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cancer, particularly of epithelial types. In advanced asbestosis an opportunity for the occurrence of carcinoma of the lung on that basis seemed to be good. Actually nothing has yet occurred to cast out that possibility.

In the intervening time, during which we were to encounter two other like cases, there appeared scattered reports of the same occurrence in other locations; until, by compilation in 1947 Harevether² states that there were then recorded at least 31 instances of cancer of the lung in 235 cases of asbestosis, an autopsy pulmonary cancer incidence of 13.2% in persons suffering from asbestosis.

* For a fully acceptable comparison of this incidence of course one would be limited to the use of an autopsy series from a closely similar group in age and sex and at least in like environment for a similar period of time except for exposure to asbestos inhalation. Even these rather loosely set criteria could hardly be met where numbers would be large enough to provide ^{much} a minimal chance of error in statistically-type calculation.

$\frac{1}{2}$ The most that can be done at the present is to take what is available as evidence for or against an etiological basis for cancer of the lung in asbestosis, at the same time recognizing that the large chance of statistical error does not allow proof to be claimed but merely suspicion to be supported or not supported.

At present such evidence as is available appears to support the suspicion and to justify further investigative effort of whatever nature may be scientifically ^{or soundly} devised. At least the available evidence does not allay the suspicion.

In South Carolina the autopsy service that has furnished the human material for our studies in asbestosis is in a general hospital that through the years might be expected to produce a cross section of the run of serious diseases of the community of location.

For such value as it may have we have analyzed the findings in the 3943 autopsies occurring in that service from 1926 to 1950 in the age period of twenty years or over, the purpose being to cover a span of twenty-five years that corresponds roughly to the period of observation of asbestosis and an age group that would also cover the occurrences of that condition.

In that total autopsy series were found 46 instances of a diagnosis of asbestosis by microscopic evidence, including all cases regardless of degree, and among these 46 were three with advanced carcinoma of the lung, an incidence of (6.5%). In all others carcinoma of the lung occurred 58 times, an incidence of (1.5%).

Obviously such a comparison is of limited value, as are all others from which the question has been posed, although taken as a whole they are at least in agreement that carcinoma of the lung has been consistently more common than was to be expected in reports on asbestosis. Our incidence of that order is less than in some other reports, while our general incidence of carcinoma of the lung is comparable to some (Homburger) but less than others (Rigdon & Kirchhoff). Our incidence in asbestosis would approach that given in other reports if the calculation were made within the group of medium and advanced grades of asbestosis, in which area the three instances of pulmonary carcinoma occurred. In that group we had 23 cases, and the incidence within the group would be 10 4%.

Incidentally, for such support as it may give to the common report of growing prevalence of carcinoma of the lung, we find that in the first third of the time period covered in our series the incidence of carcinoma of the lung was 0.9%, in the second third 1.1% and in the latest third 2.2%, apparently a steady increase during the twenty-five year period, even though still not as high as reported from some other areas.

Without at this time attempting to make a thorough analysis of the published papers and records, a few recent pertinent reports are noted.

In one of the latest, Stoll, Bass and Lagrist³ report an additional case of cancer of the lung in association with asbestosis and cast up the literature as of 1951. They refer to Kerevother's 1947 report, as previously noted herein, and also refer to a report by Myers in 1949 recording a series of 115 cases of asbestosis in which there were 17 instances of associated pulmonary carcinoma, an autopsy series incidence of 14.8%, as compared to Kerevother's 13.2%.

Homburger⁴ reported three additional cases of association of pulmonary carcinoma and asbestosis in his autopsy service. In his series of autopsies from 1918-1938 there were 45 cases of pulmonary carcinoma, an incidence of 1.06%. Asbestosis was diagnosed 8 times and in 4 of the 8 cases pulmonary carcinoma was also found.

For such comparison as may be allowable, Rigdon and Kitchoff⁵ reported in 1951 a pulmonary cancer incidence of 7.5% (67 in 892) in an autopsy series in individuals 30 years of age and older in Tex. They suggest "that frequency of cancer of the lung ^{would best} be established from a series of autopsies," on account of the unreliability of death certificates.

Counterbalancing at least some of the weight of evidence of reports of cancer of the lung associated with asbestosis is the widespread increase of pulmonary cancer in the general population that has been recognized during the same period of time. A few references will serve to focus that tremendous problem.

Graham⁶, in 1951, says, "Bronchogenic carcinoma differs from other cancers in two important respects: (1) it has shown an enormous increase in the last 35 years; (2) there has been a progressively larger incidence in the male sex."

He states that Adler in 1912 could collect only 37* cases of cancer of the lung from the world's literature, while individual experiences in this country greatly exceed that total of reported cases from the whole world, and that cancer of the lung has advanced to a position of first place in men from one of 8th place in frequency - and this all within the last 35 or 40 years.

Dall and Hill⁷ refer to a British government report which shows that for the 25 year period from 1922 to 1947 the incidence of lung cancer in autopsies, in England and Wales increased fifteen times or what it had been previously.

An editorial note in The Lancet in January, 1952, strikes a note in referring to Hill's report that "in at least 17 out of 29 boroughs (metropolitan), deaths from neoplasm of the lung and bronch were more numerous than deaths from tuberculosis" and in remarking "This is something quite new."

Smith⁸, in 1952, states that lung cancer has shown an increase over and above what could be expected as a result of increases in numbers of elderly persons. He states also that high lung mortality has been recorded for both men and women patients with asbestosis in England.

Perhaps a personal note is permissible to illustrate the apparently universal experience in autopsy services during the last forty years that carcinoma of the lung has changed from a rarity to a commonplace. As a resident in the Philadelphia General Hospital

I had done an autopsy on what I took to be a case of tuberculosis, and had discarded all organs and tissues except the small pieces from which I prepared microscopic sections. When I showed the resulting slides of carcinoma of the lung to my chief and had to acknowledge that I had thrown the lungs away, he arose sternly from his microscope and literally booted me down the stairs.

Perhaps I may also note that the scarcity of residents in pathology nowadays has ~~also~~ brought about a difference in ^{their} treatment, although possibly not so much difference in their deserts.

EXPERIMENTAL STUDIES

Because of the question raised by autopsy observation of associated asbestosis and cancer of the lung, and among the many experimental studies that ^{apparently} have been done and lost are now going on by subjection of experimental animals to respiratory exposure to a variety of suspected substances, I have undertaken to see whether evidence of carcinogenic action on the part of asbestos or of the condition of asbestosis might be gotten in this way. Now in the third year, we have such a project under way, supported in part by a National Cancer Institute grant.

In devising such an experiment, one is, of course, faced with many questions, among which are the choice of experimental animals, the methods of exposure, the mechanical questions involved in methods, the practical matters of time and help, etc., etc.

Because, so far as I am aware, no animal except man has shown bronchogenic carcinoma of the lung naturally (or experimentally for that matter)

we chose to work with a strain of mice known to develop adenocarcinomas tumors of the lung in regular pre-calculable occurrence. In this animal we have one of short life span, of known lung tumor productiveness that might be susceptible to influence in that natural occurrence, and at the same time as good as any other prospect for bronchogenic carcinoma so far as is known. The strain chosen is the $1C_1$ hybrid (A male and C female) first generation from breeding stock obtained from the Roscoe B. Jackson Memorial Laboratory. Approximately equal numbers of mice are being exposed and kept as controls. Exposure chambers are of our own devising. Regular dust counts are made, with concentrations of dust as high as may be ^{obtained} without risk of killing the animals. As near as feasible, the same asbestos as our human cases experienced is being used as dust.

As the animals are sacrificed they are autopsied and the number, size, and distribution of lung tumors recorded. An attempt to grade these will also be made. It would be premature to give any analysis of this data as yet. However, no epidermoid carcinoma has yet been observed. ^{Now 3 years?}

Because we wished to also use another and larger animal, a number of dogs are ~~also~~ being subjected to similar dusting in specially constructed chambers. ~~This is~~, of course, a much longer term experiment, and the report can be made upon it at this time. One of the reasons the dog was selected is that observation of the occurrence of asbestosoid bodies in the lung of a dog exposed in an asbestos factory is recorded.

So far as I am aware, there is only one published report of an inhalation experiment exposing mice to asbestos dust as a test

of cancerigenic action. This report, by Nordmann and Sorge,⁷
by the authors
was claimed/as positive evidence of such a relationship and has
been cited to that effect by others. Smith,⁸ however, analyzes
it to the conclusion that it not only produces no proof of a
causal relationship of asbestos in cancer of the lung but actually
to the contrary. In that report ill-defined epithelial changes
were thought to have resulted in the lungs of 9 animals out of an
original 100 mice, squamous metaplasia was found in 6, adenocar-
cinoma in one and squamous cell carcinoma in one. / Smith questions
whether the interpretation was correct as to the demonstration of
actual squamous cell carcinoma and calls attention to the common
occurrence of squamous cell metaplasia in old rats with chronic
pulmonary infections and in animals deficient in vitamin A.

The only other experiment of which I am aware where animals
under exposure to inhalation of asbestos dust developed tumors
of the lung in a way suggestive of a relationship occurred in an
uncompleted experiment of the late L. U. Gardner that came to my
attention through a courtesy from the Baranac Laboratory.

In one of Gardner's experiments in asbestosis he found a
high incidence of the type of lung cancer to which mice are disposed
since the strain he was using was unknown as to tumor susceptibility
and since the experiment was uncontrolled from that standpoint, he
stopped it, apparently intending to set up a proper experiment to
follow up the suggestion later.

* At least it does not appear that any reported experiment can
be accepted as conclusive, and I am inclined to the same view as
expressed by Smith, that up to the present no experimental proof
that the inhalation of asbestos or any other material will cause

bronchogenic carcinoma has been presented.

As the matter now stands, it appears that while additional evidence of the same sort has been collected in the meantime, the question that was raised with our first report in 1935 as to whether asbestosis can act as a producer of cancer of the lung in human beings remains as open as it was when raised.

So far as we are concerned, the conditions in the industry are so much improved that even the problem of asbestosis has become greatly lessened. The grade of exposure to the dust has been so reduced in our territory of experience that we no longer expect to see the extremes of the disease that earlier uncontrolled conditions caused.

Even so, and although our cases were these of ^{medium to} advanced asbestosis, if the exposure may be cancerigenic it could not now be certainly said that lesser grades of the primary disease would be immune to the tendency.

In all respects, therefore, the problem remains with us and should be subjected to continued investigation on its own merits, aside from any advantage that would accrue to the investigation of malignant neoplastic disease as a whole if such an etiologic factor were uncovered.

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AMERICAN AIR FORCE
OFFICE OF THE DIRECTOR
OF THE AIR FORCE

MEMORANDUM FOR THE DIRECTOR

ATTENTION: AIR FORCE

DATE: 10/10/50

AMERICAN AIR FORCE
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