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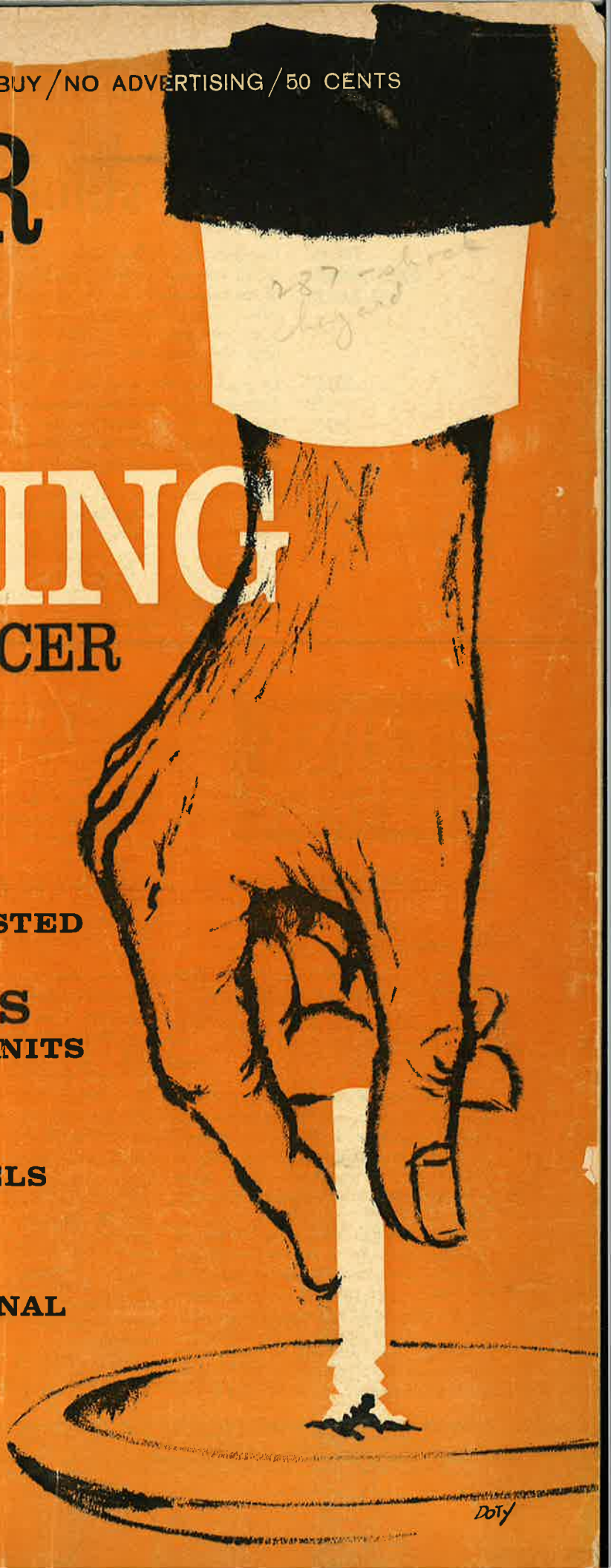
SMOKING AND LUNG CANCER

A point-by-point review of the whole range of evidence



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CONSUMER REPORTS

JUNE 1963 VOLUME 28 NUMBER 6

SMOKING AND LUNG CANCER

For detailed contents of this special 16-page section, see page 265

The cover drawing is adapted from a poster issued in Denmark by the Danish Organization for the Prevention of Cancer.

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The survey on this and the next 15 pages, in CU's judgment, constitutes a significant contribution to understanding of one of the most controversial health issues of the day. The material presented here, specially edited for this issue of the REPORTS, will appear in fuller form in "The Consumers Union Report on Smoking and the Public Interest," a major new CU book now on the press. The book, of which the section following represents about one-fifth, will be published during June, 1963. See back cover for details.

SMOKING AND LUNG CANCER

By RUTH AND EDWARD BRECHER *working with the Editors of* CONSUMER REPORTS, *CU's Medical Adviser, and other authorities*

A broad-scale, point-by-point review of the whole range of evidence implicating cigarettes in what has now become an international health problem. In four Parts:

I. WE ARE LIVING IN AN EPIDEMIC

The autopsy evidence

IN October 1920, a young University of Minnesota pathologist, Dr. Moses Barron, performed an autopsy on a 46-year-old male patient known in the medical records as L.H., and determined that he had died of lung cancer (primary carcinoma of the lung) This seemed curious, for another University of Minnesota pathologist had performed an autopsy two months before on a 42-year-old male patient, and had also found lung cancer. And then still another death from lung cancer was found later in the same month of October.

Dr. Barron had always supposed that cancer of the lung was an exceedingly rare disease. Sometimes a whole year went by without a single case among University of Minnesota autopsies. Three cases in three months aroused Dr. Barron's interest. During the months that followed his interest grew, for additional cases turned up at a rapid rate. Startled, now, Dr. Barron went back over the university's autopsy records and unearthed some facts

which he reported to the Minnesota State Medical Society meetings on August 25, 1921.

During the 20-year period from 1899 through 1918, Dr. Barron's study revealed, only four cases of lung cancer had been identified at autopsy by University of Minnesota pathologists. There had been only one case in 1919. Yet during the single year from July 1, 1920 through June 30, 1921, eight lung cancer cases had turned up. Was this, perhaps, the onset of an epidemic?

Pathologists generally present their statistics in a standard form: number of autopsies, number of cases of one kind, percentage of these cases to all autopsies. Thus a rate of 0.1% means one case in a thousand autopsies, while 1.0% means one case in a hundred. Cast in this form, Dr. Barron's figures revealed the following remarkable increase in lung cancer deaths:

1899 through 1918	0.1%	(4 deaths in 3399 autopsies)
1919 to July 1921	0.9%	(9 deaths in 1003 autopsies)

The conclusion seemed inescapable, and Dr. Barron cautiously drew it in 1921. "This disease," he wrote, "is apparently increasing in frequency, especially during the past few years." And he was right. For the period 1949 through 1952 the University of Minnesota rate reached 3.2% (264 lung cancer deaths in 8332 autopsies).

In various other parts of the world, autopsy records were telling substantially the same story. A rise was quite generally apparent, earlier in some places, later in others, often at about the same time as Dr. Barron's findings. Here, for example, are lung cancer rates drawn at five-year intervals from the autopsy records of the Charité Hospital in Berlin:

1908	0.3%	1918	0.6%
1913	0.4%	1923	1.5%

And here are the figures, for five-year periods, from Zurich, Switzerland:

1906-1910	0.1%	1916-1920	0.7%
1911-1915	0.5%	1921-1925	2.1%

All of the autopsy records, it is true, did not fit precisely this pattern. At the Royal Infirmary in Manchester, England, for example, the increase which Dr. Barron had noted in 1921 was visible much earlier. In Reykjavik, Iceland, lung cancer rates at autopsy remained low as late as 1948. But by and large the trend was irregularly upward beginning about 1920.

An autopsy series of particular value comes from Presbyterian Hospital in New York City, where Dr. David M. Spain reviewed the autopsy findings for the 45-year period from 1912 through 1956. The diagnosis of lung cancer depends primarily on the microscopic examination of cells taken from the lungs; Presbyterian Hospital had maintained microphotographs of cancer cells for its earlier autopsies and had actually preserved the cells themselves in microscope slides for the later autopsies, so that Dr. Spain was able to review the entire series personally and confirm or correct the diagnoses. His figures showed the following increase in lung cancer deaths:

1912-1921	0.6%	(6 deaths in 992 autopsies)
1922-1931	1.3%	(21 deaths in 1649 autopsies)
1932-1941	2.8%	(83 deaths in 2950 autopsies)
1942-1946	3.4%	(49 deaths in 1449 autopsies)
1947-1956	3.7%	(120 deaths in 3250 autopsies)

What was happening at Presbyterian Hospital was also happening at the University of Michigan, where 14,000 autopsies were performed from 1895 through 1954. As at Presbyterian Hospital, materials from the earlier University of Michigan autopsies were preserved and reviewed from time to time to confirm the lung cancer diagnoses and to make sure that cases diagnosable as lung cancer by modern standards had not been missed during the earlier years. The figures show a remarkably steady rise in lung cancer incidence for each thousand autopsies in the series:

	CASES OF LUNG CANCER		
1st thousand	0.2%	8th thousand	2.2
2nd thousand	0.8	9th thousand	2.4
3rd thousand	1.0	10th thousand	2.6
4th thousand	1.4	11th thousand	3.1
5th thousand	1.8	12th thousand	3.9
6th thousand	2.1	13th thousand	3.4
7th thousand	2.2	14th thousand	4.2

The rate thus rose from 0.2% to 4.2% during the sixty-year period from 1895 through 1954—more than a twenty-fold increase. (Comparable figures for University of Michigan autopsies since 1954 are not available.)

The death rate evidence

The autopsy figures presented above are all subject to a major shortcoming. They include for the most part only patients who died in hospitals and whose relatives consented to an autopsy. Evidence concerning so highly selected a group cannot be uncritically applied to the population as a whole. Suppose, for example, that during the early years of a series most lung cancer patients died at home; and that as time passed a larger and larger

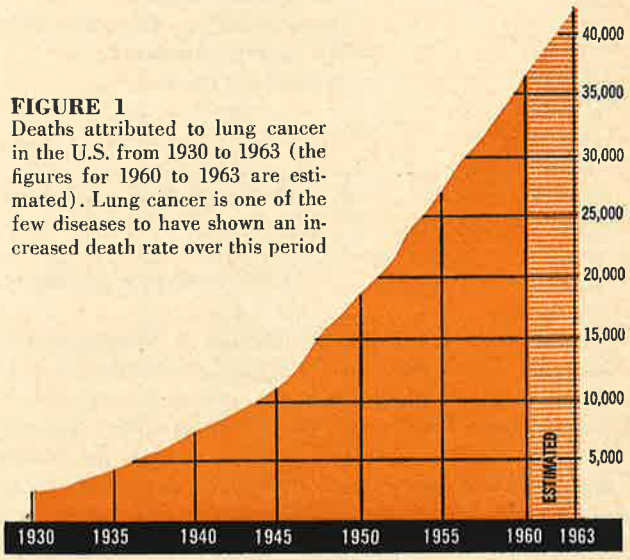


FIGURE 1
Deaths attributed to lung cancer in the U.S. from 1930 to 1963 (the figures for 1960 to 1963 are estimated). Lung cancer is one of the few diseases to have shown an increased death rate over this period

proportion died in hospitals and came to autopsy. This trend of events might have produced an *apparent* increase in lung cancer of the kind described above without any *actual* increase in the disease. To rule out this and other possibilities of this kind, the causes of deaths in a total population rather than an autopsied population must be considered. For this purpose death certificates offer the broadest possible evidence.

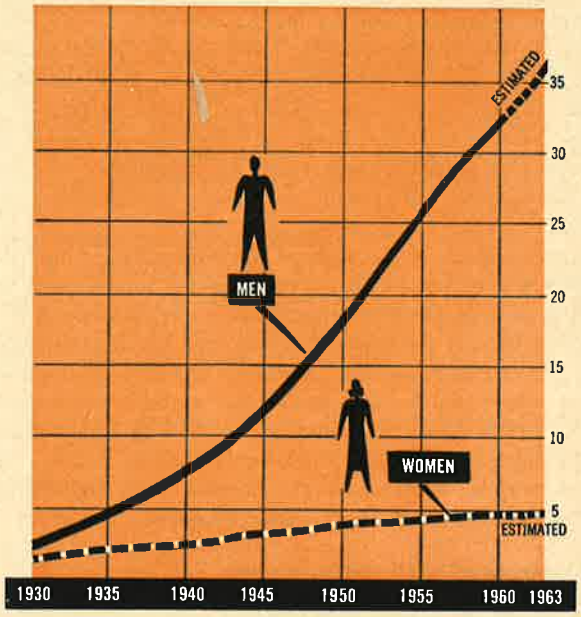
The death certificate data fully confirm the data from autopsies.

In the United States, for example, only 371 deaths were attributed to lung cancer in 1914. This number rose to 36,420 in 1960. FIGURE 1 shows the increase in graph form year by year from 1930 on.

This increase in number of deaths suggests the reason for the increasing public health concern with lung cancer. But the raw figures require corrections of several types. The U.S. population, for example, increased rapidly between 1914 and 1960; and the proportion of the population covered by uniform death certificate reporting also increased. Further, lung cancer is a disease of middle age and old age, and the proportion of the population living into the lung cancer age brackets increased considerably. Finally, the figures for the total population mask the marked differences between what was happening to lung cancer in men and in women. FIGURE 2, accordingly, makes allowances for these factors.

This epidemic, moreover, has not been limited to the United States. Indeed, the rise among men in Scotland, England, Wales, Finland, and some other countries has been even steeper.

FIGURE 2
Deaths attributed to lung cancer per 100,000 men and women in the U.S. from 1930 to 1963 (the figures for 1960 to 1963 are estimated). The figures are weighted to allow for the gradual aging of the population



Combining the evidence

Just as the autopsy evidence may be doubted on the ground that the sample of deaths coming to autopsy is a selected and untypical sample, so it is possible to doubt the death certificate evidence on the ground that physicians who fill out the certificates are not always sure of what *really* caused the death—and, in some cases, they may be merely guessing. Neither kind of evidence by itself proves that there was an actual increase in lung cancer deaths.

But when the autopsy evidence is combined with the death certificate evidence, the proof emerges very clearly. The figures based on autopsies performed by skilled pathologists at the world's great medical centers cannot be dismissed as mere guesswork; and the lung cancer death rates covering substantially all of the deaths in a dozen different countries cannot be dismissed as due to biased sampling. The criticisms of each body of evidence are answered by the fact that the other body of evidence tells the same story.

This theme of combining the evidence will reappear throughout this discussion. Only rarely can a single study, observation, or experiment stand by itself. Each of the studies we will report is subject to qualifications and limitations. But the points not covered in one study are soon covered by another study. Thus a wall of evidence is gradually erected.

During the early years of the lung cancer epidemic it was sometimes argued that the apparent increase in the disease might result from improved methods of diagnosis among physicians filling out death certificates, and from a greater alertness to lung cancer among pathologists performing autopsies.

No doubt a part of the apparent increase is due to such factors, but many separate lines of evidence indicate that most of the apparent increase is in fact a true increase.

First, the simple bulk of the increase makes improved diagnosis an inadequate explanation. Physicians and university pathologists prior to the 1920's might conceivably have missed one-half of the lung cancer deaths, though that is most unlikely. But it is utterly inconceivable that they should have missed nine lung cancer deaths out of every 10 or 19 out of every 20.

Second, improvements in diagnosis also occurred with respect to such forms of cancer as stomach cancer. Yet no comparable rise in reported stomach cancer rates generally, or in cancer at other internal sites, has occurred.

Third, lung cancer is as easy to diagnose among women as among men. The proportion of the increase due to improved diagnosis must therefore make its appearance in the women's rate as well as the men's rate. Even if the entire increase in lung cancer among women shown in FIGURE 2 were attributed to improved diagnosis—a most dubious assumption—the far more rapid increase among men would remain unexplained.

Fourth, the attempt to explain away the increase as merely the result of improved diagnosis comes to grief on the rock of the well established fact that, to this very

day, cancer of the lung remains a rare disease among certain groups.

Among Seventh Day Adventists, for example, the disease is almost unknown, and the few cases which do occur are primarily in recent converts. Lung cancer is as easy to diagnose in Seventh Day Adventists as in Baptists, Methodists, Catholics, Jews, or atheists. If the lung cancer increase were merely the result of improved diagnosis, the Seventh Day Adventist rate would be expected to rise with the other rates. (We shall have more to say about this fortunate group later on.)

Finally, there is the strange but unchallenged fact that lung cancer remains today a rare disease among men and women who do not smoke and who never have smoked. It is also relatively uncommon among men who smoke cigars or pipes or both, but not cigarettes. Improved diagnosis, to the extent that it has affected the statistics through the years, would have produced a rise among non-smokers, pipe smokers, and cigar smokers as well as among cigarette smokers. The excess rise among cigarette smokers cannot be explained by improved diagnosis.

The inescapable conclusion

The conclusion is inescapable, and even spokesmen for the cigarette industry today rarely seek to escape it: We are living in the midst of a major lung cancer epidemic. This epidemic hit men first and hardest, but has affected women as well. It is occurring not only in the United States but in a number of other countries. It cannot be explained away by such factors as improved diagnosis. And, as FIGURE 3 indicates, there is reason to believe that the worst is yet to come.

The American Public Health Association has called attention to this black future in a single dramatic statistic.

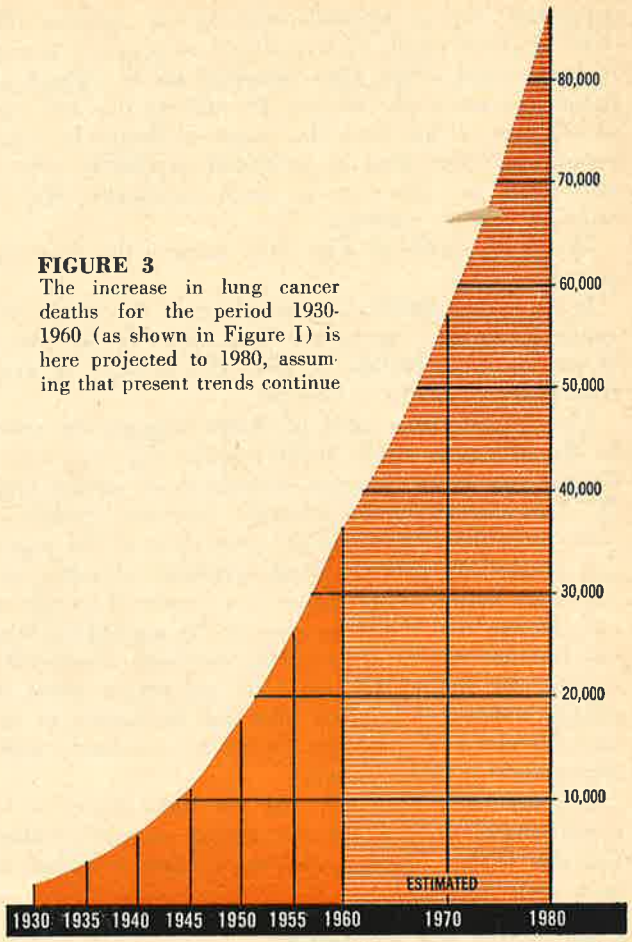


FIGURE 3
The increase in lung cancer deaths for the period 1930-1960 (as shown in Figure I) is here projected to 1980, assuming that present trends continue

If present trends continue, the Association reported in 1959, "lung cancer will claim the lives of more than 1,000,000 present school children in this country before they reach the age of 70 years."

II. THE STATISTICAL EVIDENCE

Occupation exposure studies

More than 400 years ago, in 1556 A.D., George Agricola published what may well be the first report on lung cancer, and the first explanation of it. Agricola was the town physician in Joachimsthal in Bohemia (now Jáchymov in Czechoslovakia), and his classic treatise on mining, *De Re Metallica*, called attention to a disease of the lungs shockingly prevalent then and later among workers in the Joachimsthal mines. Here is his description, translated from the Latin by Dr. (later President) and Mrs. Herbert C. Hoover:

> "Some mines are so dry that they are entirely devoid of water, and this dryness causes the workmen . . . harm, for the dust which is stirred and beaten up by digging penetrates into the windpipe and lungs, and produces difficulty in breathing. . . . If the dust has corrosive qualities, it eats away the lungs, and implants consumption in the bodies; hence in the mines of the Carpathian Mountains women are found who have married seven husbands, all of whom this terrible consumption has carried off to a premature death."

The mine dust so vividly described by Agricola contained a number of substances which might explain the lung cancer, including radium and uranium. Indeed, it was from Joachimsthal pitchblende that the Curies in 1898 isolated radium. Other suspected agents in the dust were arsenic, nickel, and cobalt. Studies published in the 1930's indicated that, as is often the case with cancer, the agent required many years before death from lung cancer actually took place. From 13 to 23 years elapsed between the time a boy or young man went to work in

the mines and the time of his death from lung cancer.

Among other occupational groups, too, very high lung cancer rates have been reported. One such group was composed of employees of six American chromate plants during the years 1940-48. Their lung cancer death rate was 29 times as high as the rate for U.S. males generally.

Among nickel workers in South Wales from 1948 to 1956, the lung cancer rate was five times as high as among workers in other occupations.

And among workers employed in the dusty areas of an English asbestos plant for 15 years or more, the lung cancer rate was 30 times greater than for males in England and Wales generally.

The correlation studies

Findings such as these among workers exposed to specific dusts or pollutants provide valuable clues to the more general lung cancer mystery. They indicate that lung cancer can follow inhalation of damaging substances, and that many years of exposure may precede death. In seeking to explain the general increase in lung cancer after 1920, accordingly, the thoughts of researchers often turned to the Joachimsthal miners, and some substance was sought which fitted the following descriptions and which might therefore explain the lung cancer epidemic:

1. It must enter the human lung.

2. It must have come into common use in countries like England and U.S. about 1900.

3. It must be in very common use in countries where lung cancer rates are high but less common in countries where lung cancer rates are low.

4. It must enter men's lungs more than women's lungs.

An obvious candidate for this role is cigarette smoke, and many studies have confirmed the extent to which it meets the description of a substance entering the lungs which has increased along with lung cancer—allowing a lag of 15 to 30 years between the smoking rate and the lung cancer rate. Most striking are recent figures from Iceland, where lung cancer remained a rare disease and cigarette smoking a relatively unpopular habit as recently as 1940. Since then, cigarette smoking has become increasingly popular—and lung cancer increasingly common. Here are the figures from the University of Iceland Department of Pathology, showing the proportion of autopsies in which death from lung cancer was found:

1932-40	0.5%	(3 deaths in 644 autopsies)
1941-45	0.6%	(3 deaths in 478 autopsies)
1946-50	1.3%	(8 deaths in 636 autopsies)
1951-55	2.2%	(17 deaths in 781 autopsies)
1956-60	2.6%	(31 deaths in 1174 autopsies)

Iceland, in short, took up cigarette smoking later than other countries—and the lung cancer epidemic hit Iceland later than it hit other countries.

The Icelandic increase cannot be attributed to air pollution, Dr. Niels Dungal of the University of Iceland points out, for at least since 1943 Reykjavik (where most of the deaths occurred) has had the purest air in Europe. A municipal heating system based on hot springs near the city has replaced both coal and oil for heating purposes.

Such data—and many additional correlations between cigarette consumption in one year and lung cancer deaths in a later year—do not, of course, "prove" that cigarette smoking is the "cause" of lung cancer. They merely indicate that smoking is a likely suspect. Other substances—for example, air pollution in general, or industrial wastes and products of industrial and domestic combustion discharged into the air through smokestacks and chimneys, or particles released into the air by the wearing of rubber tires on paved surfaces—might also fit the requirements of the role. Yet a little thought will show that the correlations between cigarette smoking and lung cancer deaths do have considerable value as evidence. For no equally impressive correlations exist for any other factor.

The retrospective studies

Fortunately we do not have to rely on mere correlations to decide the issue. Through the years researchers have developed a type of investigation known as the "retrospective study," and at least 27 such studies of lung cancer have been published.

These retrospective studies all consist essentially in starting with a group of lung cancer victims and asking this question:

What has occurred in their past histories which might explain their lung cancers?

One early answer came from an English physician, Dr. F. E. Tylecote. He reported in the British medical journal *Lancet* in 1927 that, in almost every case of lung cancer he had seen or known about, the patient was a regular smoker, usually of cigarettes.

This kind of evidence, of course, leaves much to be desired. How many cases of lung cancer had Dr. Tylecote seen or known about? How many exceptions were there to his statement that "almost every case" was a regular smoker? And what did he mean by "regular smoker"?

A somewhat more specific answer came from Drs. Aaron Arkin and David H. Wagner of Chicago. They reported in the *Journal of the American Medical Association* for February 22, 1936, that among 135 men with lung cancer they had examined, 90% were "chronic smokers." This kind of evidence is significant. If someone were to report, for example, that among patients with a particular kind of blood disease 90% were chronic users of a certain drug, the Food and Drug Administration would no doubt be urged to launch an immediate investigation. But findings like those of Arkin and Wagner, while suggestive, still hardly constitute proof; for example, they do not rule out the possibility that 90% of the men of the same age, occupation, and residence in Chicago who did *not* die of lung cancer might also be "chronic smokers."

The next step, accordingly, was to launch controlled retrospective studies, in which each patient with lung cancer was matched as closely as possible with a control who did not have lung cancer, in order to determine significant differences between the lung cancer victims and the controls.

One early controlled study was reported by Dr. F. H. Müller from Cologne, Germany, in 1939. Müller compared

80 male lung cancer patients with 80 healthy men and found much more smoking among the cancer patients.

Such a study, of course, is subject to the objection that it all depends on how you select your controls. Later studies, accordingly, have used great care in matching each lung cancer patient with a similar control case—usually a hospital patient with some other disease—of the same age, sex, residential area, occupational class, and so on.

An excellent example of such a critically controlled study was reported from England in 1950 by Drs. W. Richard Doll and A. Bradford Hill. They began with 1465 lung cancer patients, mostly from London hospitals. Each of these patients was matched by age and sex with a hospital patient who did not have lung cancer. Some of the control patients had cancer at other sites; some had diseases other than cancer. Here are two of the findings:

Only one male lung cancer patient in 200 was a non-smoker, as compared with one in 22 among the controls.

One male lung cancer smoker in four was a "heavy smoker" (carefully defined as a man smoking more than 25 cigarettes a day or the equivalent in pipe tobacco) as compared with only one in eight among the controls.

Critics of these retrospective studies might suspect that the interviewers who ask patients about their smoking habits could bias the results by consciously or unconsciously "leading" lung cancer patients to exaggerate their smoking, and not leading the control patients to the same extent. Doll and Hill were able to exclude this possibility. In some cases, the patients were interviewed at a time when it was supposed that they had lung cancer, but the diagnosis later proved to be erroneous. If the interviewers were leading the lung cancer patients to exaggerate their smoking habits, there would have been an excess proportion of heavy smokers in this group. No such excess was found.

The Doll-Hill study might also be criticized on the ground that the control group was itself composed of hospitalized patients and might therefore not be typical of the population as a whole. So, as an added precaution, Doll and Hill made a further study of a random sample of the English population as a whole. Far from exaggerating the relationship between lung cancer and smoking, this additional study revealed, the use of hospital patients as controls actually minimized the relationship, for there were more smokers and more heavy smokers in the hospital control group than in the population as a whole.

A study of the same kind, made in the United States by Drs. Ernest L. Wynder and Evarts A. Graham, then at the Washington University School of Medicine in St. Louis, was also published in 1950. They also took numerous precautions to avoid bias. In one part of their study, for example, their interviewers talked with all the patients coming to a chest clinic, without knowing whether the patients had lung cancer or some other chest condition. The diagnosis was not recorded until after smoking habits had been ascertained. Using these and other precautions, Drs. Wynder and Graham were able to settle on a number of impressive conclusions, including the following:

"Excessive and prolonged use of tobacco, especially cigarettes, seems to be an important factor in the induction of bronchogenic carcinoma [see page 278]."

"Among 605 men with bronchogenic carcinoma . . . 96.5% were moderately heavy to chain smokers for many years, compared with 73.7% among the general male population without cancer. Among the cancer groups 51.2% were excessive or chain smokers compared with 19.1% in the general hospital group without cancer."

"The occurrence of carcinoma of the lung in a male non-smoker or minimal smoker is a rare phenomenon."

"94.1% of male patients with cancer of the lungs were found to be cigarette smokers, 4.0% pipe smokers, and 3.5% cigar smokers."

The Seventh Day Adventist study

These and other retrospective studies of this kind, which start with lung cancer victims and work backward, are subject to a common flaw. They do not foreclose the possibility that some other factor associated with smoking—call it the X-factor—may be the "cause" of the lung cancer.

An example will illustrate this possibility. Heavy cigarette smokers are more likely than non-smokers to develop cirrhosis of the liver. But this does not mean that heavy cigarette smoking "causes" cirrhosis of the liver. Rather the relationship seems to involve these links:

1. Most heavy drinkers are also heavy smokers.
2. Many heavy drinkers suffer from dietary deficiencies.
3. These dietary deficiencies, in all probability, lead in turn to cirrhosis of the liver.

Heavy drinking, in short, is in all probability the X-factor by which heavy cigarette smoking is linked with dietary deficiencies and thus with cirrhosis of the liver.

It is hard to conceive of such a specific X-factor linking smoking with lung cancer, however—and the inherent implausibility of such a factor has been dramatically illustrated in a remarkable study made by Drs. Wynder, Frank R. Lemon, and Irwin J. Bross at Seventh Day Adventist hospitals throughout the country.

These Seventh Day Adventist hospitals are good hospitals, staffed with competent pathologists and diagnosticians. They treat both Seventh Day Adventists and patients of other creeds, or of no creed whatever. The study sought essentially an answer to this question:

Is there a lung cancer difference between Seventh Day Adventists and others treated in the same hospitals?

The answer, as in other retrospective studies reviewed above, was clear-cut. Patients at these hospitals who were not Seventh Day Adventists had just about the lung cancer rates to be expected. Among Seventh Day Adventists, in contrast, lung cancer was almost totally unknown. Only two cases were diagnosed among many hundreds of patients dying of other diseases. And both of these cases, interestingly enough, were among recent converts to Seventh Day Adventism.

Now let us consider the light this finding throws on the X-factor. If such a factor exists, it must (of course) have the two characteristics already noted: It must be associated with cigarette smoking (as distinct from cigar or pipe smoking); and it must cause lung cancer. In addition, we can affirm on the basis of the Seventh Day Adventist findings, the X-factor must be present in Catholics, Meth-

odists, Baptists, Jews, and atheists—but Seventh Day Adventists (except recent converts) must somehow be resistant to or lacking in it altogether!

There is, of course, a much simpler and more plausible explanation. *Seventh Day Adventists do not smoke.*

This simpler theory is buttressed by the fact that both of the converts to Seventh Day Adventism who developed lung cancer smoked a pack a day or more for 20 years or longer prior to their conversion.

Once again, no single retrospective study by itself can prove a significant association between cigarette smoking and lung cancer. Each study is subject to qualifications. But when the 27 or more retrospective studies are considered in combination, their joint value is very high.

The studies were made independently, by different scientists or groups. At least one study was launched with the expectation of *disproving* an association. Parallel results have been reported from the U.S., England, Germany, Japan, The Netherlands, Denmark, and other countries. The association was shown to hold for women as well as men, and for various age groups considered separately.

The negative evidence

Let us next consider controlled retrospective studies which show the absence of an association between cigarette smoking and lung cancer. This can be briefly done. *There are no such studies.*

No one has ever matched lung cancer victims with comparable controls and reported that the lung cancer victims smoked less than the controls, or smoked only to the same extent, or smoked only a little bit more.

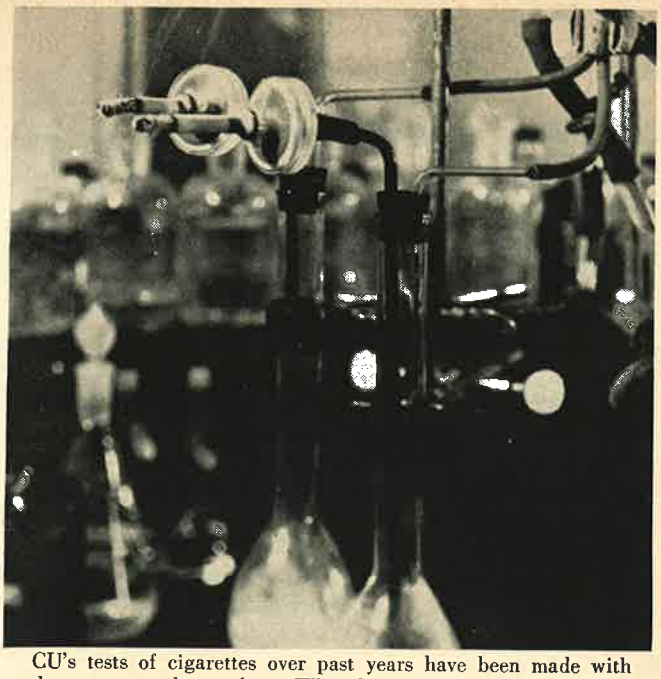
If a single population could be found—urban or rural, domestic or foreign, red, yellow, black or white—in which an increase in lung cancer is *not* linked with heavy, prolonged cigarette smoking, the case against the cigarette would concededly be weakened. But no such population has been reported.

Some widely publicized reports, it is true, may seem at first glance to provide negative evidence casting doubt on the cigarette-lung cancer theory. Let us consider three.

Dr. Geoffrey Dean noted in 1959 that white males born in South Africa were among the world's heaviest smokers, yet they had a lower lung cancer rate than male immigrants to South Africa from Britain. This seemed to suggest that something in the British environment, perhaps air pollution, was more important than smoking.

Dr. D. F. Eastcott reported similarly from New Zealand in 1956 that immigrants from Britain to New Zealand smoked no more than native white New Zealanders but had a higher lung cancer rate.

Finally, Dr. Jacob Cohen of New York University (an American Tobacco Company consultant) and Robert K. Heimann of the American Tobacco Company alleged in 1962 that employees of the cigarette division of the American Tobacco Company smoked very heavily, yet had no deaths from primary lung cancer and were very healthy in other respects. Dr. Cohen and Mr. Heimann described both their own figures and the South African and New Zealand figures as "negative findings" with respect to the cigarette-lung cancer hypothesis.



CU's tests of cigarettes over past years have been made with the apparatus shown above. What CU has learned has been that brands vary widely and change frequently with respect to tars and nicotine in the smoke taken in by the smoker. It is probably some of the tars which do the damage so far as lung cancer is concerned. But in this area of precisely *how* the smoking-lung cancer link is forged, more is to be learned than is known

But none of these studies provided a matched comparison between smokers and non-smokers alike in other respects. Instead, all *three* studies lumped smokers and non-smokers together, and thus actually concealed the smoking effect.

The danger of relying on such uncontrolled studies can be dramatically illustrated. At about the same time that Dr. Cohen and Mr. Heimann published their American Tobacco Company study with its review of the South African and New Zealand studies, Dr. Dean published additional figures from South Africa in the *British Medical Journal.* The additional report contained detailed comparisons of smokers and non-smokers missing from the earlier study. With this missing data supplied, the picture turned out to be very different.

Cigarette smokers, the new study revealed, had a much higher lung cancer death rate than non-smokers. Further, this variation of lung cancer rates with smoking habits appeared both among men born in South Africa and among the immigrants from Britain. Again, the amount of lung cancer turned out to vary directly with the *amount* of smoking; native-born South African males who did not smoke, for example, had a lung cancer death rate of 8 per 100,000 as compared with a rate of 156 among native-born South African males who smoked 50 or more cigarettes daily. And finally, the significance of the smoking factor turned out to dwarf the significance of the immigration factor which had loomed so large when it was presented in the earlier paper without the smoking-non-smoknig comparison. Far from casting doubt on the cigarette-lung cancer hypothesis, the complete South African figures with the smoking-non-smoking comparison included turned out to be one of the most impressive sets of statistics ever compiled in support of the cigarette-lung cancer theory.

Figures for New Zealand and for employees of the American Tobacco Company showing smokers and non-smokers separately have not to date been published.

The prospective studies

Like any other single kind of evidence, the retrospective studies we have been reviewing are not by themselves conclusive. But they do not stand alone. Even more impressive evidence of the cigarette-lung cancer relationship has been accumulated in a series of prospective studies.

Such studies essentially start with a group of presumably healthy smokers and a second group of presumably healthy non-smokers, and follow them through a subsequent period of months or years to find out what happens to both groups.

One important prospective study was conducted in England for the Medical Research Council by Drs. Doll and Hill, whose retrospective study has already been discussed. They began by sending a questionnaire on personal smoking habits to 60,000 British physicians aged 35 or over. Sufficient data to classify the physicians by their smoking habits were received from 40,000. After following the 40,000 physicians for the next 4½ years, Drs. Doll and Hill were able to draw the following conclusions:

- Mild smokers are seven times as likely to die of lung cancer as non-smokers.
- Moderate smokers are 12 times as likely to die of lung cancer as non-smokers.
- Immoderate smokers are 24 times as likely to die of lung cancer as non-smokers.

Because this study was limited to a well-defined population—British physicians over 35 in 1951—it had certain advantages. For example, the death certificates of *all* physicians who died could be checked, to make sure that those participating in the study were typical of the whole group. The study was on a relatively small scale, however, and it might be argued that physicians are not necessarily typical of the general population. The American prospective study by Drs. E. Cuyler Hammond and Daniel Horn for the American Cancer Society is subject to neither of these two possible qualifications.

These investigators started by training a group of 22,000 Cancer Society volunteers to get smoking questionnaires from their friends. The volunteers secured usable questionnaires from nearly 190,000 white males aged 50 to 69 who seemed well when quesitoned. During the next 44 months 187,783 of these men were followed, and 11,870 deaths among them were reported.

The results were so voluminous that only a few can be presented here. The lung cancer death rate per 100,000 men per year for non-smokers was 12.8, indicating that lung cancer is still a rare disease among non-smokers. Among those who smoked from ½ to one pack a day the comparable rate was 107.8. Among those who smoked from one to two packs a day the rate was 229.2. And among those who smoked more than two packs a day it was 264.2. These findings expressed as ratios are given on page 276.

The prospective study by Dr. Harold F. Dorn was very closely in line with the studies of Drs. Doll and Hill and of Drs. Hammond and Horn. He followed nearly 200,000 veterans holding government life insurance policies for a period of 2½ years, and reported that in this group cigarette smokers generally were nearly ten times as likely to die of lung cancer as non-smokers—and that men smoking more than a pack a day were some 16 times as likely to die of lung cancer as non-smokers.

Dr. Lester Breslow of the California State Health Department and his associates have published another prospective study which is of particular interest because it was not designed primarily to check on smoking and lung cancer. On the contrary, it was concerned with employees engaged in types of work which (it was suspected) might lead to high lung cancer rates. The Breslow group did find that some occupational groups had higher lung cancer rates than other groups; but it was the groups which smoked most which had the highest rates. The effect of smoking on the lung cancer death rate was so intense that it proved impossible to determine whether or not occupational factors were also at work.

A different, non-prospective kind of study has been pioneered by William Haenszel and his National Cancer Institute associates. They determined "standard lung cancer mortality rates" for men of various ages in various parts of the country, native born and foreign born. Among their impressive findings was the fact that regular cigarette smokers were far more likely to die of lung cancer than non-smokers *in every group they checked.* Here are some examples:

	Standard lung cancer mortality ratios for men who are not regular cigarette smokers	Standard lung cancer mortality ratios for men who are regular cigarette smokers
Foreign born	61	277
Native born	26	180
Born and currently living on farm	11	111
Born and currently living in a large city	34	198

Clearly there are differences between native-born and foreign-born populations, and between city and farm residents; but the differences between regular cigarette smokers and others dwarf all other variations.

The most recent of the prospective studies, conducted again by Dr. Hammond for the American Cancer Society, is also the largest and broadest. Launched in 1959, it covers more than a million men and women in more than a thousand counties, and it is collecting far more information about each participant than earlier studies did. It is concerned not only with smoking and cancer, but with many other health problems as well. Preliminary findings are in line with the earlier studies, but go beyond them in significant respects. For example, lung cancer turns out to be closely associated with the inhaling of cigarette smoke; indeed, inhaling may prove to be an even more important factor in lung cancer than the number of cigarettes smoked, a point we will discuss at more length further on.

III. THE EXPERIMENTAL EVIDENCE

Statistics and plausibility

Efforts have occasionally been made to discredit the kinds of evidence we have been describing on the ground that they are "merely statistical." This kind of criticism overlooks the fact that some of the central findings of science are supported solely by statistical evidence. The death of a smoker from lung cancer is not a "merely statistical" death; it is a real death. Grouping a dead smoker with large numbers of other smokers who have died of lung cancer does not alter the death or make it "merely statistical"; it simply collects the evidence from many thousands of individual cases into a coherent pattern.

The argument against placing too much reliance on "merely statistical" evidence has perhaps been expressed most forcefully by a scientist who is himself a statistician—Dr. Jacob Yerushalmy of the University of California. He likes to tell the story of a study he made on cigarette smoking during pregnancy. His study revealed, as several others have also revealed, that women who smoke during pregnancy give birth to babies who weigh less on the average than the babies of women who do not smoke. Dr. Yerushalmy's study went further, however; it showed that the weight of the babies was also lower than average among women whose *husbands* smoked, whatever the mother's own smoking habits!

Since the relationship between a woman's smoking during pregnancy and the weight of her baby is a plausible one in terms of everything known about the physiology of smoking, pregnancy, and birth weight, it is easily accepted. But a change in an infant's birth weight due to the smoking habits of its mother's husband seems unlikely enough to call for some other explanation of the apparent relationship. Let us not rely on a "merely statistical" relationship, Dr. Yerushalmy's story suggests, unless it can also be shown that the relationship is a reasonable one.

Such warnings apply with very great force, of course, to findings based on any single statistical study. They may maintain considerable force when applied to groups of statistical studies which pursue a single statistical method—the whole group of retrospective studies described above, for example. But they lose much of their effectiveness when used to attack findings confirmed by divergent statistical techniques, such as the combined correlation data, retrospective data, and prospective data reviewed above.

Still, Dr. Yerushalmy's story does have significance in connection with the smoking-lung cancer relationship. It suggests that the overwhelming statistical evidence we have reviewed would take on an even greater probative force if it could be shown through experimental and pathological studies that a relationship between smoking and lung cancer is, in fact, inherently plausible as well as statistically evident.

Evidence bearing on the inherent plausibility of the smoking-lung cancer hypothesis will accordingly be reviewed here. But first it is necessary to recall a few underlying facts about cancer in general, starting with some basic ones, thus:

¶ The human body, like plants and animals generally, is composed of myriads of cells. Each cell divides from time to time, giving rise to two daughter cells. Typically the daughter cells precisely resemble the parent cell.

¶ Each cell has a nucleus which can be seen through the microscope. In the nuclei are chromosomes, which can also be seen through the microscope and mapped. The chromosomes are composed of DNA (deoxyribonucleic acid). This substance carries a "genetic code." The two daughter cells generally follow the same pattern as their parent cell because they contain the same DNA in the chromosomes of their nuclei and thus receive the same "message" in the genetic code.

The inherent nature of cancer

Cancer cells, it is generally agreed, arise out of normal cells. But they have been altered in significant respects. They are generally larger and more irregular than ordinary cells; and instead of developing normally they grow wild. The daughter cells into which a cancer cell divides are themselves cancer cells. Instead of dividing and multiplying in accordance with the needs of the organism, they divide and multiply without limit. And instead of respecting the boundaries of nearby tissues as do normal cells, they invade nearby tissues and exhaust their supply of nutrients. Eventually, unless the cancer cells are all removed by surgery or killed by radiation or chemicals, they destroy other tissues and cause death.

Evidence increasingly indicates that it is changes in the DNA chromosomes of a cell which convert it from normal to cancerous. Indeed, one of the major signs of a cancer cell, differentiating it from a normal cell when viewed under the microscope, is the abnormal, disordered pattern of its chromosomes. A normal cell does not ordinarily become a cancer cell, or give rise to a cancer daughter-cell, at a single moment in time or even overnight. Rather, it appears, the conversion from normal cells to true cancer cells proceeds through a series of recognizable stages.

The first step is *hyperplasia.* This means simply that the cells divide more often, so that the number of cells at a particular place in a particular tissue increases. Instead of one layer or two of lining cells in the breathing passages, for example, five or six layers may be produced, or a dozen. Chronic irritation, mechanical or chemical, may produce this hyperplasia or excessive growth. The calluses on the palms of your hands which you get when you chop wood day after day are a familiar example of hyperplasia due to irritation.

The next step is *metaplasia.* This means an alteration in the cell itself, and particularly in the DNA chromosomes in its nuclei. Since these altered or metaplastic cells give rise to daughter cells which resemble themselves, a *lesion* often develops—that is, a group of neighboring metaplastic cells.

At first these groups of metaplastic cells continue to live within their own proper boundaries. Some pathologists,

accordingly, do not consider such lesions cancerous. Others call them cancer *in situ*—that is, cancer which keeps its place and does not invade neighboring tissues.

The final step occurs when the cells destroy the boundaries of their native tissue and invade neighboring tissues. Also, cells from the original lesion break loose and migrate to other parts of the body where their daughter cells build additional tumors, a process called *metastasis*. A cancer is generally curable if it is surgically removed or if all the cells are killed before metastasis occurs.

Various agents are known to give rise to cancers. One kind of cancer agent is the virus, which is essentially a bundle of chromosomes held within a protein coat. When certain kinds of viruses invade certain kinds of cells, cancer follows, presumably because the chromosomes from the virus take over control of the cell.

Another important kind of cancer agent is chemical. The chemicals which can cause cancer are called carcinogens and several hundreds of them are known. In most cases, prolonged exposure to a carcinogen precedes the appearance of the cancer. A typical test to determine whether a chemical is a carcinogen is to shave the back of a mouse and apply the chemical hundreds of times over a period of many months to the mouse's skin. If the chemical is a carcinogen, the characteristic series of events will in due course follow in some of the mice: first, hyperplasia; then metaplasia; then growths or lesions composed of metaplastic cells, but still not invasive (carcinoma *in situ*); then true invasive cancer; and finally metastasis and death of the mouse. No one knows why some mice develop cancer following exposure to a carcinogen while others do not. A possible explanation is that a very common virus is also needed for cancer to develop, and that the mice which lack the virus escape the cancer despite the carcinogen.

In addition to carcinogens there are chemicals called co-carcinogens. These substances may not cause cancer even though cells are exposed to them in large amounts repeatedly over long periods. But if cells are exposed to a carcinogen also, even a very small amount of it, chronic exposure to a co-carcinogen may produce a much higher proportion of cancers.

There is evidence that viruses, carcinogens, and co-carcinogens can work together to produce cancers. Many years ago, for example, Dr. Peyton Rous of the Rockefeller Institute infected rabbits with a virus called the Shope papilloma virus. This virus produced hyperplasia—large wartlike growths on the rabbit—but only rarely cancer. But when the rabbits received carcinogens and co-carcinogens as well as the papilloma viruses, true cancer frequently followed. Similar results have since been secured with other combinations of viruses, carcinogens, and co-carcinogens.

Next, a word about the lungs. They are essentially devices for bringing air and blood together under conditions which permit oxygen to migrate from the air to the blood and carbon dioxide to migrate in the opposite direction from blood to air. The air needed for this two-way transfer is carried from the windpipe or trachea to the lungs through a system of branching tubes called the bronchi. The bronchi are lined with a few layers of cells called epithelial cells. Careful studies have shown that most lung cancers originate in these cells in the bronchial linings.

Against this general background, let us return to the smoking-lung cancer problem.

Carcinogens and co-carcinogens

Tobacco itself contains more than a hundred known chemical compounds, including nicotine, which will be discussed in some detail in connection with smoking and cardiovascular diseases. But the chemistry of tobacco is of very little concern to us here, since some of the substances found in the tobacco remain in the ash when the tobacco is smoked, while others are profoundly altered during the combustion process; additional compounds are also produced during combustion. What primarily concerns us, accordingly, is the composition of the cigarette smoke which results from the combustion and enters the human body.

More than 270 distinguishable chemical compounds have been identified in this smoke. Of these, at least 15 are known carcinogens; that is, they have been shown to cause cancer either in animal experiments or in observations on humans exposed to them. Here is a list of carcinogens in tobacco smoke:

Arsenious oxide	Chrysene
1:2-benzanthracene	6:7-cyclopenteno—1:2 benzanthracene
3-4-benzfluoranthene	1:2-5:6 benzanthracene
10:11-benzfluoranthene	3:4-8:9 dibenzpyrene
11:12-benzfluoranthene	3:4-9:10 dibenzpyrene
1:12-benzperylene	3-methyl-pyrene
1:2-benzpyrene	2-naphthol
3:4-benzpyrene	

In addition to this list of known carcinogens, cigarette smoke contains many substances which have not yet been tested to determine whether they are or are not carcinogens. In particular, it contains additional chemicals of the class known as polycyclic aromatic hydrocarbons. Some chemicals of this class are known carcinogens, and the remainder are accordingly suspect.

The quantity of each carcinogen identified in tobacco smoke, to be sure, is very small—in some cases exceedingly small. But here another point must be noted. Cigarette smoke also contains significant amounts of phenol, a powerful co-carcinogen. Even very small amounts of a carcinogen will produce cancer when accompanied or followed by chronic exposure to phenol. And cigarette smoke in addition contains various phenol derivatives and other substances suspected of being also co-carcinogens.

Tobacco smoke itself, when collected and concentrated, is carcinogenic, capable of producing cancer in the standard mouse-skin test. Further, it has been shown to be co-carcinogenic as well; it increases the number of cancers produced when it is applied following the application of a carcinogen.

A demonstration of this co-carcinogen effect is found in the work of Drs. Joseph A. DiPaolo and Paul R. Sheehe of the Roswell Park Memorial Institute in Buffalo, New York. They performed a standard experiment in which a specified amount of a known carcinogen, urethan, was injected into

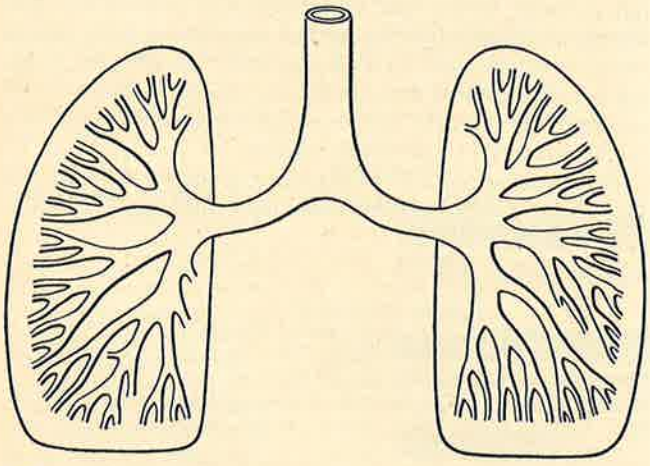
the bellies of a group of mice. Cancers appeared in due course, as expected. In addition, Drs. DiPaolo and Sheehe injected the same amount of urethan into the bellies of a second group of mice, and also painted the throats of these mice with condensed tobacco smoke five times a week for six months. These mice developed many more lung cancers than those treated with urethan alone. Indeed, the crop of cancers produced was equivalent to the crop which would have been expected if the amount of urethan injected had been multiplied by 52.

Note, too, that cigarette smoke when inhaled actually reaches the cells out of which lung cancer arises. Let us review this evidence briefly.

When you take a puff of a cigarette, the smoke first enters your mouth and throat. What happens next depends on whether you inhale the smoke or not. Few pipe and cigar smokers inhale the smoke, and few of them get lung cancer. Many cigarette smokers inhale, and most cigarette smokers who get lung cancer inhale. Inhaling means that the smoke passes on down from the throat through the trachea or windpipe to the bronchial tubes.

A bronchial tube begins at the windpipe. Then it divides or forks into two tubes, and each of these forks in turn (see the drawing below). The structure of the tubes thus resembles in part the branching of a tree, and the tubes are therefore sometimes known as the "bronchial tree." The deeper you inhale, the farther along the bronchial tree the smoke proceeds.

If you examine the drawing, you will note that each tube is necessarily wider at each fork. This widening causes the air or smoke to slow down as it enters the region of greater width and, perhaps, to deposit any particles it may contain. The process is much the same as that of a flowing river which deposits its sediment as a delta where it broadens into a lake or ocean. The exposure to the particles in the smoke is thus greatest at the points where the tube is widest —and autopsy studies of hundreds of human lungs have shown that it is in precisely these areas of maximum exposure that pre-cancerous changes (hyperplasia and metaplasia of the cells) are most likely to appear.



The structure of the bronchial tubes resembles the branching of a tree; note that the tubes are wider just before each fork. Inhaled cigarette smoke entering these regions is slowed down by the greater width; exposure to particles in the smoke is thus greatest where the tubes are widest. Autopsy studies have shown that pre-cancerous cell changes are most likely to occur here

Thus a very plausible case can be made for a direct causal (in addition to a statistical) connection between smoking and lung cancer. Some smokers draw the smoke into their lungs and some do not; it is mainly the smokers who inhale the smoke who run the excess risk of lung cancer. The smoke contains carcinogens and co-carcinogens. The cells which become cancerous are those along the lining of the bronchial tubes through which the smoke is drawn. And the lesions are most likely to appear at the very spots, the wide places, where exposure to the smoke is most intense. Here at the very least is a *prima facie* case for a direct relationship between the statistics reviewed earlier and the events which occur in the human lung.

Many reputable investigators feel that this explanation of lung cancer as the result of carcinogens and co-carcinogens found in cigarette smoke is only part of the story. They call attention to such additional factors as those noted below.

Mucus, cilia, irritation

The surface of the bronchial tubes into which smoke is drawn is normally moist with a fluid called mucus, excreted by cells along the surface. Further, many of the surface cells are decked with tiny whiplike fringes called cilia, which wave back and forth in such a way as to propel the mucus upward and outward. This is clearly a protective mechanism. Irritating or poisonous particles entering the lung are likely to be trapped in the mucus; and, as the mucus is propelled upward and outward by the cilia, the trapped particles are themselves ejected and the lung thus protected from them.

Cigarette smoke, however, paralyzes the ejecting action of the cilia in the bronchial tubes. As hyperplastic changes occur in the lining of the tubes, moreover, the cilia disappear altogether. Thus, inhaling smoke deprives the bronchial tubes of their normal protective mechanism. Some researchers attribute the relationship between smoking and lung cancer at least in part to this effect on the cilia rather than solely to the direct action of carcinogens and co-carcinogens.

Further, abundant evidence indicates that cigarette smoke is an irritant. No smoker who feels the irritation in his mouth or who develops a cough following smoking doubts this. Chronic, day-after-day irritation can itself evoke hyperplasia, metaplasia, and cancer in some tissues; and some investigators prefer to attribute the relationship between smoking and lung cancer to this factor of chronic irritation.

Note that the four theories based on carcinogens, co-carcinogens, paralysis and disappearance of cilia, and chronic irritation are *not* mutually exclusive or incompatible. Nature often proves far more complex than investigators initially assume. It is not at all inconceivable that two, three, or even all four of these factors may be found to play their role in the genesis of lung cancer. Cigarette smoke might initiate the damage by paralyzing the cilia, then produce hyperplasia through chronic irritation, and finally produce metaplasia and invasive metastatic cancer through both its carcinogens and its co-carcinogens. Or it may turn

out that a virus is also involved, and that the smoke acts by opening the door for the virus—or that the virus paves the way for the damaging effects of the smoke.

None of these possibilities is offered here as *the* explanation of the relationship between cigarette smoking and lung cancer. All that need be established is that they provide plausible explanations. The statistical evidence firmly establishes the relationship. The pathological and experimental evidence shows that the relationship is not so wildly improbable as to cast doubt on the credibility of the statistics.

Smoke and the lungs of mice

One theme often stressed by spokesmen for the cigarette industry is the lack of experiments proving that smoking can cause lung cancer.

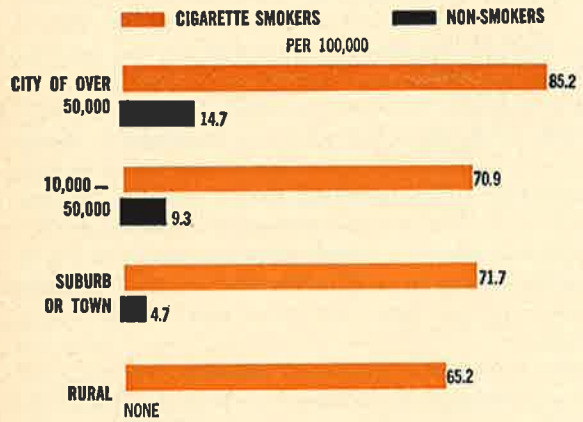
One such experiment can be readily imagined. Hundreds of sets of identical twins might be selected at birth. They would be brought up together in exactly the same way. At a specified age one twin in each pair would be set to smoking a specified number of cigarettes at a specified tempo to a specified butt length each day for the rest of his life, while the other twin in each pair would be monitored continuously throughout his life to make sure he never smoked a single cigarette. All twins dying would be autopsied, and a search made for lung cancer. After some 50 or 60 years, the surviving twins would be slaughtered and their lungs and bronchial tubes similarly examined. If the twins who smoked had a higher proportion of lung cancer, and if the number of lung cancers were proportional to the number of cigarettes they smoked, almost everyone except possibly the cigarette industry would agree that the smoking had caused the lung cancers.

Such an experiment is hardly feasible in a human population, of course. And even in a population of mice it raises serious difficulties. In the first place, mice breathe through their noses, not their mouths; and their nasal passages contain a series of excellent protective filters which remove particles from the air before it reaches the lungs. Thus, a mouse in a smoke-filled room gets far less of the smoke into his bronchial tubes than a smoker who inhales. Further, mice and other small animals are quite sensitive to the acute poisonous effects of nicotine or other substances in cigarette smoke. If subjected to the intensity of smoke which a human smoker draws into his lungs when he inhales, some mice keel over immediately and die; many others die soon thereafter.

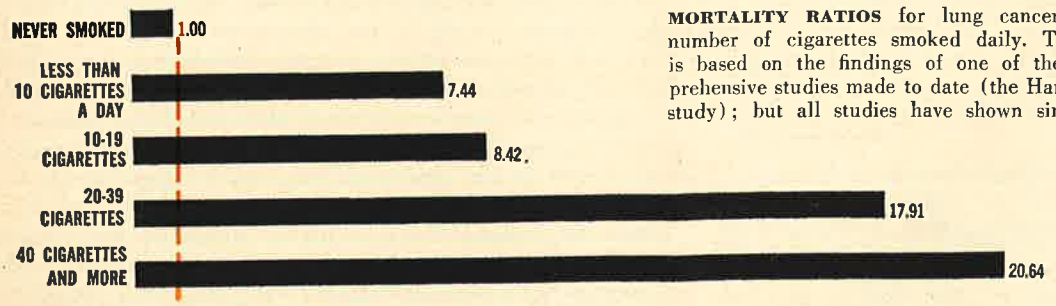
The most that can be accomplished with mice and presumably other small animals is to simulate exposure to cigarette smoke very roughly comparable to that experienced in the lungs of a casual cigarette smoker who smokes only a few cigarettes a day.

Such an experiment has been performed by Drs. Cecilie and Rudolph Leuchtenberger and Paul F. Doolon, supported by a grant from the Tobacco Industry Research Committee. They used an inbred strain of mice closely resembling each other in genetic inheritance. Half of the mice were placed in one enclosed chamber and half in another; six hundred mice in all were used. A cigarette-smoking machine was attached to each of the chambers, and one of the machines smoked eight cigarettes a day, five days a week month after month. The other chamber was exactly the same, and the mice in it were treated in exactly the same way except that the second cigarette-smoking machine did not actually smoke any cigarettes. The experiment thus closely duplicates the impractical experiment with human twins except that the smoke from eight cigarettes per chamber per day, inhaled through the mouse nose, was much less concentrated than the smoke which reaches the lungs of a human cigarette smoker who inhales.

After various periods of exposure in the smoke chamber, both the smoke-exposed mice and the control mice were sac-



DEATH RATES from well-established cases of lung cancer for cigarette smokers vs. non-smokers (meaning men who never at any time smoked regularly) in urban and rural areas. Adenocarcinoma cases, less linked to smoking than other kinds of lung cancer, are not included



MORTALITY RATIOS for lung cancer deaths by number of cigarettes smoked daily. This diagram is based on the findings of one of the most comprehensive studies made to date (the Hammond-Horn study); but all studies have shown similar results

rificed, and their lungs examined.

The bronchial tubes of the mice exposed to the tobacco smoke differed from the bronchial tubes of the control mice in several significant ways. First, there was more hyperplasia, or "proliferative changes"—an increased number of cells. Second, there was more metaplasia, or changes in the type of cells and in their nuclei and DNA chromosomes. Third, the researchers were able by subtle means to demonstrate actual changes in the DNA found in individual cells. Finally, whole groups of cells or lesions demonstrating these characteristics were noted in the mice exposed to smoke—the kind of lesions which might be labelled carcinoma *in situ*.

Invasive, metastatic carcinoma did not turn up during these experiments, and several reasons may be advanced for this failure of the smoke-induced lesions to take the last, fatal step. The exposure of the mouse lungs to smoke was, of course, relatively mild as compared with the exposure of the lungs of a human smoke-inhaler who gets true cancer. Also, the mouse's life is short; three years or so as compared with the 20 years or more to which a human's lung is ordinarily exposed to cigarette smoke before a cancer appears. The significant point about this experiment, at all events, is not that the metaplastic lesions in the mouse bronchial tubes failed to become invasive and metastatic, but rather that all of the pre-cancerous changes from hyperplasia through metaplasia and the formation of lesions did appear following a relatively mild exposure of the bronchial tube lining of the mice to the smoke.

In this experiment, as in many other smoking-lung cancer experiments, the smoke did not induce uniform changes in all the mice exposed to it. Despite the fact that all of the mice came from the same inbred strain, some appeared to be strangely immune to the effects of the smoke—or, looking at the matter the other way round, some appeared to be strangely susceptible. The Leuchtenbergers and Doolon themselves suspect that a virus may prove to be the explanation of this difference in response. The mice with hyperplastic and metaplastic changes and with lesions, they suggest, may be the ones infected with some virus or other. The virus by itself, according to this theory, rarely produces changes, and neither does tobacco smoke by itself; it may be the tobacco smoke acting on virus-infected cells, or the virus entering such smoke-damaged cells, which produces the changes noted.

"Mice are not men"

Even though the changes typical of cancer formation can be experimentally produced in mouse bronchial tubes with tobacco smoke, mice are not, of course, men—as spokesmen for the cigarette industry always point out in commenting on experiments of the kind just described. They want evidence that this also occurs in *human* bronchial tubes.

Here is the evidence.

For more than eight years four competent researchers have been engaged in a microscopic study of human lungs taken from the body at autopsy. The four are:

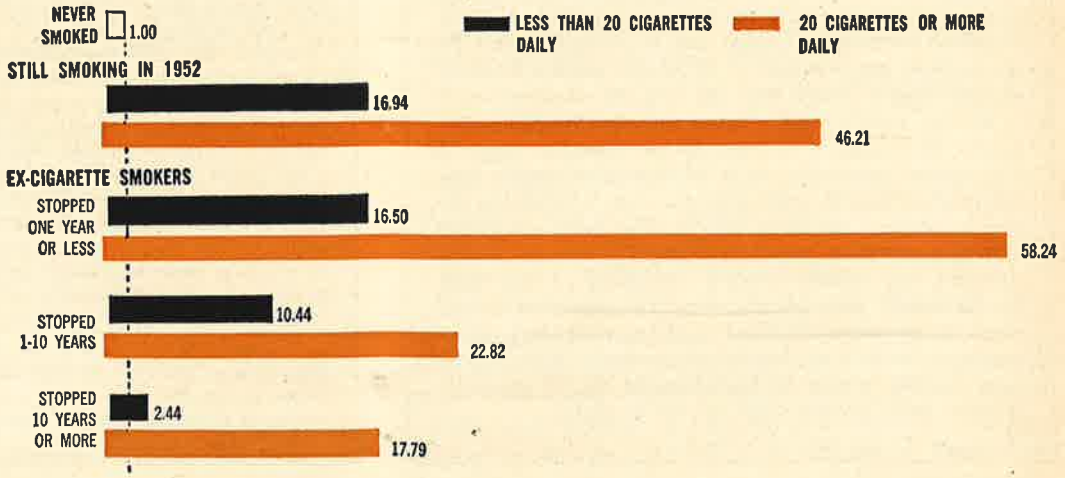
DR. OSCAR AUERBACH, Senior Medical Investigator at the Veterans' Administration Hospital in East Orange, New Jersey, and Associate Professor of Pathology at New York Medical College

DR. ARTHUR PURDY STOUT, Professor Emeritus of Surgery at the College of Physicians and Surgeons, Columbia University

DR. E. CUYLER HAMMOND, Director of Statistical Research, American Cancer Society

LAWRENCE GARFINKEL of the Statistical Research Section, American Cancer Society

The Auerbach-Stout-Hammond-Garfinkel study, financed by the American Cancer Society, comes closer than any other project except the statistical studies to nailing the relationship between smoking and lung cancer. In the course of the project more than 100,000 separate slides containing cells from the bronchial tubes of 1522 men and women were examined under the microscope—a tremendous undertaking. Dr. Auerbach examined every one of the 100,000 slides to assure uniformity of judgment. Dr. Stout checked Dr. Auerbach's findings by re-examining a selection of slides to see if he reached the same conclusions. Some of the tissue examined came from non-smokers, some from light smokers, heavy smokers, and ex-smokers. All of the 1522 patients had died of causes other than lung cancer. Relatives were interviewed to ascertain the smoking history of the men whose lungs were examined; the interviewers were not, of course, informed



MORTALITY RATIOS for lung cancer deaths in terms of smoking habits (also from the Hammond-Horn study and based on well-established cases of the two most common kinds of lung cancer linked to smoking—epidermoid and undifferentiated carcinoma). The relatively high figure for smokers who had stopped for one year or less is explained by the fact that many of these smokers stopped because of the onset of disease symptoms

of the microscopic findings at any time, and, to avoid any chance of bias, Drs. Auerbach and Stout were not informed of the smoking histories until after they had examined the slides. Each slide was identified only by a serial number selected at random, so that if any errors were made in reading the slides, they would be random errors, affecting slides from the lungs of non-smokers along with those from the lungs of smokers.

The findings from his human study closely parallel the mouse findings of the Leuchtenbergers, but go at least one important step farther.

Like the Leuchtenberger study, the Auerbach study found each step in the cancer process clearly identifiable—hyperplasia, or excessive number of cells; metaplasia, or characteristic changes in the cells and in their nuclei; and the formation of lesions composed entirely of such cells (carcinoma *in situ*).

The Auerbach study established that the pre-cancerous changes were most likely to occur at the places where the bronchial tubes forked—that is, at precisely the places where the exposure to the smoke is greatest.

The study noted occasional cases of hyperplasia and metaplasia among men and women who had never smoked. This is in line with the statistical finding that lung cancer does occur occasionally in non-smokers.

The proportion of hyperplasia, metaplasia, and cells with atypical nuclei, however, was very much higher among cigarette smokers than among non-smokers. Further, carcinoma *in situ*, strictly defined, was found only among smokers. Cigar and pipe smokers had more pre-cancerous lesions than non-smokers, but fewer than cigarette smokers.

The number of places in the bronchial tubes showing hyperplasia, metaplasia, and carcinoma *in situ* was proportional to the amount of smoking. The heavy smokers—those who smoked a pack a day or more—had the largest number of these pre-cancerous changes in their lungs. Indeed, the bronchial linings of heavy smokers who died of causes other than lung cancer closely resembled in almost every respect the lungs of lung cancer victims. In some cases, ominously enough, actual invasive cancers were found—small cancers which had not yet made known their presence when death ensued from other causes.

The Auerbach-Stout-Hammond-Garfinkel data can be interpreted in several ways. They are consistent with the carcinogen theory, the co-carcinogen theory, and the chronic irritation theory. They are even consistent with the virus theory, for it may be a virus which ultimately determines whether or not the changes noted will progress. And Dr. Hammond points to still another interpretation.

A few definitions

The term "cancer of the lung" has various meanings in various contexts; a few definitions may prove helpful.

Carcinoma is cancer which arises from skin cells or from the cells lining the mouth, bronchial tubes, stomach, and other "hollow organs." The other main kind of cancer is *sarcoma*. Almost all lung cancer is carcinoma.

Primary carcinoma of the lung means cancer which has originated in the lung rather than spreading or metastasizing to the lung from some other site.

Bronchogenic carcinoma is cancer of the lung originating in the lining cells of the bronchial tubes which distribute air through the lung. This is by far the commonest kind of lung cancer.

Epidermoid carcinoma, undifferentiated carcinoma, and *adenocarcinoma* are the three major kinds of bronchogenic carcinoma. (These can be identified only by microscopic examination of the cancer cells.) Smoking is most closely linked with the first two of these three.

In this presentation, "cancer of the lung" usually means bronchogenic cancer. Where statistics refer to lung cancer generally, or to bronchogenic cancer generally, they usually *understate* the true relationship between smoking and lung cancer. The most impressive statistics are those which link smoking directly to epidermoid and undifferentiated carcinoma of the lung. In one study, for example, these two forms of cancer were found to be *88 times as frequent* among heavy cigarette smokers as among non-smokers. Most studies refer to lung cancer or bronchogenic cancer generally because more precise data are not available.

The experts speak out

As the evidence above—and great masses of additional evidence from many other sources—has accumulated, more and more public bodies in the United States and in other countries have spoken out on the issue, usually after reviewing the evidence in some detail. Among such organizations are the American Cancer Society, the American Heart Association, the National Cancer Institute, the National Heart Institute, the National Tuberculosis Association, the American College of Chest Physicians, the American Public Health Association, the Health Council of The Netherlands, the Medical Research Council of Great Britain, the World Health Organization, the Research Council of Sweden, and the Royal College of Physicians of London.

Surgeons General of the U.S. Public Health Service have issued three clear statements on the subject:

". . . the weight of the evidence is increasingly pointing in one direction: that excessive smoking is one of the causative factors in lung cancer."—***Surgeon General, September, 1957***

"The weight of evidence at present implicates smoking as the principal etiological factor in the increased incidence of lung cancer."—***Surgeon General, November 28, 1959***

"The weight of scientific evidence . . . demonstrates that cigarette smoking is a major cause of the increase in cancer of the lung. It is clear that an individual's risk to lung cancer rises in relation to the number of cigarettes smoked. Everyone should be aware of these conclusions because of their importance to health."—***Surgeon General, April, 1962***

As this issue went to press, a 1963 Surgeon General's Advisory Committee on Smoking and Health was again reviewing the evidence, this time on a broader scale and with reference to cardio-vascular, respiratory, and other conditions as well as cancer. A preliminary report is expected later this year.

Bronchial lining cells, he suggests, may develop hyperplasia and metaplasia spontaneously, without any external agent causing these changes. This is shown by the fact that some non-smokers develop these changes, and even progress to lung cancer. The environment in the normal lung, however, favors the survival and multiplication of normal cells in their competition with the pre-cancerous cells; this would explain why so few of the non-smokers with abnormal cells in their lungs go on to develop lung cancer.

In the lung of the cigarette inhaler the environment is very different. The cilia are paralyzed, they disappear; the cells are exposed to many chemicals which affect their chances of survival. Under the altered conditions introduced by the inhaling of cigarette smoke, Dr. Hammond suggests, the metaplastic cells may gain some important competitive advantage over the normal cells. They multiply, and the cancer results from the competitive advantage thus acquired.

All competent researchers in this area agree that the full story is not yet available. Much more research is urgently needed. But already we know that cigarette smoke as a "cause" of lung cancer is not a remote or implausible suggestion to be dismissed out of hand. On the contrary, it is a highly plausible and reasonable suggestion. It is strictly in line with the experimental and pathological evidence assembled to date.

Any one of the approaches discussed would be enough to show the plausibility of the conclusion that cigarette smoking *can* cause cancer. When combined with the statistical evidence that cigarette smoking *does* cause cancer, there is no remaining room for reasonable doubt.

IV. SMOKING AND LUNG CANCER: SUMMING UP

"Cause," the great red herring

The attentive reader will no doubt by now have noted that the word "cause" has been used only rarely in this presentation, and then generally in quotation marks. For though most laymen, if asked, would no doubt assure you that they know what the word "cause" means, there are considerable difficulties in defining it precisely—and even greater difficulties in determining whether a particular set of facts does or does not fit the chosen definition of "cause" and "effect." Philosophers, logicians, and scientists have thought much and debated more on the meaning and applicability of these terms.

The difficulties inherent in these concepts, moreover, have been obscured recently by those whose main aim seems to be to make sure that the cigarette-smoking-lung cancer relationship shall *not* be described as a cause-and-effect relationship. This can be done by setting up definitions of cause and effect so stringent that nothing can ever be shown to be the cause of anything else. This saves cigarette smoking from being labeled a cause of lung cancer, of course; but it also requires the introduction of some new term to characterize the relationship.

We propose to detour around this debate over words almost altogether, and to consider instead at this point the two questions which should really interest laymen when they consider whether smoking "causes" cancer.

The first practical question the layman should bear in mind is quite simply, "If I start smoking cigarettes, will my chances of dying of lung cancer go up significantly?" The answer, as we have seen, is Yes.

The other practical question is for men and women who already smoke cigarettes: "If I stop smoking them, will my chances of getting lung cancer go down?" The answer is again Yes.

Statistical evidence on the latter score comes from the prospective studies reviewed earlier. The Doll and Hill study of deaths among British physicians, for example, produced the following data:

	Lung cancer deaths per 100,000 man-years
Non-smokers	10
Ex-smokers who gave up smoking 10 years or more before study began	24
Ex-smokers who gave up smoking 1 to 10 years before study began	64
Smokers who continued to smoke	112

The Hammond-Horn prospective study of American smokers and non-smokers, because it dealt with a larger study population, was able to display the same effect separately among both heavy and light cigarette smokers.

Among the heavy smokers (a pack a day or more) the figures were as follows:

	Lung cancer deaths per 100,000 man-years
Non-smokers	3
Ex-smokers who gave up smoking 10 years or more before study began	61
Ex-smokers who gave up smoking 1 to 10 years before study began	78
Smokers who continued to smoke	158

Among the light smokers (less than a pack a day) the effect of stopping was quite similar:

	Lung cancer deaths per 100,000 man-years
Non-smokers	3
Ex-smokers who gave up smoking 10 years or more before study began	8
Ex-smokers who gave up smoking 1 to 10 years before study began	36
Smokers who continued to smoke	58

The mouse-lung experiments of the Leuchtenbergers fully confirm the statistical findings in this respect. Some mice were examined immediately after a series of exposures in the smoke chamber, and other mice after several months of "recovery" in a smoke-free chamber. The mice allowed to recover showed more changes in their lungs

than those never exposed to smoke, but fewer than the mice examined immediately. The findings indicate that the lesions caused by the smoking—at least up to the final, fatal change to invasive and metastatic cancer—are reversible.

Next, the human lung observations of the Auerbach-Stout-Hammond-Garfinkel group fully confirm both the statistical and the experimental evidence. These researchers compared tissues taken from the lungs of 72 ex-smokers with tissues taken from the lungs of 72 non-smokers and 72 smokers who continued to smoke until lung cancer was diagnosed. The three groups were matched for age, occupational status, and urban-or-rural residence. Metaplastic cells with altered nuclei were found in 1.2% of the slides from the lungs of non-smokers, as compared with 6.0% for ex-smokers—and 93.2% for current smokers!

Further, the Auerbach group found in the lungs of ex-smokers a kind of cell that they had never seen anywhere else, in either smokers or non-smokers. These cells had a contracted nucleus and seemed to be dying; the Auerbach group named them "disintegrating cells." The suggestion is that they represent pre-cancerous cells which are dying out in ex-smokers instead of reproducing and multiplying. The Auerbach group concludes:

"We feel that the findings of an increase in the number of cells with atypical nuclei following exposure to cigarette smoke, and a decrease in such cells with cessation of smoking, provides a reasonable explanation for the now well-established relationship between cigarette smoking and lung cancer."

These data, of course, should be of the greatest practical interest to men and women who are wondering whether or not they should stop smoking cigarettes. But in addition they have overwhelming theoretical significance.

One objection sometimes raised to the smoking-lung cancer theory is the possibility that some other factor associated with smoking—call it once more the X-factor—may be responsible for the lung cancer. As noted earlier, this suppositious factor would have at least the following curious characteristics:

- Smokers must have this factor and non-smokers must lack it.
- Pipe and cigar smokers must have less of it than cigarette smokers.
- Seventh Day Adventists must lack it.

To this unlikely list must now be added a fourth implausible characteristic of the hypothetical X-factor; it must occasionally disappear in men who have had it for years or even decades—and this disappearance must occur among the men who stop smoking!

Cigarette smoking is not the only "cause"

While the evidence accumulated to date, and the conclusions drawn from the evidence by competent, impartial public bodies, leaves no reasonable room for doubt that cigarette smoking causes lung cancer in the usual meaning of the word "cause," it certainly does not follow that cigarette smoking is the *only* cause or the only factor in lung cancer.

Heredity, for example, may play a role in the disease. There are studies suggesting that the close relatives of a lung cancer patient are somewhat more likely to contract the disease than others. But the hereditary factor is mild, indeed barely discernible, as compared with the overwhelming impact of the cigarette-smoking factor.

Viruses, as we have seen, may somehow or other be involved in the causation of lung cancer. They may explain, for example, why some heavy smokers get lung cancer while others do not. But virus-lung cancer evidence, if it were to become available later on, would in no way mitigate the direct, overwhelming impact of cigarette smoking.

Air pollution is quite probably also a factor in lung cancer. Indeed, a quite convincing case can be made out for such a relationship, including the known presence of carcinogens and co-carcinogens in the polluted air of our cities. A detailed review of this case falls outside the scope of this discussion of *smoking* and the public interest. The prospective studies do show, however, that of the two factors, cigarette smoking is by far the more significant. The possibility has not been ruled out that smoking and air pollution may have a combined effect which is greater than either factor considered separately.

. . . and lung cancer is not inevitable

Finally, the statistics do not, of course, point to an inevitable death from lung cancer for all cigarette smokers. Even among those who smoke two packs or more a day from boyhood to old age, eight or nine out of ten will die of something else. But it is now very clear that the risk of lung cancer for cigarette smokers as a group is enormously increased, and that the risk is directly proportional to the amount smoked.

The preceding material constitutes approximately one-half of the section on medical aspects of smoking in CU's forthcoming book, "The Consumers Union Report on Smoking and the Public Interest." The other half of the medical section reviews evidence linking smoking to other types of cancer, to cardiovascular diseases of many kinds, to various other conditions, and to general health; this section also includes an evaluation of numerous approaches to reducing the smoking risk, from the use of selective filters to self-imposed smoking techniques. The medical section is one of several sections in the book—for details of the book as a whole see the announcement on the back cover of this issue.

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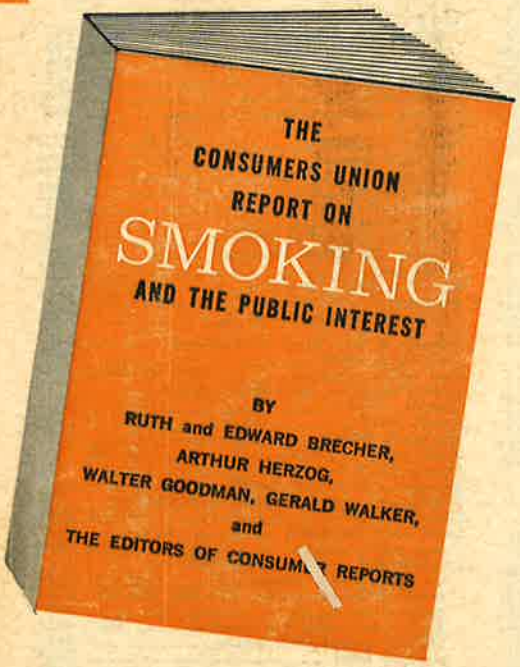

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- *a broad-scale review of the whole range of evidence implicating cigarette smoking in what has now become an international health problem*
- *a report on the tobacco industry's actions in the face of this problem*
- *some steps for both individuals and governments to take in dealing with the problem*

An excerpt from Part I of this book appears on pages 265-280 of this issue.

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