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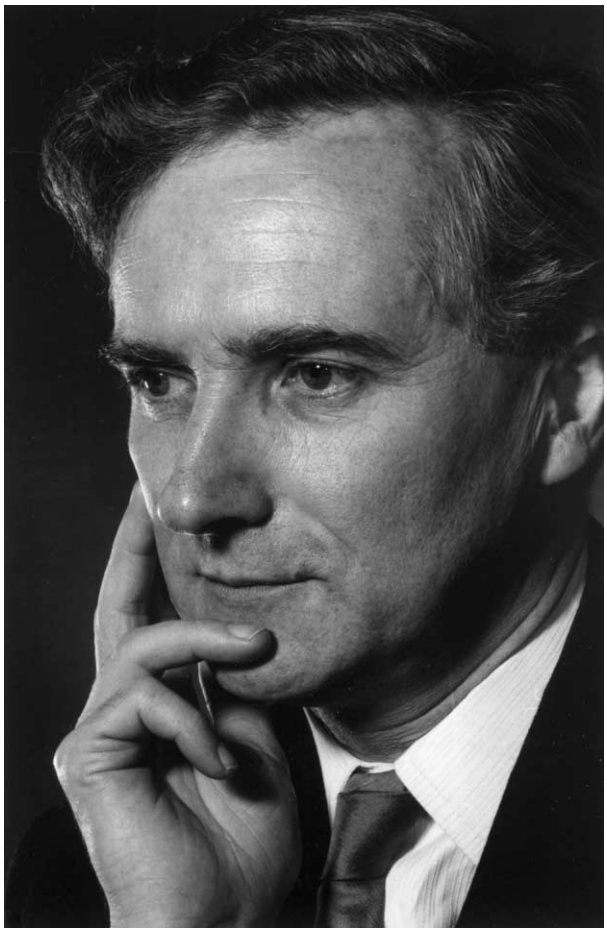
A tribute to Dr Francis Roe: 50 years of outstanding achievement



This photograph was taken during 1970 by Ken Moreman.

The occurrence of skin cancer (scrotum) in chimney sweeps exposed to soot and of bladder cancer in aniline dye workers, first noted in 1775 and 1895, respectively, are often cited as the key observations that led to the birth of experimental chemical carcinogenesis in the early 20th century.

For several decades from 1915, when skin-tumour induction by coal tar was reported in rabbits, various chemicals were shown to be carcinogenic in animal models, such as polycyclic aromatic hydrocarbons (skin tumours in mice), *o*-amidoazotoluene (hepatomas in rats) and aniline dyes (bladder cancer in dogs). By the 1940s, mouse skin carcinogenicity assays provided evidence of a two-stage process of tumour development involving initiation and promotion. This concept aroused considerable interest since it held promise of understanding the fundamental nature of neoplasia. Another important landmark in the history of experimental chemical carcinogenesis was the observation in 1956 of liver carcinoma in rats by dimethylnitrosamine, which expanded into the fertile field of nitrosamine carcinogenesis.

By this time Dr Francis Roe, a young and undoubtedly enthusiastic pathologist, had already arrived on the experimental chemical carcinogenesis scene. In a career spanning 50 years (with an impressive 840-plus publications to his credit), Francis Roe has made substantial and invaluable contributions both in this area and in toxicology as a whole. As a tribute to this tremendous achievement, this special issue of *Food and Chemical Toxicology* contains a

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collection of invited papers and reviews by friends and colleagues touching on the wide-ranging interests with which Francis Roe has been associated. It is particularly fitting that this tribute should appear in *Food and Chemical Toxicology* because of Francis Roe's prolonged interest in this journal, dating back to its inception in 1964, as a founder member of the editorial board and, more recently, as the Review Editor. Aware of the exponential growth of commercially-available chemicals by the 1960s, Francis Roe campaigned for more research on the identification of chemical carcinogens and mechanisms of experimental carcinogenesis as a means to prevent cancer in humans. Others also saw the need, and two important programmes were initiated in the 1960s: the US National Cancer Institute programme of rodent carcinogenicity bioassays and the International Agency for Research on Cancer (IARC) evaluation on the carcinogenic risk of chemicals to humans.

Thousands of chemicals have been tested by the rodent carcinogenicity bioassay, which remains the bedrock of carcinogenicity testing. The assay's fundamentals have barely changed over several decades. However, contentious issues, such as diet optimization in laboratory animals and the rationale of dose selection of the test material, as keenly debated by Francis Roe and others, have not yet been sufficiently resolved to enhance the robustness of this bioassay. It remains to be seen whether short-term tests and the use of transgenic animal models will fulfil their promise as suitable replacements.

In the decade following the development in 1973 of the Ames test—a rapid in vitro assay for determining the mutagenic potential of chemicals requiring metabolic activation to the active form—interest focused on the correlation between the mutagenic and carcinogenic potential of many chemicals. From this emerged the ability to distinguish between genotoxic and non-genotoxic carcinogens, a particularly important development in the regulatory control of such chemicals.

Enhancing our understanding of the mechanisms of chemical carcinogenesis will continue to improve interpretation of carcinogenicity findings in animals in terms of human risk. Various mechanisms are now known to be operative. For genotoxic carcinogens, the stage of tumour initiation may involve structural damage at the level of the gene or effects on the expression of relevant genes (proto-oncogene mutation and expression and tumour-suppressor gene inactivation). The stage of initiation, which occurs in single cells, may advance to the stage of promotion by clonal replication of a minority of the initiated cell population in the presence of a promoting agent from endogenous or exogenous sources. In this phase, the continued presence of the promoting agent is required to selectively stimulate initiated cells to replicate. For non-genotoxic carcinogens, the early primary phase involves effects on cell behaviour (increased secretion of trophic hormones, activation of particular receptors involved in growth and differentiation, cell proliferation and hyperplasia). Subsequent transformation towards neoplasia may involve the DNA-damaging action of endogenously-produced reactive intermediates or by impairment of DNA-repair mechanisms in proliferating cell populations.

With the rapid progress in molecular biology, significant advances in experimental chemical carcinogenesis over the next decade are to be expected. But the imaginative and pragmatic approaches of the pioneers of experimental chemical carcinogenesis of the likes of Francis Roe have laid the foundation for future successes.

A particular feature of Francis Roe's approach to problems has been that he sees them three-dimensionally. It is not surprising, therefore, that his hobby is portrait sculpture and that a bust by him of the pathologist, Dr Cuthbert Dukes, is on permanent display at the Royal College of Pathologists in London.

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