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CIGARETTES AND CANCER

The steady increase in the recorded deaths from cancer of the lung is startling. In 1922 there were 612 deaths from this cause in England and Wales, compared with 9,287 in 1947—a fifteenfold increase. The trend is the same in all countries where Western civilization is predominant, except apparently in Iceland. There can be little doubt that the incidence of cancer of the lung is really increasing, and tarred roads, exhaust gases, common respiratory infections, certain types of occupation, and tobacco smoking have all been blamed for the greater frequency of the disease. Of these possible causes smoking seems the most likely, for the rise in the death rate from cancer of the lung has followed a great increase in the consumption of tobacco and cigarettes. Several groups of workers have undertaken investigations to prove or disprove the suggested association. It is not easy to adopt an unbiased attitude to the concept that smoking may cause cancer: we are all either smokers or non-smokers, and each group may regard the other as prejudiced. It is said that the reader of an American magazine was so disturbed by an article on the subject of smoking and cancer that he decided to give up reading. Those who smoke more than 40 cigarettes a day, allowing ten minutes per cigarette, are occupied with smoking for about 6½ hours. There are no days off, and therefore the heavy smoker smokes for about 46 hours a week. This almost amounts to an occupation. Moreover, smokers heavily outnumber non-smokers, and this complicates statistical considerations. Even so, the proof that cancer of the lung is associated with smoking must obviously be based on statistical and not on clinical evidence. In this country Dr. Richard Doll and Professor A. Bradford Hill, whose paper is published in the opening pages of this issue, have carried out a meticulously conducted inquiry, the results of which have very serious implications, for they conclude that "smoking is a factor, and an important factor, in the production of carcinoma of the lung." They also put forward the admittedly speculative suggestion that above the age of 45 the risk of developing the disease is fifty times as great among those who smoke twenty-five or more cigarettes a day as among non-smokers.

The ideal investigation would be to compare the incidence of lung cancer in a population exclusively com-

posed of non-smokers with that in populations composed of smokers of various grades, from very light to excessive. The method adopted by Doll and Bradford Hill, who began their inquiry in 1947, was to obtain notifications of patients with cancer of the lung, stomach, and large bowel from twenty London hospitals, and to arrange for the interview of these patients by one of four almoners who were allotted to this work. The patients with cancer of the stomach and large bowel served for purposes of comparison, but the almoners also interviewed a control group of patients who did not have cancer but who, case for case, were of the same age and sex as the patients with cancer of the lung. The patients thus interviewed amounted to 2,475 and included 489 cases of cancer of the lung confirmed by necropsy, biopsy, or exploratory operation, and 220 others in whom the diagnosis was probably correct but made on different grounds. All the patients were asked whether they smoked or not, and, if they smoked, how many cigarettes or ounces of tobacco. An obvious preliminary difficulty was to decide where the line should be drawn between smokers and non-smokers, and also how to classify those who had once been smokers but had stopped. The definition of a smoker adopted in this inquiry was "a person who had smoked as much as one cigarette a day for as long as one year."

By comparing the proportion of patients with lung cancer who were smokers and the proportion of smokers in the comparable group of patients without lung cancer, Doll and Bradford Hill were able to show not only that the vast majority of men with carcinoma of the lung had been smokers at some period of their lives but also that the very small proportion (0.3%) of those who were non-smokers was most significantly less than the corresponding proportion (4.2%) in the control group. Further, there were relatively more heavy smokers among the patients with cancer of the lung (26% of the men and 14.6% of the women) than among the controls (13% of the men and none of the women). The risk, in fact, seemed to vary in approximately simple proportion to the amount smoked. Very similar results to those obtained by Doll and Bradford Hill have recently been reported from the U.S.A. by Wynder and Graham.¹ Their study covered 684 cases of bronchogenic carcinoma, 634 of the patients having been personally interviewed. They found that the non-smokers among male patients with cancer of the lung amounted to 1.3% of the total, compared with 14.6% of non-smokers among men in the general hospital population without cancer. Whereas only 19.1% of men in the latter were classified as "excessive and chain-smokers," as many as 51.2% of the patients with cancer came into this category.

In a recent report from Iceland Dungal² has drawn attention to the comparative rarity of lung cancer in

that island. His study is based on the records of 1,939 necropsies performed in Reykjavik from 1932 to 1948. There were 417 malignant growths in this series and 12 cases of primary lung carcinoma. This is a very much smaller proportion than is found in other comparable communities. Dungal points out that smoking, and particularly cigarette smoking, has only recently become popular in Iceland on a scale at all resembling that in most European countries. In 1945 the consumption of tobacco per head in Iceland reached 1 lb. per annum, whereas this figure was passed in Great Britain as long ago as 1920. It remains to be seen whether the incidence of lung cancer increases in Iceland during the next twenty years.

In the English investigation great pains were taken to avoid any sort of bias. The most likely source of error would seem to be in the interviewing, for even those who have no possible reason for being untruthful can be badly let down by their memories. Nevertheless, it is difficult to suggest what other precautions Doll and Bradford Hill might have taken to counter all possible criticisms of their method of investigation. They have even been able to show statistically that the results were in no way influenced through the fact that the interviewers knew in most cases whether or not the patient they were questioning had cancer of the lung. One unexpected result of the investigation was that inhaling cigarette smoke was not distinctly associated with lung cancer. In fact patients with this disease inhaled slightly less often than the controls. Wynder and Graham found that the proportion of men who smoked cigarettes as opposed to pipes among the patients with bronchogenic carcinoma was greater than that among the general hospital population of the same age-group, and they concluded that "the greater practice of inhalation among cigarette smokers is believed to be a factor in the increased incidence of the disease." Doll and Bradford Hill also found that pipe smoking was less closely related to cancer of the lung than cigarette smoking. They were not able to demonstrate with the data at their disposal that cancer of the lung is commoner in men than women because men smoke more, but they do suggest that their findings are consistent with the theory that, apart from the influence of smoking, the risk of developing carcinoma in the lung is the same in both men and women.

There is shortage of convincing experimental evidence about tobacco as a cause of cancer. Animals subjected to an atmosphere of smoke from mechanically smoked tobacco can be compared, not with smokers, but with non-smokers in a smoking compartment. It has never been proved experimentally that carcinogens are formed during the smoking of tobacco, though this would

not be surprising in the light of the probable results of destructive distillation of any organic matter under conditions of restricted oxygenation. Kennaway³ prepared carcinogenic tar from such different material as yeast and human skin. The distillation of coal in gasworks yields carcinogenic tar, and workers in the tar and pitch industry are eligible for compensation if they contract cancer of the exposed skin. Apart from the carcinogens which may be formed as a result of the burning of tobacco, it is also possible, as Doll and Bradford Hill point out, that arsenic in the insecticides with which the tobacco plants are sprayed could act as a carcinogen.

The practical question which the doctor in practice has to answer is whether any of his patients—for instance, those with smoker's cough—should be advised to give up smoking. In most textbooks of medicine and pathology reference is made to betel-nut chewer's cancer of the mouth. This is accepted as a well-established case of causal relationship, yet the actual incidence of cancer of the mouth in the population at risk would be difficult to compute accurately, since the habit is almost universal in many Asian communities. Certainly most betel-nut chewers do not contract cancer of the mouth; nor do many pitch and tar workers contract cancer of the skin, nor chimney-sweeps cancer of the scrotum. There is no evidence about the degree of risk which cigarette smokers take, but it does apparently increase in direct proportion to the amount smoked daily and to the total duration of the habit.

MECHANISM OF RELIEF IN RHEUMATOID ARTHRITIS

Increased fat deposition is one of the signs of Cushing's syndrome, many of the metabolic features of which are widely attributed to increased adrenal cortical activity. Knowledge of the alterations in fat metabolism caused by adrenal steroids is less far advanced than that of changes in carbohydrate metabolism. The deposition of liver glycogen which may be thus induced is accompanied by hyperglycaemia and glycosuria. There is also known to occur a process of gluconeogenesis whereby the conversion of amino-acids to carbohydrates is increased. This process will not account for the total increase in carbohydrate which may be observed—which suggests diminished utilization. Carbohydrates "spared" in this way may undergo conversion to fat. Since Kendall¹ showed that 11-dehydrocorticosterone could induce an increase in the total fat content of the mouse carcass there has not been much work on this problem, though Evans and his colleagues² succeeded in demonstrating that adrenocorticotropin had the same effect on hypophysectomized rats. Ingle and his

¹ *J. Amer. med. Ass.*, 1950, **143**, 329.

² *Lancet*, 1950, **2**, 245.

³ *J. Path. Bact.*, 1924, **27**, 233.

Finally, I would ask all those interested in animal welfare whether they are happy about the facilities for laboratory inspection, and whether they have never met a physiologist whom they thought would be better employed outside a laboratory.—I am, etc.,

London, W.2.

H. ROBINSON.

Bact. coli and Infantile Gastro-enteritis

SIR,—The letter from Dr. C. Giles (*Journal*, September 2, p. 577) tends to emphasize the role of *Bact. coli* in infantile gastro-enteritis, and at the same time the existing muddle in the classification of *Bact. coli* organisms. At the risk of perhaps increasing the muddle for some, and yet, I trust, of clarifying it for others, may I call attention to a classification put forward by me in 1943 of such organisms as I consider play an important role in this and like conditions (see my *Synoptical Table of Aerobic Excretal Bacteria*¹)? As a matter of passing interest the term "beta" is therein used over and over again to define serological types of *Bact. coli* belonging to differing biochemical subgroups.

That a multiplicity of phage-susceptible coliform organisms appears to be concerned in the gastro-enteritis of infants is borne out by the records of Dr. Bathia Kanievsky, who in an unpublished investigation into the use of tablets of dried phage carried out in 1943 at a child-welfare clinic in Alexandria recorded a curative response in six out of seven cases treated. Her cases ranged in age from 4 months to 2 years. The phage-preparation employed was made at the expense of 80 coliform organisms of my C₁ to C₆ subgroups (see the aforementioned table), 45 dysentery group organisms, 39 salmonella group organisms, 24 meta-dysentery group organisms, and 18 giunai-form group organisms, all phage-susceptible, which had been isolated by me from intestinal upsets ranging from simple diarrhoea to full-blown bacillary dysentery at all ages in the Alexandria area. Dr. Kanievsky's failure case, which was unaffected by sulphaguanidine, responded ultimately to "enteroviform." But as no laboratory work was done on the case it is just possible the infection may have been of a lamblial rather than of a bacterial origin, which, if so, would account for the seeming phage-therapy failure.

With the writer of your annotation (*Journal*, July 22, p. 205) I am afraid I cannot agree, that the close association between infantile diarrhoea and *Bact. coli* was first recognized in this country. If he will consult my writings of 1941-4² he will find abundant evidence that in Egypt we were fully aware of such connexion, and took steps to deal with it, as concerns both adults and infants.

Your annotator finishes by challenging the belief that certain *Bact. coli* cause infantile diarrhoea, and states that this "at present rests only on epidemiological evidence." The assumed epidemiological causes operating, and the specific treatment effects realized, in our work with Dr. Kanievsky constitute to my mind quite definite additional evidence of a cause and effect connexion here.—I am, etc.,

London, W.2.

ARTHUR COMPTON.

REFERENCES

- ¹ Compton, A., *C.R. Soc. Méd. et Hyg. trop. d'Egypte*, 1943, 8, 124.
² *British Medical Journal*, 1941, 2, 280; 1942, 1, 719; 1942, 2, 676; 1943, 2, 178; *Lancet*, 1944, 2, 865; 1944, 2, 192; *British Medical Journal*, 1944, 2, 641.

Cigarettes and Cancer

SIR,—I would like to be allowed to comment briefly on the able and instructive paper by Dr. R. Doll and Professor A. Bradford Hill in your issue of September 30, page 739. The spectacular sudden increase in carcinoma of the lung began about the end of the first decade of the present century. During the greater part of last century, and at least the earlier years of this one, men in debilitating climates chain-smoked strong cheroots, yet carcinoma of the lung was a rarity. During the first five years of this century there was no sign of any increase in that condition, yet I should think that arsenical sprays were by then in use. Apart from this, industrial diseases associated with working with arsenic have never included carcinoma of

the lung. The new increase in the disease has not spared non-smokers and children and those who live in countries where non-urban roads are not tarred and where there is no factory contamination of the air. In these circumstances surely none of these factors can be the cause of the suddenly increased incidence. Whether they are capable of aggravating it is doubtless another question.—I am, etc.,

Stanmore, Middlesex.

H. GALL,
Colonel, late R.A.M.C.

SIR,—The article in the *Journal* (September 30, p. 739) shows that pipe smoking is less closely related to cancer of the lung than cigarette smoking. This suggests an interesting possibility—i.e., that it is the saltpetre or other substance used to make the tobacco more easily inflammable that is the carcinogen.

It is well known that manufactured cigarettes contain more of this substance than pipe-smoking tobaccos. If the "roll your own" cigarette smokers were subjected to the very interesting analysis that has been carried out under the headings of cigarette and pipe smokers, the result might well put them in the pipe-smoking liability class. Should saltpetre be definitely incriminated it would be easy to make smoking less lethal. Of course the pipe smoker does not smoke burnt paper.—I am, etc.,

Essex.

ERIC J. TRIMMER.

SIR,—In your leading article (September 30, p. 767) you state, quite correctly, that those who smoke 40 cigarettes a day are occupied with smoking for about 46 hours a week. I should like to point out, however, that the average number of inhalations per standard size cigarette is about 13, each inhalation of approximately eight seconds' duration. The person who smokes 40 cigarettes a day therefore spends most of his smoking time simply burning tobacco. His lungs will be full of smoke for about 69 minutes per day, 104 seconds per cigarette, or just over eight hours per week.—I am, etc.,

Midlothian.

A. D. COLLEDGE.

SIR,—In "A Counterblast to Tobacco" James I seems to have reached much the same conclusion as Dr. Doll and Professor Bradford Hill (*Journal*, September 30, p. 739), although admittedly on less scientific and laborious lines. "A custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black, stinking fume thereof nearest resembling the horrible Stygian smoke of the pit that is bottomless."—I am, etc.,

London, W.1.

A. PINEY.

Safety in Prams

SIR,—Following the recent letter of Dr. David Thomas (*British Medical Journal*, July 22, p. 219) a good deal of publicity has been given to the subject of accidents to children through prams tipping, but I have yet to read a really authoritative and instructive statement on the matter by anyone competent to make one. I claim to know something of this subject, having dealt with this problem many times during a period of over a quarter of a century in the retail pram trade, and I propose therefore to supply the facts of the case, which I think the public are entitled to know and which the trade will do well to study.

First let me say that in spite of all this publicity the actual number of accidents is extremely small and mothers need not fear that in buying any reputable make of pram they will be taking any undue risk. My recommendation on this point is—go to a firm of repute and on the advice given select a make of repute. No pram by any reputable maker will tip unless misused, which usually happens in one of the following ways:

(a) Tipping forwards through overloading at the handle end by excess weight in shopping receptacles.

(b) Tipping forwards through the wrong use of a single pram for two children.

(c) Tipping backwards through wrong use of the safety-strap.

(a) Requires no special explanation, as the remedy is obvious—do not carry excess shopping if it can be helped, and if it must be carried put some of it in the well and as far back in it as space will allow.