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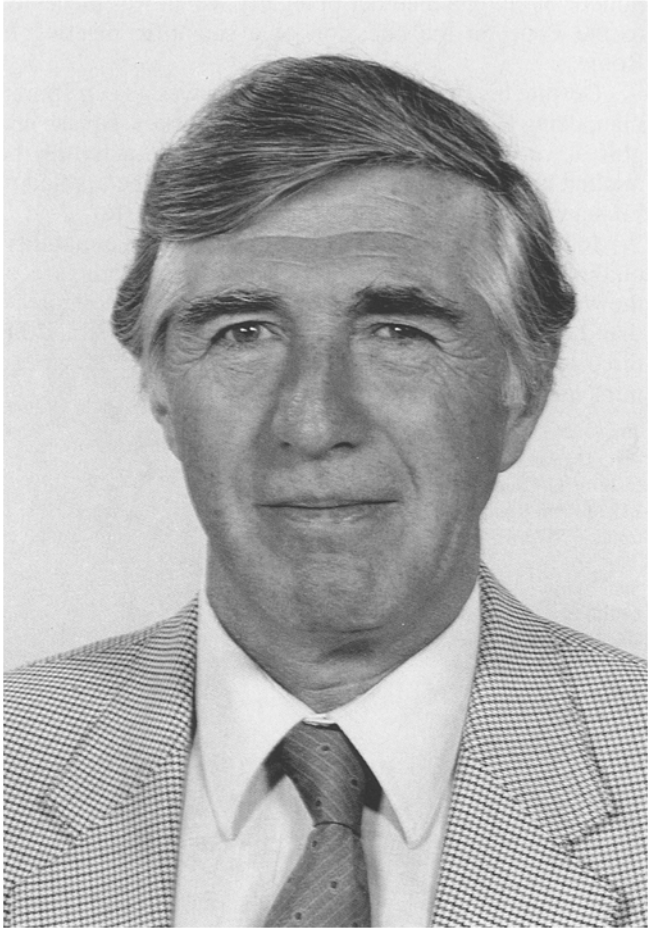
Cancer Chemotherapy and Pharmacology

Obituary

Professor John J. Roberts 1926–1990



John Roberts died on the 10th October, 1990, following an operation for adenocarcinoma of the lung. He died peacefully in the presence of his wife and 3 sons.

After leaving Raynes Park Grammar School, John spent 4 years at the Organon Laboratories as a development chemist during which time he obtained a B.Sc. (Hons) degree in chemistry from London University in 1948. He then joined the Chester Beatty Research Institute (Institute of Cancer Research) in Fulham Road, London, and remained with the Institute for the following 41 years, being the longest serving member of the scientific staff.

He worked initially with Professor Kon and then with Professor Walter Ross and, later, with Professor Franz Bergel, all distinguished organic chemists, and was awarded the Ph.D. in 1952. During this time he synthesised a number of nitrogen mustards as potential anti-tumour agents. The most active of these was chlorambucil, one of the first drugs to be patented by the Chester Beatty Research Institute, and which is still in wide clinical use for the treatment of cancer.

In 1957 John made the first of many visits to the U.S.A. to attend the N.Y. Academic of Science Conference on the biological effects of alkylating agents. John often recalled the pleasures of those transatlantic journeys on the liner "Queen Mary".

In about 1956 he began a close collaboration with Dr. Gerry Warwick. Both scientists saw a need to use techniques which required the use of radioactivity labelled alkylating agents. Suitable facilities were only available at Pollards Wood Research Station – The Institute's laboratory in the countryside of Buckinghamshire, to which John moved in 1958. This collaboration resulted in 20 joint publications during the following 10 years.

At first, Roberts and Warwick studied a monofunctional alkylating agent (ethyl methanesulphonate) and subsequently several other difunctional agents, in particular myleran (1:4-dimethane-sulphonyloxybutane). Initially they investigated the alkylation of proteins and reported the production of alkyl mecapturic acids. This led to the first demonstration that proteins can be alkylated *in vivo*. Subsequently they switched their attention to alkylation of DNA, particularly in the liver of rodents, and pointed out the relevance of carcinogen-DNA binding for hepatocarcinogenesis.

Following reports of the repair of DNA damage in bacterial cells, John and colleagues began studies of DNA repair in mammalian cells. In collaboration with Austin Crathorn he reported evidence of the excision of chemically-induced DNA-adducts and demonstrated non-semi-

conservative (repair) synthesis in mammalian cells. He and his colleagues used synchronised cell cultures to show that alkylation of DNA resulted in its inactivation as a template for DNA replication, leading to cell death. As a follow up to these experiments, he investigated the inhibition of DNA repair by caffeine in the hope that this compound might potentiate the cytotoxic effects of alkylating drugs which cross link DNA.

The wealth of expertise in DNA binding and repair which John had amassed by these studies was next deployed in unravelling the mechanism of action of the antitumour platinum drugs, whose potential in cancer chemotherapy had been quickly recognised by Sir Alexander Haddow, then Director of the Chester Beatty Research Institute. John, with his colleagues, showed that diamminedichloroplatinum-II (cisplatin) and related compounds formed interstrand cross-links in the DNA of hamster cells. These studies led John to conclude that the mode of action of the platinum drugs in killing cells was essentially the same as for other difunctional alkylating agents, such as sulphur mustard (di-(2-chlolorethyl)sulphide) and that the mechanism of cell killing of several of the second generation platinum drugs (such as Carboplatin) was effectively the same as that of cisplatin. The specificity of response of certain tumours, particularly human testicular non-seminomatous germ cell tumours, towards different platinum compounds remained to be explained. John Roberts and his team showed that human and mouse embryonal cells were extremely sensitive to cisplatin as judged on the basis of platinum adducts bound to DNA, and almost as sensitive as the fibroblasts of patients with xeroderma pigmentosum and Fanconi's anaemia, the latter syndrome being associated with hypersensitivity to difunctional alkylating agents. John's work on the platinum drugs was generously supported by the Johnson-Matthey Co. who in appreciation of his major contributions, has endowed a prize dedicated to his memory.

Towards the end of his life – and now working at the Institute's laboratories in Sutton, Surrey – John returned to the question of the mechanism of action of the drug CB1954 (5-(aziridin-1-yl)-2,4-dinitrobenzamide), a problem which he had encountered many years earlier. With his colleagues he showed that CB1954 was converted into a new cytotoxic DNA interstrand cross-linking agent, 5-(aziridin-1-yl)-4-hydroxylamino-2-nitrobenzamide by a form of NAD(P)H dehydrogenase (quinone) which they isolated from Walker 256 rat carcinoma cells. A further paper on this topic is in press at the time of writing, as is John's initial study of monoclonal antibodies against platinum DNA adducts – an area of research creating much interest in several laboratories.

John received many academic distinctions during his career. He became a Senior Lecturer in 1960, a Recognised Teacher in the University of London in 1970 and was awarded a D.Sc. in 1974. In 1985 the University conferred upon him the title of Reader and in June 1988 he received the title of Professor of Molecular Pharmacology.

He served on several academic committees and as a member of the editorial board of 4 well known journals. In addition to his research and committee duties he supervised postgraduate students and visiting workers and was an external examiner of many candidates for higher degrees. John enjoyed travelling and was invited to numerous scientific meetings in all parts of the world. He had the honour of being a member of a party which was presented to the Pope on the occasion of a scientific meeting in Rome.

Despite his busy scientific life John was a keen sportsman, being actively involved in rugby, hockey, squash and golf at various stages of his life. To these activities he applied himself with the same dedication as he applied to his science, and as a result was equally successful.

John was a genial man of great charm and amiability, qualities which made him very many friends in all parts of the world. We shall all miss him greatly, but none more so than his family – Gaynor, his wife for 41 years, and his three sons Mark, Paul and Nick – to whom we all extend our sympathy and condolences.

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