INTRODUCTION

The relationship between the environmental chemicals and the increase of lung cancer in man is now well established. In fact, the first occupational cancer reported by Pott in 1775 (23,24) was caused by a complex mixture of coal soot. In this case the soot in contact for long periods with the scrotal skin of chimney sweeps induced local irritation and squamous cell carcinoma. We can also cite the epidemiological evidence for a correlation between the increase of lung cancer and exposure to cigarette smoke and industrially polluted atmospheres (12-14).

In 1915-1918, Yamagiwa and Itchikawa demonstrated the carcinogenicity of coal tar in rabbits and mice (26). The identification by Kenna­way's group of benzo(a)pyrene (BaP) in coal tar (15) started a major scientific endeavor to understand the role of this carcinogen and the other polycyclic aromatic hydrocarbons (PAHs) in the potential carcinogenicity of PAH mixtures in the air. Based on the carcinogenicity of BaP in animals, it was proposed as an indicator for air quality in terms of cancer hazard. Subsequent studies on the mechanism of tumor initiation (1) and the relationship between its mutagenicity and carcinogenicity (22), led to the utilization of short-term mutagenicity bioassays for detection of the carcinogenic potential of complex environmental mixtures.

The objectives of the studies described here were to evaluate the carcinogenic potential of complex mixtures and to elucidate lung cancer etiopathogenesis. At the beginning our research was concerned essentially with the cigarette smoke condensates (CSCs), but later this work was extended to diesel exhaust extracts, city air pollutant extracts (7), and water organic micropollutants. This chapter summarizes the in vitro and in vivo studies of cigarette smoke condensates and diesel exhaust extracts.
About 1960, it was accepted that tobacco smoke is a cancer hazard. As it was impossible to stop people from smoking, the elaboration of a safer cigarette appears obvious. The problem to us was how to evaluate rapidly and with some certainty the quality of the various tobaccos and cigarettes in terms of carcinogenicity. At the time, the choice was very limited. However, Guerin and Cuzin (11) developed an epidermal hyperplasia induction (EHi) test combined with the already-existing sebaceous gland destruction (SGd) test (2,25), and two short-term skin tests for carcinogenic potential, detection, and evaluation (17). So, these tests were adopted for screening investigations on carcinogenic potential of pure and complex chemicals. Simultaneously, to verify the correlations, long-term skin tests and inhalation experiments for carcinogenicity were performed.

As the inhalation experiments about 1960 were negative, we assumed that the smokers were also exposed to some other carcinogens playing the role of initiator, implicitly tobacco tar playing the role of promoter, we used for long-term skin tests on normal mice and BaP-pretreated (initiated) mice.

Results

We studied more than 1,000 CSCs in short-term skin tests, more than 40 CSCs in long-term skin tests, and some cigarettes in long-term inhalation experiments. One part of the data was published (3,19,20). Briefly, the two short-term skin tests, SGd and EHi, showed a dose-response relationship opening the possibility of comparative evaluations, the results of the two tests are correlated in between; finally they correlated well with the results from long-term skin tests and particularly with the promoting activity of the CSCs. Actually we know that EHi is related to the promoting effect through epigenetic mechanisms.

Association of Skin Tests and Inhalation Experiments

The results from short- and long-term skin tests with two CSCs (A and B) showed that CSC-A, compared to CSC-B, induced higher levels of epidermal hyperplasia, and exhibited higher carcinogenic and promoting activities in the same manner as 12-0-tetradecanoylphorbol-13-acetate (TPA) and phorbol, 12,13-didecanoate (PDD) (5). At the section entitled "Discussion," I will cite the results from direct cell exposure to diesel exhaust. To verify if such a difference should appear in an inhalation experiments, Syrian hamster cells were exposed to the smoke of cigarettes A and B using Borgwald (Hamburg) smoking machines according the Dontenwill's method (9). The results expressed as total proliferative lesions in the respiratory tract (larynx, trachea, lung) (Tab. 1) and tumors (Tab. 2)—clearly confirmed the results obtained with the respective CSCs in short- and long-term skin tests. The smoke of cigarette A induced more local (respiratory tract) proliferative lesions than the smoke of cigarette B. The smoke of cigarette A also significantly increased the incidence of other tumors. Thus, it appears that cigarette B is less hazardous based on the lower inactivity in these different tests for carcinogenicity. Cigarette B also had three times less tar per cigarette.