The Carcinogenicity and Mutagenicity of Therapeutic Coal Tar—A Perspective

Coal tar is an ill-defined, aromatic, complex brown-black substance resulting from the destructive distillation of coal. Depending upon the conditions (temperature and pressure) under which the coal is combusted, myriad numbers of polyaromatic hydrocarbons are generated. Polynuclear polycyclic hydrocarbons are among the oldest known skin carcinogens. In 1775, Percival Pott, a London surgeon, first showed that a specific type of skin neoplasm (scrotal cancer) preferentially occurred in chimney sweeps as a result of their chronic exposure to soot [1]. He also pointed out the lengthy latent period (years) between the onset of exposure and the development of overt neoplasia.

Experimental studies early in the 20th century showed unequivocally that crude coal tar had oncogenic properties in rabbit skin [2]. Subsequently several polynuclear polycyclic hydrocarbons were isolated from coal tar, purified and shown to be potent skin carcinogens in mice [3]. Among the best known of these chemicals extracted from coal tar is benzo(a)pyrene, a ubiquitous environmental pollutant that is generated whenever fossil fuels are combusted. Despite the identification of a few constituents, coal tar remains for the most part a poorly characterized and extremely complex mixture containing at least 10,000 structural compounds.

The carcinogenicity of coal tar products for human skin has been amply confirmed in numerous studies. Perhaps the most complete statistical data verifying the oncogenicity of coal tar has come from the study reported by Henry in Britain [3]. He showed that between 1925 and 1943 more than 3,700 cutaneous cancers had been reported among factory workers there. Of these, at least 2,200 were due to exposure to various coal tar products. Henry reemphasized Pott’s initial observation that chronic (15–25 yr) repetitive exposure to high concentrations of coal tar products was required to evoke human skin cancer.

The neoplasms were predominantly squamous cell carcinomas and they occurred almost exclusively on the head and neck, the arms, and the scrotum. Unlike occupational exposures, the carcinogenicity of coal tar products used therapeutically remains unclear. Hodgson reported a single case of a squamous cell carcinoma which developed in the periareal area of a man with pruritus who had repetitively applied a coal tar product for 7 yr [4]. Subsequently, Rook, Gresham, and David reported a patient who developed 2 squamous cell carcinomas of the skin of the thigh after 32 yr of treatment with a solution containing coal tar [5]. Their review of the literature in 1957 indicated that at least 6 cases of skin cancer related to chronic topical application of coal tar had been reported. More recently Greither, Gisbertz, and Ippeh found a total of 13 cases of human skin cancer that were probably related to the prolonged use of therapeutic coal tar preparations [6].

Perhaps the most widely used therapeutic regimen utilizing coal tar is the Goeckerman regimen. This modality has been the mainstay of the treatment of moderate to severe psoriasis for more than 50 yrs. It generally involves daily application of crude coal tar in concentrations of 2–5% and its partial removal prior to incremental doses of ultraviolet light.

Although most authors agree that the acute toxicity of the Goeckerman regimen (ultraviolet erythema and folliculitis) is minimal, there is concern about the long-term hazards of repeated skin exposure to the 2 separate oncogenic agents that constitute the modality (coal tar and UVB). Despite this concern, virtually nothing is known about the skin carcinogenicity of the Goeckerman regimen in human populations. Recently, Stern et al reported an increased risk of skin cancer in psoriatic patients exposed for many years to large amounts of coal tar and ultraviolet light [7]. This was based upon patient recall of the degree of prior exposure. However, Muller et al reviewed their experience at the Mayo Clinic with patients treated with the Goeckerman regimen [8] and were unable to detect any difference in cancer incidence in their patients as compared to data obtained in the National Cancer Survey. In summary, the carcinogenicity of coal tar for the skin of experimental animals, and for the skin of human workers chronically exposed to large amounts of the material is unquestioned, whereas the risk of developing cancer from the use of therapeutic coal tar products remains unclear.

In recent years great efforts have been made to develop short-term procedures for the evaluation or screening of chemicals for their oncogenic potential, particularly since carcinogenicity studies in experimental animals are extremely expensive and time-consuming. According to the somatic mutation theory of chemical carcinogenesis, the initiation of a tumor requires that an irreversible change occur in cellular DNA and it is this change that ultimately may result in unregulated proliferation of cells and the development of a tumor. Chemical compounds known to be carcinogenic would, according to the somatic mutation theory, be expected to be mutagenic. Stated another way, all carcinogens should be mutagens.

Among the convenient experimental systems available for screening the mutagenicity of chemicals are microorganisms. An early screening procedure developed for the study of chemical mutagenicity utilized the ability of a substance to mutate bacteria from streptomycin-dependence to streptomycin independence. More recently Ames et al have developed a series of tester strains of S. typhimurium which have provided a most convenient assay system for assessing mutagenesis [9, 10]. Briefly, these bacteria are unable to grow in minimal media because of a genetic defect in the pathway of histidine biosynthesis. For the assay, bacteria are grown with trace amounts of histidine which permits an initial brief period of growth of the histidine-dependent bacteria so as to provide a “target” for the chemical compound to be tested. Damage to DNA, caused by the chemical, results in a mutation which is expressed as a functional gene product: in this case, reversal of defective histidine synthesis (reverse mutation). Revertants to histidine-independence are seen as colonies growing on the surface of the histidine-poor agar. Mutagenesis is expressed as a ratio of the number of colonies on the plate containing the test chemical compared to plates without the test chemical (spontaneous mutants). Ames selected several tester strains of S. typhimurium including TA 1535 which detects mutations resulting from base substitutions and TA 1538 which detects frameshift mutations. Further refinements have yielded strains known as TA 100 and TA 98 which are even more sensitive. This enhanced mutagenic sensitivity results from induced alterations in the lipopolysaccharide cell wall which enhances the permeability of the bacteria to test chemicals, to the deletion of the enzyme system responsible for excision repair of damaged DNA and to the incorporation of an R-factor (plasmid containing antibiotic resistance genes) which is associated with error-prone recom-
bination repair. All of these modifications enhance the sensitivity of the bacteria to mutagenesis. These tester strains developed by Ames provide a simple, inexpensive and highly sensitive assay procedure that is extremely useful in screening large numbers of chemical compounds. Other techniques using eukaryotic cells in addition to prokaryotes have also been developed in recent years [11].

With the extensive use of the Ames assay in the 1970's, it was soon recognized that there was considerable disparity between the mutagenicity and the carcinogenicity of certain compounds. Thus some chemical agents that were clearly carcinogenic in experimental animals had no demonstrable mutagenicity in the Ames assay. Because it became known that certain chemical carcinogens undergo metabolic transformation into reactive species that are the ultimate carcinogenic moieties. Ames modified his assay system by incorporating a source of microsomal enzymes (rat liver 9,000 xg supernatant). This modification greatly enhanced the sensitivity and specificity of the procedure such that 90% of a large series of chemical carcinogens were shown to be mutagenic in the Salmonella test. Conversely, most mutagenic chemicals are carcinogens. These findings have greatly strengthened the validity of the somatic mutation theory of chemical carcinogenesis. Although long-term animal and human studies are the only ones capable of providing conclusive evidence concerning the carcinogenic effects of a chemical, short-term tests such as the Ames assay provide a screening procedure that can quickly evaluate large numbers of chemicals to which humans are exposed. However, it is also important to emphasize that no correlation can be made between the quantitative aspects of carcinogenicity and mutagenicity [12]. In fact in at least one study in which 25 polyaromatic hydrocarbons were tested for mutagenicity using the Ames assay, only 58% of the compounds demonstrated a positive correlation between carcinogenicity and mutagenicity [13]. Thus, to maximize the predictive value of short-term tests it is imperative that multiple types of assay procedures be used.

It is extremely hazardous to extrapolate data obtained in short-term tests in prokaryotes to lifetime studies in eukaryotes (animal studies). It should be equally apparent that extrapolation of animal data to the human population is also fraught with difficulty. It is of interest, however, that at present, most mutagenicity data relating to short-term tests extrapolate reasonably well to the carcinogenic potency of a compound in animal tests.

Elsewhere in this issue of the Journal, Wheeler, Saperstein, and Lowe have reported that urine extracts prepared from patients undergoing Goeckerman therapy contain unidentified material(s) that is mutagenic in the Ames assay [14]. Mutagenicity of human urine extracts has been previously reported in patients treated with the trichomonicade, metronidazole, and the antischistosomal agent, niridazole, as well as in urine from cigarette smokers. Furthermore, urine from children wearing pajamas treated with the flame retardant mutagenic chemical 2,3-dibromopropyl phosphate (tris-BP) was found to contain 2,3-dibromopropanol, a known metabolite of tris-BP.

Crude coal tar is a complex mixture rich in polyaromatic hydrocarbons among them benzo(a)pyrene, benz(a)anthracene and dibenz(a,h)anthracene each of which is a known skin carcinogen and each of which has been shown to be mutagenic in the Ames assay. For example, it is estimated that therapeutic coal tar preparations may contain anywhere from 0.06 to 0.9% benzo(a)pyrene by weight. Saperstein and Wheeler have previously shown that as little as 100 μg of crude coal tar is mutagenic in the Ames assay [15]. Many patients with psoriasis undergoing the Goeckerman regimen may be treated with the topical application of several hundred grams of crude coal tar daily and it is not surprising that trace amounts of this material could be absorbed into the body. The studies of Wheeler, Saperstein, and Lowe unfortunately have not identified the mutagenic material in the urine extracts of the patients. Is it simply trace amounts of absorbed coal tar, is it one or several chemical constituents of the tar or is it metabolites of these?

It is imperative to maintain a clear perspective in interpreting the significance of the findings of Wheeler, Saperstein, and Lowe. The presence of unidentified mutagenic material(s) in the urine of patients treated with coal tar is a most interesting and important observation. It reinforces the necessity to continue careful surveillance of all patients treated with these agents. These preliminary findings should not, however, discourage the use of coal tar products in the management of patients with dermatologic disease who are appropriate candidates for the use of these drugs. Many therapeutic agents that are widely used in medical practice have significant potential to cause toxic effects. The risk/benefit ratio must always be considered in selecting any potentially harmful treatment for human disease. At this time the beneficial effects of coal tar products continue to outweigh the risks associated with their use. In the future it is hoped that newer and potentially less toxic-treatment modalities will be developed thereby rendering obsolete the use of coal tar products.

REFERENCES