-endothelial blockade, the theory being that if an animal were injected with non-antigenic material, such as carbon black, the reticulo-endothelial system would be so preoccupied that it would be unable to produce antibodies. Much work was also being done to support this theory in determining which organs and tissues, after injection of antigen, produced antibody earliest or in the highest concentration. Oakley argued that the mere presence of high concentrations of antibody at a particular site was not proof of local production since it ignored the possibility of leakage of circulating antibody into the site, especially if it were inflamed as a result of the injection, and also the fact that antibody can be extracted more easily from some tissues, such as spleen, than from others such as skin or bone. Oakley got over these objections by injecting two separate antigens into two separate sites and determining the antibody concentration of both antibodies in various tissue extracts; he considered that if the antibody in the tissues was a result of leakage from the circulation, then the ratio of the two antibodies produced would be the same as in the serum and that if any divergences occurred in such ratios it would indicate local production or storage of antibody. The experiments he made were in guinea pigs, rabbits and horses, using a secondary stimulus of alum-precipitated tetanus and diphtheria toxoids injected into separate sites. It was clearly shown from the ratios obtained with extracts from various tissues that antitoxin was produced in the lymph glands draining the area injected with the antigens. It was also shown that in some cases antitoxin

was produced in the skin where the injection had taken place, especially if the area so injected had been stimulated by a primary injection with the same toxoid. There was no evidence from the ratios obtained of the production of antitoxin at any other sites. Furthermore, the local production of antitoxin was shown to persist after toxoid injection for at least three years. In a later study Oakley showed by similar methods that after one secondary injection of toxoid specific antitoxin was produced in the skin, fat or voluntary muscle of rabbits or guinea pigs but that no antitoxin production was obtained in the liver, spleen or bone-marrow similarly injected. Finally, he carried out experiments on antibody production in transplants. It was shown that rabbit fat or muscle which had been secondarily stimulated with diphtheria or tetanus alum-precipitated toxoid could continue to produce antitoxin when transplanted into recipients of the same species just as they would have done had they remained in the donors. Similar results were also obtained with the transplantation of rabbit lymph glands draining the sites injected with these toxoids. This work on localization of antibody production, as well as that of others working in the same field, was brought together by Oakley in his presidential address in 1953 to the Section of Comparative Medicine of the Royal Society of Medicine and in an excellent chapter he wrote in 1960 in *Modern trends in pathology*.

Another line of work which greatly interested Oakley was that which he did with F. W. R. Brambell of the University College of North Wales on the selection of antibodies by the foetal membranes of rabbits. This was a subject with Brambell had been involved in for some time and Oakley's collaboration in this work proved most valuable with regard to the preparation of suitable diphtheria, tetanus and welchii antitoxins and the determination of antitoxin levels in the various samples, such as foetal body fluids and sera, resulting from the experiments. He was a strong exponent of the value of antitoxins as markers in demonstrating and quantifying the transfer of large molecules across membranes.

Personal

Oakley was a very shy, often remote and extremely serious-minded man. He always gave praise where it was due, but sometimes his criticisms were rather harsh, probably because he failed to understand the difficulties some of his associates had with their own scientific problems. Nevertheless, he was essentially a kind man and was most generous in the help and advice he gave to his colleagues and in the materials, such as toxins and antisera, with which he provided the many workers who regularly visited him, especially when he was at Beckenham. He was also very considerate to his technicians, taking particular interest in the provision of 'day release' classes and in helping them with revision for examinations; there are many technicians in senior posts today who owe a great deal to the unobtrusive way he cared for their interests. He played an active part in scientific societies and was a familiar and much loved figure at scientific meetings. His voluntary activities were many and were duly recognized by the award of the C.B.E. in 1970. To mention a few, he was a founder fellow and member of the

Council of the Royal College of Pathologists; from 1963 to 1973 he was a member of the Agricultural Research Council and Chairman of its Animal Research Committee; he was associated with the Animal Health Trust for many years; he was a member, from 1965 to 1970, of the Medical Sciences Committee of the University Grants Committee. He also did a great deal of social and charitable work of which he seldom spoke.

Oakley had a happy family life. He was married in 1933 to Emily Meadows, who was then Assistant Matron at University College Hospital. Together with their two daughters, Anne and Helen, they enjoyed a closely knit companionship. His wife and two daughters survive him.

Oakley died in Leeds on 27 March 1975 at the age of 67. He had lived a full life, had given his best in his scientific work and has an honoured place among the great immunologists. It was very sad that he died before he had time to enjoy his retirement, a period which he often said he owed to his wife. Furthermore, he still had an active and critical mind and his wise and quiet guidance would have been invaluable to the many medical, veterinary and scientific bodies with which he was associated. His death also brought great sadness to his scientific colleagues, as well as those who were closely associated with him in all his other varied activities and who highly respected him for his honesty, intellect and judgment.

I am especially grateful to Mrs Oakley for her help in compiling these memoirs, particularly with many of the personal aspects of Professor Oakley's life.

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