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THE CIGARETTE AND LUNG CANCER

Nothing is more necessary in discussion than a rest period; it is comparable in principle to the refractory state of nerve tissue, and like it should lead to subsequent continued activity. With this in mind we are glad to publish the following excellent retrospective comment on the relationship between cigarette smoking and lung cancer. It is taken from the CANCER NEWSLETTER *for February 1960 published by the Canadian Cancer Society.*

It is ten years since the first report suggesting a causal relationship between lung cancer and smoking was published; it is over five years since evidence was presented that there were substances in the tar of tobacco smoke which could cause cancers of the skin of experimental animals.

These reports were followed by debate and by acrimony which have not subsided. Indeed, the scientific and lay press have continued to print new evidence in support of, and argument against, the truth of the validity of the relationship.

Since the future of a very large and prosperous industry may be dependent on the outcome of the argument, it is understandable that there have been strong emotional overtones. These have been heightened by another factor which will be mentioned below.

From the welter of statement and counter statement several contributions emerge as being particularly worthy of study. The first is from the Medical Research Council of Great Britain. After reviewing the statistical and laboratory evidence, the report concluded that a "proportion of cases [of lung cancer], the exact extent of which cannot be defined, may be due to atmospheric pollution. Evidence from many investigations in different countries indicates that a major part of the increase is associated with tobacco smoking, particularly in the form of cigarettes. In the opinion of the Council the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect."

The second statement was from the U.S. Public Health Service. After reviewing the evidence it concluded that "the weight of the evidence is increasingly pointing in one direction; that excessive smoking is one of the causative factors in lung cancer".

These statements were released in 1957. At that time a similar review was undertaken by a committee of the National Cancer Institute of Canada. Its conclusion was that "while it has not been established that cigarette smoking is a cause of lung cancer, statistical studies show that cigarette smokers have a greater risk of dying of lung cancer than have non-smokers, and the risk increases with the amount smoked".

In November of last year the Surgeon-General of the United States restated the belief of the Public Health Service that smoking was the principal cause in the increased incidence of lung cancer, and that no method of filtering the smoke or treating the tobacco had been demonstrated to be effective in reducing this hazard.

The evidence which has been examined by all of these groups consists of a number of studies carried out in several countries. The studies have been of two types. In the first type, called retrospective studies, groups of patients with lung cancer were investigated to determine their smoking habits. In the second type, known as prospective studies, samples of the population have been selected, the smoking habits of its members have been determined and the causes of death over a period of some years have been tabulated.

The findings have been consistent in each type of study; the death rate for men smoking cigarettes has been up to forty times that of non-smokers.

It will be noted that the statements quoted have used such terms as "the most reasonable interpretation", "the weight of evidence is pointing", "while it has not been established that cigarette smoking is a cause of lung cancer". These qualifications have been applied because of several unresolved questions. For example, it has been claimed that the samples of population chosen have not reflected the situation for the general population accurately; it has been claimed also that statistical evidence is subject to misinterpretation as compared with experimental evidence: the critics point out that the smaller increase in lung cancer in women has not been adequately explained and that the possible contribution of atmospheric pollution to the problem remains to be determined.

When the debate reached public attention for the first time there was a temporary decrease in the sale of cigarettes in the United States which persisted for approximately two years. Since then there has been an annual increase. In 1957—the year when two of the major statements, referred to above, were released—the increase in consumption was approximately 6%. This was considerably greater than the increase in population. This in-

crease in the face of widespread public discussion illustrates the second major factor which has given the matter such emotional content—the fact that smoking is a form of addiction. No other reason would be a satisfactory explanation to the findings in a recent survey that half of all smokers questioned would like to give up smoking if they could do so easily. By comparison, the result of one public statement to the effect that a certain chemical which had been used in connection with the growth of cranberries and produced cancer in rats, led to a collapse in the market for that food.

One of the most severe critics of the conclusions drawn from the statistical studies, a distinguished scientist, admits that there may be cause for concern and that it would be a rational attitude for one to say, "there seems to be some danger, I can't assess whether it is infinitesimal or serious. This habit of smoking isn't very important to me. I will give up smoking as a kind of insurance against a danger which I am unable to assess."

There is much that remains to be done to settle the dispute. Statistical studies, such as those already described, should be continued. The search for specific agents in tobacco smoke which may be harmful should be maintained and the contributions to the problem from other sources, such as the pollution of the urban air by industrial waste, should be assessed.

The Canadian Cancer Society believes that those of teenage who are deciding whether or not to smoke should be made aware of the possible risk associated with the practice. For this reason its pamphlet intended for use in the schools outlines the evidence and suggests that this should be taken into consideration along with other factors which might influence the decision.

Editorial Comments

INTERFERON

Following Hoskins'[1] observation that a neurotrophic strain of yellow fever virus protected monkeys against a viscerotrophic strain of this virus, and the subsequent demonstration[2] that monkeys inoculated with Rift Valley fever virus were protected from infection with the antigenically unrelated yellow fever virus, numerous examples of viral interference have been encountered. Prior intracerebral inoculation of MEL virus, a non-neurotrophic strain of influenza, interfered with multiplication of a serologically distinct neurotrophic strain NWS;[3] and non-neurotrophic PR8 influenza virus interfered with proliferation of western equine encephalomyelitis virus in mouse brain.[4]

In tissue cultures, Andrewes[5] found that influenza virus strains WS or PR8 inhibited multiplication of strain NWS. Recently, viruses grown in tissue culture from patients with common colds[6] interfered with multiplication of para-influenza I and ECHO II viruses.

Influenza virus inactivated by heat[7] or ultraviolet irradiation[8-10] interfered with multiplication of either homologous or heterologous strains of living virus inoculated subsequently. Solid interference was established in the shortest time if large doses of inactive virus were inoculated,[11] but limited multiplication occurred if active virus was inoculated two hours or less after inactive virus.

Myxoviruses including influenza, mumps, Newcastle disease, and para-influenza carry an enzyme (neuraminidase) which specifically destroys all receptors for this group. Ultraviolet-irradiated Newcastle disease virus[12] interfered with growth of active homologous virus by destruction of cell receptors. However, heated influenza virus without enzymic activity[7] induced interference, but ultraviolet-irradiated virus lost its interfering activity before its neuraminidase activity was affected.[13] Factors other than destruction of cell receptors seemed to be responsible for interference.

When chick-embryo chorioallantoic membrane was incubated with heat-inactivated influenza virus, a substance called interferon was produced.[14] Interferon[15, 16] is a protein, slightly smaller than antibody, molecular weight *ca.* 100,000, non-antigenic, and stable at pH2; it possesses low tissue toxicity and is produced by cells of many animal species after incubation with living or inactivated viruses.

Interferon inhibits the growth of many myxoviruses, pox viruses and arthropod-borne viruses in chick embryos,[14, 15] rabbit skin[17] and tissue culture,[18] although it does not inactivate these viruses *in vitro*. It does not affect the absorption of these viruses to cells. Several hours elapse before interference is established, following incubation of tissues with interferon at 37° C. Interferon produced by chick cells protected chick-embryo cells against infection by viruses.[17] This principle has been employed satisfactorily for assay of interferon by plaque reduction.[18] However, interferon derived from chick cells did not protect rabbit cells against viral infection,[17] nor did rabbit cell interferon protect chick-embryo cells from infection with vaccinia virus.

Interferon stimulates glycolysis in chick-embryo fibroblast culture cells as shown by increased CO_2 production relative to amount of oxygen absorbed, and increased lactic acid production.[19] However, no effect on cell division has been observed so far. Increased glycolysis was found in MCN cells persistently infected with Newcastle disease virus.[20] These cells were resistant to superinfection with vesicular stomatitis virus. This resistance was due to production of interferon by persistently infected cultures.

Following infection of human kidney cells with a chick-embryo adapted type II poliovirus, a factor was produced which inhibited growth of homologous virus in human amnion cultures, and of heterologous polioviruses and Sindbis, vaccinia and herpes simplex viruses in human amnion or human kidney cells.[21] This inhibitor was distinct from active virus or viral antigen, and closely resembled interferon.