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"I have said that we should try to think with the whole of our past. One of the thoughts most strongly induced by this practice concerns the unevenness of progress. The most striking gains prove, on examination, to have involved serious loss. An example is alphabetic writing. This surely, one would think, is a wholly beneficent achievement of human ingenuity. It was, in fact, a necessary pre-condition of the emergence of large-scale organization, yet it wrought so decisive a change in human consciousness that it all but obliterated the memory, and certainly destroyed the understanding, of the age-old culture of pre-literate societies. The invention of the alphabet blinded men to the knowledge of some thousands of years of our human story. Much research and a great effort of the historical imagination were needed to restore to the twentieth century an appreciation of the oral cultures which writing destroyed. Yet so accomplished a stylist as Plato was near enough to the world of oral tradition to view the dissemination of the alphabet with a critical eye. He had two main fears. One, that writing would impair the memory. Has it not done so? 'Without writing,' notes Tom Harrison, 'memory is perfect, tradition exact.' Secondly, Plato felt that a book was an inadequate substitute for a living teacher. We may note that the two greatest teachers in the European tradition, Socrates and Jesus, never wrote a book. In our own educational practice at its best, books are treated only as an adjunct to the spoken word." ("Science and the Classics," Professor B. Farrington, *Nature*, September 30, 1961.)

TOBACCO SMOKING AND VENTILATORY FUNCTION OF THE LUNGS

BY

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It is a matter of everyday clinical observation that the majority of patients with chronic obstructive lung disease* give a significant history of tobacco smoking. In the minds of many this leads to the undocumented extrapolation that "smoking causes bronchitis."

A number of clinical studies have convincingly demonstrated an increased incidence of cough and sputum among smokers (see Higgins, 1959). Studies relating objective assessment of lung function to smoking habits are less susceptible to simple or uniform interpretation. At the international level (United Kingdom versus Denmark) a higher incidence of smoking in a community (U.K.) has been shown to be associated with a lower mean maximum breathing capacity (M.B.C.) (Olsen and Gilson, 1960). Smokers have been found to have a lower mean M.B.C. than non-smokers in both urban and rural areas of Great Britain (Higgins, 1957, 1959). Maximal expiratory flow rate (M.E.F.) has been shown to diminish more rapidly with increasing age in smokers than in non-smokers in a group of hospital in-patients (Flick and Paton, 1959). On the other hand, the diminution in ventilatory capacity does not run parallel with the amount of tobacco smoked (Higgins, 1959); differences between cigarette smokers and pipe smokers are sometimes more marked than differences between cigarette smokers and non-smokers (Olsen and Gilson, 1960); the scatter of ventilatory capacity among smokers as a whole is wide (Flick and Paton, 1959); and the position of ex-smokers is obscure (or even ignored) in some studies.

Sydney has a mild climate and an atmosphere that is relatively unpolluted compared with many parts of Northern Europe. Clinically, gross bacterial infection of the airways is far less common in patients with chronic bronchitis in Australia than it is in Great Britain. It was felt that a pilot study of ventilatory function in relation to smoking habits under these conditions might yield more straightforward data than earlier studies.

Methods

The subjects of the study were 302 people, aged 18 years or more, interviewed in the out-patient department of Sydney Hospital, in the following groups: (1) ambulant out-patients waiting to be seen at the gynaecology, urology, neurosurgery, general surgery, and dermatology clinics (general and special medical clinics were specifically avoided); (2) friends waiting with patients; (3) members of the medical, nursing, and lay staff associated with these clinics. On certain mornings and

*This term, recommended by a Ciba Guest Symposium (1959), is used in preference to the terms "chronic bronchitis" or "emphysema."

afternoons a female clerk unselectively asked people in these categories to co-operate in a simple investigation. Refusals were rare. From among these subjects only those with a personal history of bronchial asthma were subsequently excluded before analysis of the results.

For each subject a form was completed, giving details of age, height, weight, and occupation; and a personal history of respiratory illness and current respiratory symptoms (cough, sputum, dyspnoea). A detailed smoking history was obtained after this in an effort to avoid observer bias. All forms were completed by the same medical observer.

Each subject then performed a series of five maximal forced expirations into a Wright peak flow meter (Wright and McKerrow, 1959). The best value of the five was used in the presented results. All determinations of maximal expiratory flow rate were supervised by one observer.

A non-smoker was regarded as a person who had never smoked more than one cigarette a day for one year. All ex-smokers had ceased smoking at least three months earlier, so that no difficulty arose in separating smokers from ex-smokers.

Results

Table I shows the distribution of the 302 subjects by sex and smoking history. From the results obtained for maximal expiratory flow rate (M.E.F.) in non-

TABLE I.—Distribution of Subjects by Sex and Smoking Habits

	Males	Females
Non-smokers	46 (27%)	81 (61.5%)
Smokers	91 (53.5%)	43 (32.5%)
Ex-smokers	33 (19.5%)	8 (6%)
Total	170	132

smokers with no cough or sputum (44 males, 76 females) the best predicting regression equations were calculated for the prediction of "normal" M.E.F. in each sex at various ages (Selby and Read, 1961). These regression equations were:

$$\text{M.E.F. (l./min.)} = 3.2 H - 2.1 A + 71 \text{ (males).}$$

$$\text{M.E.F. (l./min.)} = 452 - 1.2 A \text{ (females less than 60).}$$

$$(H = \text{height in cm.; } A = \text{age in years.})$$

With these regressions a "normal expected" M.E.F. could be calculated for each subject in the entire series, and each observed M.E.F. could then be expressed as a *plus* or *minus* difference from the predicted value. The effects of body stature and the normal ageing process were thus standardized for the whole group. The individual results have been expressed in this fashion in Figs. 1 to 4, in which variation of observed from predicted M.E.F. is plotted against age. By definition on such a grid, the non-smokers without symptoms will have a mean on the zero line and a "range" extending 2 standard deviations above and below it. This mean and range are represented in Figs. 1 to 4 by the dotted lines. Any additional effects attributable to smoking should emerge as further downward regressions.

The results in the two non-smoking males with cough and sputum fell below the normal range.

Fig. 1 shows the results for male smokers who denied having any cough or sputum. Most fell within the normal range, but, looked at as a linear regression group, they did differ from non-smokers. They lost, on the average, an additional 2.23 litres per minute of M.E.F. each year compared with asymptomatic non-

smokers, and the difference in regression is significant ($P < 0.01$). In the individual cases the amount smoked did not appear important in determining the degree of ventilatory incapacity.

Male smokers with cough only (Fig. 2) formed a small but compact group. They lost an average of 3.2 litres per minute of M.E.F. each year more than asymptomatic non-smokers. They differed significantly from non-smokers ($P < 0.01$), but the difference between them and smokers without symptoms did not reach conventional levels of significance. Again, the amount smoked in the individual case did not appear crucial.

FIG. 1.—Ventilatory studies in asymptomatic male smokers (52). Ordinate: Variation of observed M.E.F. from predicted in litres per minute (see Results). Abscissa: age in years. The dotted lines represent the mean and ± 2 standard deviation range for asymptomatic non-smokers. Black squares: Heavy smokers; white squares: light smokers; crosses: moderate smokers.

FIG. 2.—Ventilatory studies in male smokers with cough only (18). Conventions as in Fig. 1.

FIG. 3.—Ventilatory studies in male smokers with cough and sputum (21). Conventions as in Fig. 1.

Male smokers with cough and sputum (Fig. 3) showed an even greater loss of ventilatory function with increasing age. They lost, on the average, 4.4 litres per minute of M.E.F. each year more than asymptomatic non-smokers. The difference from non-smokers was highly significant ($P < 0.001$) and that from smokers without symptoms just so ($P = 0.05$). The "mean" line for this group fell below the lower limits for asymptomatic non-smokers from the late forties onwards.

Ex-smokers (Fig. 4) formed a good replica of the asymptomatic non-smoking group. They had ceased smoking from 3 months to 40 years earlier. Even those with cough and sputum (black dots, Fig. 4) did not in general show the marked loss of ventilatory capacity seen in smokers with those symptoms. Only 2 out of 33 ex-smokers, both with cough and sputum, fell appreciably below the non-smokers' range.

FIG. 4.—Ventilatory studies in male ex-smokers (33). Black dots represent those with cough and sputum.

The results among women did no more than show a similar trend to the results among men: on statistical grounds they were not nearly so clear-cut. This may have been partly due to the smaller numbers of female smokers in each symptom-group, and especially of those over the age of 55. To summarize the female data: three (out of five) non-smoking women with symptoms had M.E.F.s within but at the lower limit of the asymptomatic non-smokers' range. Female smokers with no symptoms or with cough only did not differ significantly in ventilatory capacity from non-smoking females. Female smokers with cough and sputum showed a falling off of ventilatory capacity similar to that seen among males with these symptoms, but the correlation did not reach conventional levels of significance.

Table II shows the overall incidence of cough and sputum among smokers and non-smokers. The influence of duration of smoking and amount smoked (averaged over smoking life) on the incidence of symptoms (cough, or cough *plus* sputum) was examined for the male subjects. There was no significant increase

in the incidence of symptoms in increasing ten-year age-groups ($\chi^2 = 8.405$; $n = 5$; $P = 0.1-0.2$), nor did the incidence of symptoms differ significantly as between light (1-14 g./day), moderate (15-24 g./day), and heavy (> 25 g./day) smokers ($\chi^2 = 0.764$; $n = 2$; $P = 0.5-0.7$).

The group contained no pure cigar smokers, and only five pure pipe smokers. All five had M.E.F.s closer to the mean for cigarette smokers of the appropriate age and symptoms than to the mean for non-smokers.

Discussion

Note must be taken of the nature of the population used in the present study. It was certainly not a random population sample such as those of Higgins (1957, 1959) or Olsen and Gilson (1960). On the other hand, the use of ambulant "non-medical" out-patients, their friends and attendants, should obviate many of the objections to the use of hospital populations in general. The present group should be more representative of the general population than the hospital in-patient group studied by Flick and Paton (1959). Among the non-smoking asymptomatic subjects the results were examined separately for "patients" and "friends and staff." At all ages the mean values for M.E.F. were almost identical in the two groups.

The determination of M.E.F. with the Wright peak flow meter appears to be an acceptable measure of ventilatory function at the epidemiological level. Higgins (1957) found a high degree of correlation between the M.E.F. so measured and the M.B.C. Supervision of all the ventilatory tests by one observer should have overcome the variation in M.E.F. sometimes obtained by different observers in the same subjects (Dr. C. M. Fletcher, personal communication).

In seeking information about respiratory symptoms the subjects were first asked whether they ever coughed, and if so when and how often. If they denied cough, the question was reiterated as, "So you never cough, not even first thing in the morning?" A similar routine was followed in obtaining information about the sputum. Those who coughed at all first thing in the morning or who brought up any sputum at all were counted as having cough or sputum respectively. This did not provide the same detailed information of the admirable M.R.C. (1960) questionnaire on respiratory symptoms. However, Elmes *et al.* (1959) found that a person's replies to questions about cough and sputum do not necessarily correspond closely with the data recorded for him under observation, and we sought some basis for division, albeit relatively coarse, into groups with different clinical responses of the bronchial mucosa to the environment. In terms of likely errors, the group who denied cough and sputum is probably the most heterogeneous, containing some subjects with one or both symptoms. The group with "cough only" might really contain some with minimal amounts of sputum. The group who admitted both cough and sputum is unlikely to contain subjects with neither symptom.

Even granting the coarseness of the clinical criteria, separation into groups based on them led to certain functional correlations among male subjects. Among non-smokers the few with cough and sputum had a lower M.E.F. than those without these symptoms. Asymptomatic smokers showed a reduction of mean M.E.F. compared with asymptomatic non-smokers, but the presence of either cough or cough with sputum was associated with further decrements in ventilatory

TABLE II.—Percentage Incidence of Symptoms in Various Groups

	Males		Females	
	Cough + Sputum	Cough $\pm$ Sputum	Cough + Sputum	Cough $\pm$ Sputum
Non-smokers	4.4	4.4	4.9	6.2
Smokers	23.1	42.9	18.6	48.8
Ex-smokers	21.2	30.3	—	—
Smokers/non-smokers ratio	5.3	9.8	3.8	7.9

function. There was no distinction on the basis of M.E.F. between those who coughed only first thing in the morning and those who coughed during the day. To reduce the regressions to some absolute values, an average man aged 60, and 175 cm. tall, was likely to have an M.E.F. of 505 litres per minute if he was an asymptomatic non-smoker, compared with 322 litres per minute if he was a smoker with cough and sputum.

Elmes *et al.* (1959) demonstrated an inverse relationship between sputum volume and indirect M.B.C. in 118 London postal workers without regard to smoking habits. The present data confirm and extend the significance of their findings in showing a gradient of ventilatory loss from non-smokers, through smokers without symptoms, those with cough alone, and those with cough and sputum.

Division of smokers into three groups by symptoms illustrates a further point. Flick and Paton (1959) found a very wide range of values for ventilatory capacity among smokers in general with increasing age. In the present series separation of the smokers by symptoms has provided three groups of subjects with individual ranges of ventilatory capacity very little wider than that for asymptomatic non-smokers. In other words, Flick and Paton's "variable effect of smoking in different persons" at the ventilatory level is reflected in their symptomatic responses to smoking. At the international level, it is of interest that the rate of fall of M.E.F. in males with age in Higgins's (1957) general population sample in South Wales (6.34 litres per minute each year) is comparable with the rate of fall in the worst-affected group in the present series, smokers with cough and sputum (6.5 litres per minute each year, made up of 2.1 litres per minute for males in general and 4.4 litres per minute for their specific group). This would support the belief that chronic bronchitis and its sequelae are less dramatic in progression in Australia than in the United Kingdom; and add to the validity of the present study as one in which the effects of smoking are less complicated by "background" influences.

The data for ex-smokers (Fig. 4) indicate that the loss of ventilatory function associated with smoking need not necessarily be permanent. In general, M.E.F. in this group is entirely comparable with that for lifelong non-smokers. Even when cough and sputum persist (black dots, Fig. 4) most subjects' ventilatory function falls clearly within the normal range instead of showing the striking reductions of Fig. 3. Other considerations apart, these results suggest that, under atmospheric and climatic conditions such as those in Sydney, patients with reduced ventilatory capacity (with or without cough and sputum) may be advised to give up smoking with some confidence that their ventilatory function will improve. Only two ex-smokers with cough and sputum remained below the normal range for M.E.F.—essentially the same incidence (6%) as among non-smokers (4.4%).

Table II shows the incidence of these apparently important symptoms among smokers and non-smokers. Smoking is associated with a fourfold to fivefold increase in the incidence of cough plus sputum and an eightfold to tenfold increase in the incidence of all bronchitic symptoms.

It could be suggested that this increased incidence of bronchitic symptoms among smokers merely reflects a simple quantitative effect of tobacco smoking on the bronchial mucosa. If this were so, two corollaries ought to follow: increased tobacco consumption and increased

duration of smoking should be associated with an increased incidence of symptoms. It was demonstrated that neither of these two corollaries is true of the present data. Higgins (1959), too, "surprisingly" found no trend in M.B.C. with increasing tobacco consumption. (It is only fair to point out that by using another approach in *part* of the whole series a different interpretation might be reached: considering only smokers less than 50 years old, the asymptomatic group contains an excess, and the symptomatic group a deficiency, of light smokers. But, *per contra*, this relationship does not hold for those over 50.) Within individual subgroups of smokers, Figs. 1, 2, and 3 illustrate that there was no tendency for heavy smokers to have poorer ventilatory function than light smokers. Since the smoking categories were based on whole-of-smoking-life averages, they are not likely to be heavily biased by changes of smoking habits late in life consequent upon the development of symptoms or incapacity.

Genetic and Environmental Factors

The data thus do not support the hypothesis that smoking has a simple quantitative effect on the bronchial mucosa. Any alternative hypothesis must be largely speculative, but a study of the present data indicated that, within certain limiting assumptions, they were compatible with a hypothesis linking genetic and environmental factors.

Assume the existence of two alleles V and v such that homozygous VV subjects develop bronchitis and marked ventilatory loss even in the absence of external irritants, homozygous vv subjects do not develop bronchitis or marked ventilatory loss even in the presence of external irritants, and heterozygous Vv subjects only develop bronchitis and marked ventilatory loss in the presence of external irritants. In the present context the external irritant is tobacco smoke, but it might equally include atmospheric pollution and many other factors. The incidence of VV homozygotes in the group may be found from the proportion of non-smokers with bronchitic symptoms. The proportion of asymptomatic subjects among smokers would give the incidence of vv homozygotes.

In the Appendix it is demonstrated that the distribution of subjects by symptoms in the present study is entirely compatible with such a genetic hypothesis. There is one obvious statistical objection to its too ready acceptance: the calculations in the Appendix (though not the thesis itself) assume random genetic distribution among smokers and non-smokers. It has been pointed out that VV homozygotes, because of their "genetic weakness," might tend not to take up smoking or else rapidly to become ex-smokers. Also, heavy smokers appear to differ from light and non-smokers on one genetic ground—ability to taste P.T.C. (Thomas and Cohen, 1960). On the other hand, data which "fit" separately for males and females, and indicate similar allele frequencies for the two sexes, probably add a little further support to our thesis.

Such a hypothesis then would postulate a genetically determined reaction of the bronchial mucosa to an external irritant such as tobacco smoke. There is nothing intrinsically unacceptable in such a postulate on biological grounds. The similar incidence of cough and sputum plus reduced ventilatory capacity among non-smokers (4.4%) and ex-smokers (6%) could be interpreted by suggesting that these were the VV

homozygotes in each group. Among smokers, genotype would determine whether a subject remained asymptomatic and lost a moderate amount of ventilatory capacity, or developed bronchitic symptoms and lost a good deal more. On such an all-or-none basis for symptoms the amount and duration of smoking would cease to be a prime factor as in the present and in Higgins's data. Among ex-smokers the incidence of cough plus sputum was the same as that among smokers, but the incidence of cough alone was much less; it is suggested on this basis that the persistence or otherwise of symptoms in ex-smokers depends on their relative severity.

At present this hypothesis is offered as a speculative but not unsupported alternative to a direct and quantitative deleterious effect of tobacco smoking on the bronchial mucosa. It appears to merit further investigation.

Summary

Ventilatory capacity has been assessed in 302 subjects in Sydney in relation to smoking habits and respiratory symptoms. Among males, smoking, in the absence of symptoms, leads to some reduction of ventilatory capacity. The presence of cough or cough and sputum is associated with further impairment of ventilatory function. These same symptoms are associated with loss of ventilatory capacity among non-smokers. The ventilatory loss appears to be largely reversible in those who cease smoking. Among females there are similar trends, but the results are not nearly so clear-cut.

The data are not apparently explicable on the basis of a simple quantitative effect of smoking on the bronchial mucosa. As alternative hypothesis based on a combination of genetic and environmental factors is offered, and this alternative hypothesis is supported by the present findings.

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APPENDIX

Among males, assuming random genetic distribution among smokers and non-smokers, and using the groupings in "Discussion":

Incidence of ? VV homozygotes = 0.044 (2/46)
Incidence of ? vv homozygotes = 0.571 (52/91)
Incidence of ? Vv heterozygotes = 0.385 (by subtraction)

If these proportions obtained throughout the whole group of smokers and non-smokers (137) we would have 6.0 ? VV subjects, 52.7 ? Vv subjects, and 78.3 ? vv subjects.

On the basis of the Hardy-Weinberg law (Stern, 1949), we may calculate the expected number in each group if they follow the postulated genetic pattern, using the observed incidence in the ? homozygous groups and the ? heterozygous group to calculate allele frequencies. On this basis, the allele frequency of V (p) is 0.236 ($VV + \frac{1}{2}Vv$) and of v (q) is 0.764 ($vv + \frac{1}{2}Vv$). The expected frequencies of VV (p^2), Vv ($2pq$), and vv (q^2) subjects are thus 0.056, 0.361, and 0.584 respectively, and the expected numbers among 137 subjects become 7.6 VV, 49.4 Vv, and 80 vv. These correspond closely with the observed figures above, and on a statistical basis do not differ significantly from them ($\chi^2 = 0.5933$; $n = 2$; $P = 0.7-0.8$). As a further indica-

tion that the observed incidences would closely fit such a genetic hypothesis, we may apply the criterion that $\sqrt{VV} + \sqrt{vv}$ should equal 1. In this case they equal 0.964, a disagreement of less than 4% *pro rata*.

A similar measure of agreement may be calculated for the female data. The allele frequencies for females become 0.275 for V and 0.725 for v, not very different from the calculated male frequencies.

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TOBACCO SMOKING AND SERUM LIPIDS IN OLD MEN

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The interrelationships between coronary heart disease, serum lipids, and cigarette-smoking have been demonstrated by authors from several countries in recent years (Hammond and Horn, 1954; Gertler and White, 1954; Gofman *et al.*, 1955; Doll and Hill, 1956; Thomas, 1958; Karvonen *et al.*, 1959; Dawber *et al.*, 1959; Bronte-Stewart, 1961). Their work has, however, been chiefly concerned with men below or during middle age, whereas it seems that over the age of 65 years there is little relationship between death from coronary heart disease and a previous history of smoking (Doll and Hill, 1956) or between clinical evidence of myocardial ischaemia and raised serum cholesterol (Oliver, 1958; Acheson, 1961). It is therefore a matter of some interest whether serum lipids are related to smoking habits in men aged 65 and over.

Material and Method

The Sample.—The men were all pensioners on the list of Messrs. Arthur Guinness Son and Company Ltd. (Dublin), and their names were selected in a random manner as follows: every man aged between 75 and 85 was chosen, between the ages of 70 and 74 every third name was omitted from the list, and between the ages of 65 and 69 alternate names were omitted. This method of selection produced 267 names in all, and each man was sent a postcard inviting him to attend in the company's medical department for clinical examination; the actual attendances (221) are shown