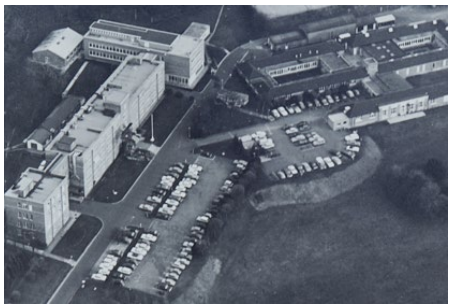
MRC Toxicology Unit- History 1947-

The Toxicology Unit was established by the MRC in the spring of 1947 under the directorship of Dr John Barnes for the experimental investigation of toxicological problems, with special reference to industrial hazards. Barnes was a medical experimental pathologist who had briefly worked on penicillin with Florey in Oxford. Establishment of the Unit turned out to be an inspired and long-term initiative by the MRC at a time when new pesticides and other chemical products were being developed and widely used. Initially the Unit was accommodated at the Porton Down Chemical Defence Establishment in Wiltshire but in 1950 it was moved to join other Units at the MRC Laboratories in Carshalton, Surrey, the first of three moves. Early and subsequent MRC annual reports emphasized that the mission statement of the Unit was not only to study particular chemicals of toxic concern but to learn more about normal physiological and biochemical processes by investigating physical and chemical induced injury. This multidisciplinary approach of combining fundamental molecular studies with pertinent toxicology and pathology has under pinned the philosophy of the Unit to the present time. Dr W. Norman Aldridge, a founder member of the Unit, until his retirement was pre-eminent within the Unit and internationally in promoting a rigorous and systematic mechanistic approach in toxicology that is still of fundamental importance to understand real hazard and risk from chemicals for humans [1]. Indeed this philosophy is the basis of 'molecular initiating event' and 'adverse outcome pathway' approaches in modern toxicology. Some members of the Unit moved to senior positions in other establishments, including in the USA, taking this philosophy with them.

Carshalton



Initial studies on beryllium which was of increasing industrial importance, showed that contrary to early reports acute administration of soluble salts caused focal necrosis in the liver and bone tumours after chronic exposure. Subsequent studies investigated the weed killer dinitro-*o*-cresol and 2,4-dinitrophenol and the recognition

that these were uncouplers of oxidative phosphorylation. The associated toxicity from unwise pedalling of such chemicals for weight loss are now health and regulatory concerns. The mechanisms of toxicity of DDT, carbon tetrachloride, carbon disulphide, cadmium, mercury, lead and the neurotoxicity of acrylamide and mercury rapidly led to the recognition of the Unit as a major international centre of toxicology expertise and WHO collaborating centre. Studies on the effects of cold-acclimation and body temperature on experimental and patient injuries were highly innovative in understanding biochemical processes in tissue damage. The discovery in the Unit that nitrosamines are highly carcinogenic led to a rapid increase in our understanding of the hazard and risk from these chemicals and used subsequently by many laboratories in the understanding of the processes of chemical-induced carcinogenesis. Study of plant toxins such as pyrrolizidine alkaloids and mycotoxins like aflatoxin known to be hazardous and carcinogenic to domestic animals and humans through food and supplements, broadened the interest of the Unit beyond industrial chemicals. In neurotoxicity, differences in behavioural toxicity of specific alkyl- tin and lead compounds were shown to be the consequence of selective mitochondrial interactions in hippocampus and myelin sheath. Of particular interest were the new classes of organophosphate anti-cholinesterase inhibitors being developed as alternative pesticides to chlorinated chemicals, and already of concern in non-agriculture spheres for producing delayed neuropathies, as they are still today. Some of the first studies on the highly potent chlorinated contaminant 2,3,7,8-tetrachloro-p-dioxin formed in the manufacture of some chlorinated herbicides and other chlorinated aromatics were reported in the MRC unit. In all investigations the emphasis was always on mechanistic understanding rather than descriptive elements.

In 1976 Dr Tom A Connors from the Cancer Research Institute was appointed Director following the untimely death of Barnes. Many of the research interests continued including the consequences of DNA methylation by nitrosamines, the molecular mechanism of aflatoxin carcinogenicity and defence processes, the biochemistry and selectivity of delayed neuropathy caused by organophosphorus pesticides, toxicity of mercury/cadmium and the transport across the blood-brain barrier and metabolic rates in brain compartments. However, the trauma team focussing on basic science in the response to tissue ischaemia and bacterial endotoxin in injured patients, was moved to a new MRC unit in Manchester. Neurophysiology skills were acquired to complement established pathological expertise especially in the assessment of the mechanisms of mammalian neurotoxicity of pyrethroid insecticides, the successors to the organophosphorus pesticides. These showed complex actions depending on the types of

sodium and chloride ion channels inhibited. One continuing experimental area was the effects of drugs and other chemicals on hepatic nonerythroid haem and its metabolism and pertinent to clinical investigations of triggers for some emerging genetic diseases associated with haem metabolism. This was particularly important in the demonstration of the suicidal destruction of cytochrome P450 during metabolism of many unsaturated chemicals. Haem is now recognised to be a key component of other important cellular functions in most organs including aspects of cell signalling. Related investigations demonstrated the species and genetic susceptibility of hepatic and cardiac iron accumulation modelling aspects of haemochromatosis and the influence of iron chelating drugs. With the increasing recognition of the importance of cellular and alternative to animal studies in toxicology, the Unit developed expertise in the factors for the maintenance of drug response of hepatocytes, and lymphocytes and single cell organisms in culture. Similarly, molecular biology skills were acquired for the cloning of some genes and their selective altered regulation and expression as pre-neoplastic markers of genotoxic hepatic and oesophageal carcinogenesis and effects of antioxidants. Following from concern regarding genotoxic carcinogens, an extensive programme was the use of sensitive mass spectrometry methods to detect covalent adducts of alkylating mutagens after human exposure to environmental, occupational and medicinal sources. Firstly alkylated haemoglobin was studied as a surrogate e.g. for styrene exposure, and then adducts of DNA nucleotides as mass spectrometric techniques were refined. In subsequent years this novel methodology was utilised to detect incidences of alkylation in people exposed to products like ethylene oxide and degrees of alkylation by endogenous agents such as those from lipid peroxidation. Research expertise of asbestos fibres from the MRC Pneumoconiosis Unit in Wales and particulates, sulphur dioxide and other atmospheric pollutants from the Clinical Toxicology Unit in St Bartholomew's Hospital, London were also incorporated into the Toxicology Unit.

University of Leicester

Following the appointment of a new Director Dr Lewis L. Smith with an industrial background, the Unit was moved in 1993 to a purpose built institute, the Interdisciplinary Research Centre for Mechanisms of Human Toxicity in the University of Leicester. This also accommodated university research groups with interests that complemented toxicology. Some programmes such as strategies for cancer treatment and prevention, genetic

susceptibility to xenobiotics, pulmonary toxicology and neurotoxicology evolved from previous programmes. The molecular esterase target of organophosphate pesticide delayed neuropathy was identified and dinitrobenzene shown to be a selective toxicant for glial cells. High resolution chromatographic, mass spectrometric and ^{32}P-post labelling techniques were greatly refined in biomonitoring and metabolism studies of alkylated and intracellular oxidised DNA and haemoglobin after human environmental and drug exposure. This allowed sensitive detection of adducts not only of acrylonitrile from cigarette smoking and benzene from petrol but also reactive metabolites from normal metabolism. New programmes were also introduced including molecular studies of chemically-mediated programmed cell death (apoptosis) including the role of caspases and endonucleases and the release of cytochrome c from mitochondria with down-stream signalling consequences, especially with respect to cancer cells and the actions of some anticancer drugs. Understanding the mechanisms of toxicity of some novel anticancer drugs and food-induced cancer chemoprevention and investigating some multidrug resistance transporters moved Unit research into studies related to direct clinical issues. A major multidisciplinary programme was initiated to understand the mechanisms and human relevance of the genotoxicity and carcinogenicity of the breast cancer drug tamoxifen in experimental animals and the health significance of the possibility of endometrial cancer for women especially in prevention trials. The increased interest in drug studies was a shift for the Unit that had been encouraged to focus on toxicological issues of occupational, food and environmental chemicals rather than safety of drugs that previously were deemed the responsibility of the pharmaceutical industry. Electron microscopy capabilities were upgraded and the Unit was one of the first laboratories to introduce toxicogenomics with gene arrays being printed in purpose built facilities.

Professor Pierluigi Nicotera from the University of Konstanz became Director in 2000 following the return of Lewis Smith to industry. Nicotera had a clinical background and scientific interest in cell death research especially in neurology. Major changes occurred in research programmes to orientate the Unit towards more fundamental molecular studies particularly associated with understanding mechanisms of cell death and tissue damage and their relevance to human disease and treatment and included importation of research programmes from Europe. Programmes benefited greatly from upgraded or new microscopic, laser micro-dissection and proteomic facilities. One aim was to discover new significant common endpoints for cytotoxicity and biological responses that might be used as biomarkers. Programmes of neurodegeneration and neurotoxicity included transgenic models of stroke and

dementia and mechanisms of mitochondrial control in cell death. Although a causal link between toxic agents and different neurodegenerative disorders is debated, understanding the signalling and reaction of the nervous system to injury provided relevant information to better predict neurotoxic risk. Particular emphasis was placed on Ca^{2+} overload, contrasting actions of statins in neurons, association of haem deficiency with aging of neurons and a new signalling pathway involved in neuronal plasticity and long-term effects of nicotine. A neurophysiology programme to study mechanisms of neurotoxicity at the synaptic interface evolved from expertise developed in Leicester University. Continued detailed investigations of molecular determinants of apoptosis and receptor-mediated cell death in cancer cell models greatly enhanced understanding of apoptosome formation and composition, cytochrome c release, the involvement of caspases and regulation of the proteasome amongst many other molecular findings. Interactive research was also initiated with a clinical-based programme with the University medical school on chromosomal instability in B-cell lymphomas and leukaemias. New intense studies focussed on down-stream pathways during cell death in mechanisms involving the p63 and p73 members of the p53 family with respect to cancer, immunology, development and aging. To ensure strong interaction of the Unit with mainstream toxicology, a nationwide scheme was initiated (the Integrative Toxicology Training Partnership, ITTP) whereby the MRC acted as a hub to fund and train PhD students in molecular toxicology to build future expertise for the UK. In 2010 Pierluigi Nicotera moved to become Scientific Director of DZNE, Germany

Professor Anne E Willis from the University of Nottingham was appointed Director in 2010. Professor Willis came to the Unit with a considerable reputation in cancer cell biology and drug treatment, particularly with respect to RNA biology and understanding the role of post-transcriptional control. These skills and knowledge have since been directed at many drug-safety and environmental hazards. These include a cross Unit programme on the mesothelioma-inducing potential of carbon nanotubes, and novel studies to explore the on and off target toxicities of RNA-based therapeutics such as modified in vitro transcribed RNAs and antisense oligonucleotides. The latter hold great potential to drug the un-targetable proteome, but are currently limited by safety concerns. The Unit also continues with its research surrounding fundamental exposure-associated disease processes, in conjunction with many national and international collaborators. In 2018 the UKRI MRC Unit transferred to University of

Cambridge and in 2020 physically relocated from Leicester to the refurbished Gleeson Building, on Tennis Court Road in central Cambridge.

The fundamental objectives of the Unit have not changed since its formation, in understanding causal molecular mechanisms of external and endogenous toxic agents with adverse outcomes in humans, and embracing new research fields and technology. Since the Unit was formed in 1947 general scientific progress has been remarkable and is reflected in the cutting-edge molecular and technological facilities now available to the Unit [2].

The present research interests of the Unit are shown in the current MRC Toxicology Unit programmes.

[1] W.N. Aldridge, *Mechanisms and Concepts in Toxicology* (1996) Taylor & Francis Ltd, UK.

[2] In contrast to sophisticated modern technology:

MRC Toxicology Unit's first 'portable' pH meter 1948.