

## Obituary

### Dr John J Burns, 1920–2007

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Dr John J Burns, a legend in pharmaceutical industry research and an outstanding scientist in his own right, died on 29 July 2007. Born in Flushing, New York on 8 October 1920, he was a graduate of Queens College with a BS degree in 1942, and from Columbia University in 1950 with a PhD degree. During World War II, he served in the US Army where he was assigned to a research group developing new anti-malaria drugs.

During his years as Vice President and Director of Research at Burroughs Wellcome and Hoffmann La Roche, Dr Burns supported basic research more than any other pharmaceutical executive, both within his company as well as in the academic community. One of his most outstanding contributions was the establishment of the Roche Institute of Molecular Biology. This institute, which earned a worldwide reputation for outstanding research, is one of John's legacies. John's view that great basic research would always lead to practical results was confirmed when a collaboration between the Roche Institute and Genentech led to the development of important drugs, and many years later, to Roche owning a controlling interest in this now major biotechnology Co.

In his earlier years, John did outstanding research and was the author of several hundred original research papers.

Dr Burns did much of the early pioneering work on the biosynthesis and metabolism of vitamin C (ascorbic acid). He demonstrated that ascorbic acid is formed in the rat by the following steps: glucose or galactose, D-glucuronolactone, L-gulonolactone, L-ascorbic acid, and he demonstrated that man, monkey and the guinea pig lacked the ability to metabolize gulonolactone to ascorbic acid, which explains why these species require ascorbic acid to prevent scurvy. Dr Burns found that the half-life of ascorbic acid was 4 days in guinea pigs, compared with about 18 days in man. The longer half-life of ascorbic acid in humans explains why they require a much longer time to develop scurvy than the guinea pig.

Dr Burns' fundamental studies in the area of drug metabolism helped explain the multiple action of certain drugs. His metabolic studies identified metabolites with high biological activity, which have later been used in the medical profession for the treatment of various diseases. Dr Burns showed that in man phenylbutazone is converted to two major metabolites. One product is formed by the introduction of a phenolic group in the para position of a benzene ring (metabolite I), and the other by the introduction of an alcohol group on the butyl side chain (metabolite II). Metabolite I has the potent antirheumatic and sodium-

retaining effects of phenylbutazone, whereas metabolite II possesses little sodium-retaining and antirheumatic properties, but is considerably more potent as a uricosuric agent. These two metabolites can explain the antirheumatic, sodium-retaining and uricosuric activities that are observed when phenylbutazone is administered to man. Metabolite I (oxyphenbutazone, tandearyl) has been used in man as a potent antirheumatic agent in acute gout and rheumatoid arthritis, and a sulfoxide metabolite (sulfinpyrazone) of a thio-ether derivative of phenylbutazone is a potent uricosuric agent that is useful for the treatment of chronic tophaceous gout. Sulfinpyrazone was identified by Dr Burns as a urinary metabolite of the thio-ether derivative of phenylbutazone. The extensive studies by Dr Burns and his associates on the metabolism and pharmacological activities of phenylbutazone and its analogs have markedly enhanced our knowledge of the pharmacology of these compounds, and were early studies indicating the metabolism of drugs to active metabolites.

As part of his research on phenylbutazone, which was published in the *American Journal of Medicine* in 1954, Dr Burns compared the anti-inflammatory action of this drug with the steroid cortisone, and observing the similarity in mechanism of action between the two compounds, used the term 'nonsteroidal anti-inflammatory' to describe phenylbutazone. This was the first use of this term, which is commonly used today to describe drugs such as motrin, aleve and celebrex.

Dr Burns performed pioneering research on species differences in the rates and pathways of metabolism of phenylbutazone, oxyphenbutazone, ethylbiscoumacetate, mepredine and ascorbic acid. The results of these studies emphasized the difficulties involved in extrapolating drug metabolism data from one species to another, and from animals to man. Dr Burns also performed pioneering research on individual variations in human drug metabolism. He found a greater than 10-fold variation in the rate of metabolism of ethyl biscoumacetate (tromexan) among different human subjects and about a four-fold difference in the rates of metabolism of phenylbutazone in different subjects. There are now many examples of drugs that are metabolized at different rates in different patients. Because of person-to-person differences in drug metabolism, some human subjects metabolize a drug so rapidly that therapeutically effective blood levels are never achieved, whereas other individuals metabolize the same drug so slowly as to result in toxic side effects. These were early studies on person-to-person differences in the metabolism of drugs.

Dr Burns found that administration of several drugs such as chloretone and barbiturates, as well as polycyclic aromatic hydrocarbons, stimulates the metabolism of glucose and galactose via the glucuronic acid pathway to glucuronic, gulonic and ascorbic acid, and he found that those drugs that stimulated ascorbic acid biosynthesis also stimulated the liver microsomal metabolism of drugs.

Dr Burns was the first to demonstrate the clinical importance of microsomal enzyme induction. He provided early evidence that enzyme induction decreased the action of drugs in both animals and man. Dr Burns demonstrated that chronic administration of several drugs to rats or dogs stimulated the drugs' own metabolism and decreased their toxicity. These studies have had an important impact on both the interpretation and design of chronic toxicity tests. Studies by Dr Burns also demonstrated the usefulness of microsomal enzyme induction and inhibition as tools for determining whether drugs are active *per se* or require metabolism to an active metabolite.

In addition to the fundamental research contributions which are described above, Dr Burns has made enormous contributions to pharmacology and toxicology in the United States and abroad by his leadership role in the affairs of the American Society for Pharmacology and Experimental Therapeutics, the International Union of Pharmacology, the American College of Neuropsychopharmacology, the Committee on Problems of Drug Safety of the National Academy of Sciences, as Senior Consultant to the Pharmacology-Toxicology Program, National Institute of General Medical Sciences, and as a consultant to many other groups. Dr Burns was elected for membership in the National Academy of Sciences in 1975 because of his important contributions to science.

In addition to the above contributions to pharmacology and toxicology, Dr Burns while directing research at Burroughs Wellcome and at Hoffman La Roche was

instrumental in the discovery and/or development of drugs such as levodopa (Parkinson's), rocaltrol (kidney dialysis), accutane (cystic acne), limbitrol (depression), versed (anesthesia) and interferon (hepatitis).

Dr Burns served as Adjunct Professor of Pharmacology at the Weill Medical College of Cornell University. He also was a scientific advisor to a number of new biotechnology companies. Dr Burns was a member of the Institute of Medicine, served as President of the American Society for Pharmacology and Experimental Therapeutics, and as President of International Union of Pharmacology. In 1974, Dr Burns was a member of the Herbal Pharmacology Delegation to the People's Republic of China, and in 1973 was a member of the Panel on Chemistry & Health of President Nixon's Scientific Advisory Committee. Dr Burns was a member of the Steering Committee of the National Academy of Sciences/Institute of Medicine that developed the National Strategy for AIDS. In 1987, he was awarded Honorary Membership in the Japanese Pharmacology Society. In 1987, he received an Honorary Doctor of Science degree from Queens College on the occasion of the College's 50th anniversary celebration.

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