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This Week's Citation Classic®

Lawley P D. Some chemical aspects of dose-response relationships in alkylation mutagenesis. *Mutat. Res.* 23:283-95, 1974.
[Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Chalfont St. Giles, Bucks., England]

Alkylating agents were classified according to their mode of reaction with DNA (ability to cross-link, or to react at extranuclear O- or N-atoms as opposed to ring N-atoms), and mode of reaction was correlated with biological effects such as cytotoxicity, mutagenicity, and DNA repair. [The *SCI*® indicates that this paper has been cited in more than 275 publications.]

Trying to Correlate Chemistry and Biology

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This publication is based on a paper presented at the Annual Conference of the Zentrallaboratorium für Mutagenitätsprüfung in October 1973 at Bad Krozingen. I recall being very impressed with the definitely modern but pleasant splendour of the conference venue, which appeared to be devoted to the welfare of the German old-age pensioner desirous of "taking the waters" at a typical spa, and manifestly superior to anything on offer to his British counterpart. Interest in the topic of environmental mutagenesis was already widespread, as evidenced by the expression of some controversy between certain participants. Whether this was the main reason the publication of the conference proceedings was delayed I can only guess, but I was subsequently surprised to hear from Dr. F. Sobels, the editor-in-chief of *Mutation Research*, that he wished to publish my paper irrespective of the rest. I had good reason to thank him, if only on the grounds that "all is grist to the mill" in the world of scientific publications, but I can now justifiably invoke the cliché "little did I know" that this would become a *Citation Classic*!

I had been appointed to the staff of the Chester Beatty Institute a mere 20 years previously to investigate the chemistry of the mode of action of cancer chemotherapeutic agents. The then-director, the late Sir Alexander Haddow, after whom of course the laboratories where I now work are named, was the first to acknowledge that many chemotherapeutic agents, notably alkylating agents, such as nitrogen mustards, are unfortunately themselves mutagenic and carcinogenic, and were termed "radiometric." At that time, DNA had not long been recognised as the genetic material, and the Watson-Crick structure for DNA and the model for its replication were announced shortly afterwards. For those few who, like myself, had previously worked with this then-largely esoteric substance, these concepts could justifiably be termed revolutionary. They explained with dazzling clarity what little we had already learned and provided a rich field for future studies of DNA as the target of cytotoxic and carcinogenic chemicals.

I was privileged through the courtesy of the European Environmental Mutagen Society to have the opportunity to record elsewhere[1] a brief history of those enjoyable early days. Salient features were that some headway was made towards explaining the cytotoxicity of difunctional mustards through their ability to alkylate and cross-link DNA *in vivo*,[2] and to account for the carcinogenic potency of the polycyclic aromatic hydrocarbons through DNA aralkylation,[3] despite their not generally being recognised as mutagens at that time.

A further important theme, derived from a concept due to our colleague Dr. Anthony Loveless, stemmed from the finding that the outstandingly potent methylating carcinogens, acting through the methyldiazonium ion, were distinguished by their ability to cause extensive O-alkylation in DNA, notably inducing the powerfully miscoding base O^6-methylguanine,[4] which could in turn activate a specific type of DNA repair.[5] This early work led to a more coherent perception of the part played by mutagenic chemicals in the carcinogenic process, and the impact of the paper presently under discussion may well now be seen to result from its listing what appeared then to be significant factors relevant to that perception and which have stood the test of time.

1. **Lawley P D.** Mutagens as carcinogens: development of current concepts. *Mutat. Res.* 213:3-25, 1989.
2. **Brookes P & Lawley P D.** Reaction of mustard gas with nucleic acids *in vitro* and *in vivo*. *Biochem. J.* 77:478-84, 1960. (Cited 170 times.)
3. -------. Evidence for the binding of polynuclear aromatic hydrocarbons to the nucleic acids of mouse skin: relation between carcinogenic power of hydrocarbons and their binding to DNA. *Nature* 202:781-4, 1964. (Cited 645 times.)
4. **Lawley P D & Thatcher C J.** Methylation of DNA in cultured mammalian cells by MNNG: influence of cellular thiol concentration on extent of methylation and O-6 of guanine as a site of methylation. *Biochem. J.* 116:693-707, 1970. (Cited 480 times.)
5. **Lawley P D & Orr D J.** Specific excision of methylation products from DNA of *Escherichia coli* treated with MNNG. *Chem.-Biol. Inter.* 2:154-7, 1970. (Cited 155 times.)

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