FILE NAME: Saranac 7th Symposium (SSY)

DATE: 1952

DOC#: SSY018

DOCUMENT DESCRIPTION: Transcript of Presentation by Dr. Levin with Discussion

TAKEN FROM PAGE 344.

BY DOCTOR LEVIN:

Thank you, Doctor Rhoads. Ladies and gentlemen, I am supposed to talk to you on the philosophy of the biostatistics of environmental pulmonary cancer, and I have never been sure, up until this moment, whether I was supposed to concentrate on philosophy or biostatistics or environmental pulmonary cancer. I shall probably try to do all three, and succeed in neither of them or not one.

I certainly would like very much to second the remarks of Doctor Rhoads as made and perhaps I can do so and make some comments on some of the things he has said, by telling you what my own point of view is in this matter.

It is primarily that of an epidemiologist which is the field in which I received most of my medical training. An epidemiologist, as you probably know, is not a statistician necessarily, although he has to know something about statistics and use them and know when he is in trouble, some - so he can go to someone who is a statistician.

An epidemiologist is, primarily, a fellow who is interested in two questions, first of all, whether a certain group of people actually do or do not have more of a certain disease than other groups do have. He's interested in knowing whether that's really so, and so he is rather critical of things which may look like that, and nevertheless are not really good evidence, and he is interested in knowing, if that is so, what the reasons might be, and his reasoning for those interests are quite practical, because he is the man who is usually called upon to make certain decisions or to give certain advice as to whether certain things should or should not be done in a given situation.

Now, it just happens that historically, that type of question usually arose with our epidemic diseases and that's why, I suppose, the term epidemiology, is usually thought of as referred to with people who deal with infectious diseases, but precisely the same question can arise in almost any type of disease, and certainly they do arise in industry.

Now, the epidemiologist's point of view on pulmonary cancer and the evidence respecting various etiological agents is, I would say, highly critical. That is, we are aware from long experience, that a lot of things which look like etiological relationships are not necessarily such. The other point of view, I would say, perhaps

would seem to you to be opposite, but I would offer to you as the result of long reflection on the part of a good many people.

We epidemiologists suspect that, from the standpoint of the causation of pulmonary cancer, our best experimental animal may be man rather than any animal we can study in a laboratory. Now, man is not a very good experimental animal, but it seems as if in cancer, he may be our only one in some forms, and the laboratory may or may not confirm what we find in man, but we have a strong feeling that we are missing a pretty good bet in not studying much more intensively, possible relationships which may be etiological to man.

We have about twenty-five thousand cases of pulmonary cancer each year in this country, and it seems very unlikely that those twenty-five thousand people do not have a good many characteristics which distinguish them from their fellows, which may have some relationship to the fact it involves lung cancer, about which we stilldo not know very much.

Now, Doctor Rhoads mentioned the relationship to smoking tobacco, especially cigarettes. I know of no observations which would imply or implicate any other type of smoking, and I mentioned the work of one investigator or rather two, Winter and Graham. Now, I happen to know Doctor

Winter and I like him very much, and I agree with Doctor Rhoads' estimate of him as a very energetic, a capable and an enthusiastic chap. The kind of observation, however, which Winter and Graham made about relationship between smoking and cancer is precisely the kind of observation which you will find in the literature for the last twenty years. If you look up one of the earliest multigraphs on lung cancer published about 1930, you will find about four pages devoted to the relationship to smoking cigarettes.

Now, those observations were never taken seriously, and they were never picked up, precisely because of the uncritical, over-enthusiastic type of analysis on which they were based, in other words, they were based on inadequate controls, they were studied in such a way that one could see that the person making the study has a pretty strong bias in the first place, as to what he would find. It's not the sort of evidence which really tells you anything that you can rely on.

Now, it happens that the observation of Winter and Graham have been confirmed as to their general tenor. There is a relationship between smoking in tobacco. There is a great difference in the quantitative observations. If we are to believe the observations of Winter and Graham, pulmonary cancer is extremely rare in people who do not smoke cigarettes, about three percent of lung cancers,

according to their data, three to five percent, occur in people who do not smoke cigarettes.

That is not in accordance with observations which we have made, and I, frankly, doubt whether it is in accord with what the facts are. I think that is one of the crucial questions which remains to be proven or to be further tested.

However, I did not intend to really go into the question of that particular observation, because that is not our topic. What I thought I would do is to give you some general quantitative background for this whole question of lung cancer which would serve as sort of a backdrop for the papers which are to come, first of all, the importance of this topic, this form of cancer as a human tumor.

May I have the first slide? This first slide is simply the characteristic age curve of cancer, that is the incidence of cancer by age among males and among females as usually occurs in New York State where, as you know, cancer is a reportable disease. These are all cases reported from all sources for various periods of time, put on an annual basis. That is a very interesting curve, for one thing, because it does not follow the type of curve that you would expect in most forms of cancer which keeps going up with age. Most forms of cancer start in lower, younger age groups and keep going straight up. In lung cancer.

after about fifty-five, the rate drops.

There are a number of things which can be said about that observation, and I don't propose to go into all of the possible explanations, but it does mean, one thing, it does suggest one thing, that for some reason, people who were born, this is 1945 roughly, and people aged sixty in 1945, were born in 1885, as my arithmetic informs me. People born before 1885, for some reason, had less, have less lung cancer than people born at an earlier age, an at earlier period.

That may not be self-evident to you, but it follows from a further analysis of these curves which show that when you analyze these curves by the year of birth, they keep on going straight up, and they keep on going up in a much higher fashion depending on when the person was born. That is not the sort of thing that you would expect in a carcinogen, if it is a carcinogen, which occurs generally, such as a carcinogen in the air. It's apparently something which picks out certain ages and not others.

Now, in most - the important point that I wish to bring out in this slide is that you couldn't analyze any two groups of people, say the number of lung cancers in two factories, or the number of lung cancers in one factory as compared with the number of lung cancers in the surrounding countryside, unless you took into account the age factor,

because obviously if you did have a lot of people in this age group, you would have more or less cancer than if you had a lot of people in this age group or this age group. You would certainly have to adjust for age, and it's surprising to find that some studies do not even take into account such a symple and obvious variable which has got to be adjusted.

Now, when you take this type of curve, that is the number of cases which occur by age in one year and apply to an ordinary life table, which is the expectancy, the expectancy of living, at various ages in the duration of life, you will get a table such as the next slide, which will tell you about how many cases of cancer of various types one might expect to occur in the population today throughout the rest of their lives. These figures are all based on an a base of one, that is this top figure gives you the probability of skin cancer occurring in males throughout life, and the figure .02 means that two out of a hundred, two percent of all males, almost two and a half percent of all males, using the type of data which I have just described, this is the actual incidence of cancer as determined by reporting applied to the life table, two out of a hundred males throughout the rest of their lives will develop some form of skin cancer.

Now, for lung, the figure is just over one percent,

about one percent of all males according to New York State data, may be expected to develop lung cancer. That may be considered a sort of backdrop of this whole problem.

It is a problem which, at a minimum, will effect one percent of the male population. I'd like to stress the point that that is a minimum. First of all, these figures are based on the data for '42, '44, since then, the rates for lung cancer have gone up and the death rates from all causes gone down, which means that the opportunity for developing lung cancer has increased and the rate at which it develops has also increased, so that figure one percent is definitely minimum, but it is at least one percent of the general population.

May I have the next slide now? This -- oh, there is a paper slide in between there -- may I have the first of the paper slides then? I don't know whether you can see this. I think this is another of the important observations about lung cancer which we have to remember concerning this whole problem, and that is the increase which has occurred over the past two or three decades.

These are the actual mortality rates in New York State between 1931 and 1948 in females and in males, standardized for age, that is the age factor has been kept constant in the two periods. The striking thing here is the difference in the increase in the sexes. In females, the

increase has been about from 2.5 to 4.3 deaths per hundred thousand per year, an increase of about seventy percent. In males, the increase has been from 4.7 to 19 per hundred thousand, an increase of over three hundred percent.

Now, an increase in lung - in any form of cancer, as you know, may be due and often is attributed to the fact that our diagnostic procedures are more effective. If that is the explanation for this increase, then we would have to ask ourselves why, diagnostic procedures were three hundred percent more effective now as compared with 1931 in males, but only seventy percent more effective than in females.

I would say that certainly that causes or casts considerable doubt on the explanation that such an increase can be due to diagnostic procedures alone and makes it extremely probable that there has been a real increase in lung cancer over this period, probably in both sexes.

Another bit of evidence -- may I have the next slide -- which leads in the same direction, is the different way in which the ages have been effected in this increase. Now, that's the slide that you showed, the last slide that you showed before this one. That's it. I - this is the mortality rate in the United States. I call your attention to the upper left, your upper left-hand corner here which gives you the age specific mortality rates.

This is age down here in '30, '39 and '49, and you will notice that the increase has been more marked here in the middle period than here in the older periods, which again conicides with the observation that there is something happening in these people around sixty, which apparently is not happening nearly so markedly in people who are older than that. That again is the sort of thing that one would not expect to see if this were purely a diagnostic phenomenon. There is no reason to suppose that diagnosis may - in a disease with high case fatality such as cancer of the lungs, should make such a marked difference according to the age, should show such a marked different according to age alone, so that putting these data together, one would lead to the conclusion that one could not safely assume that this increase was purely artificial and due to the fact that we found more lung cancer, one would certainly have to assume that there was a very strong probability that this was something real.

Now, one of the points that one can make about real changes in cancer incidence over time, is, as a matter of fact, in incidence in any disease over time, that if they are real, they are probably due to some environmental factor. The reason for that goes back to one of the laws of genetics, if you will remember your genetics. You will recall that, according to the way the genes operate, their

proportion from one generation to another remains constant under most circumstances, so that if genetic factors, if constitutional factors were the ones which obtained, we would not expect the incidence of the disease to change from year to year. If we find a real change, we should suspect some environmental cause rather than some genetic cause as the reason for that change.

So I would feel safe, from the philosophic viewpoint here, speaking as an epidemiologist that we have good reason to suppose, first, that there has been a real change in lung cancer and, second, that that change is probably due to something in the environment. Whatever that may be, of course, remains to be seen.

Now, how would we go about studying the possible relationship of lung cancer to various environmental factors? Now, may I have the next slide. I have placed on this next slide, a hypothetical situation in a - I don't know whether you can see this or not. I have here a state or a population group in which there are five million males in whom nine hundred cases of lung cancer occur in a year, and we have in that same population group an industry, we call Industry A, which has ten thousand males among whom nine cases of lung cancer occur in a year, so that in the entire group, that is in the entire state, if this is a state we're talking about, there are nine hundred and nine

cases of lung cancer in one year.

Now, suppose one wanted to study lung cancer as to whether it was related to, say, some particular industry. According to -- we could use at least two methods which might be called the case method or the retrospective incidence method. We could take all nine hundred and nine cases of lung cancer, as we do here, and we could take comparable number of controls, we take a thousand controls, and if we were interested in Industry A, if we had reason to suspect Industry A, we'd find out how many of these nine hundred and nine lung cancer cases were people who worked in Industry A. If we got all our cases, we'd find that there were nine of them and in our control group, which should be representative of the total male population, we should find the same proportion of industry A workers as ten thousand is to five million, that is the proportion of male population to males in industry A.

Now, ten thousand to five million is two per thousand, so we'd find two cases, two people who worked in Industry A in our controls. Now, mind you, I assume that we don't know these facts. We simply have these nine hundred and nine cases and we're interested in whether Industry A has anything to do with lung cancer. If that is what we did, and we were successful in getting all nine hundred and nine lung cancer cases and if your control group is

properly selected, in other words, it wasn't biased in such a way as to accidentally drop out these two Industry A cases, or if our lung cancer cases were poorly selected so we might not - we may have missed these nine cases, in other words, if our experiment were perfect, we'd find that there was one percent Industry A people in the lung cancer cases and two per thousand Industry A people in the controls, which amounts to a ratio of five to one, that is one percent is five times as much as two tenthsof one percent. This gives you five to one.

Now, if you go back to our postulated population, this is a method, nine hundred and five million is a rate of ninety per hundred thousand and nine per ten thousand is a rate of eighteen, it's just - it's just the other way around. This is eighteen per hundred thousand and this nine should be here and the relation between eighteen and ninety is five to one, which is exactly what you would find in your case method.

In other words, your case method, if it were properly performed would give you the true situation with respect to the incidence of lung cancer in industry A as compared to the population. If there was five times as much lung cancer in Industry A as in the population, assuming, of course, that the age factor and other possible variables which might effect lung cancer had been given

consideration, I am assuming that that has been done. The other way in which you might do that would be the retrospective incidence method. You take ten years of Industry A and how many cases of lung cancer occurred in ten years.

Now, if nine cases occurred in one year; in ten years, ninety cases could be expected to occur in the ten years, and they'd be - you'd have to ask yourself, how many cases do occur in that period, and one of the ways in which you might answer that question is, why, you would say, I expect or would expect the same number of cases that would occur if industry A had the same incidence as the general male population. That would give you ten years times ten thousand males, which is the same thing as a hundred thousand and one, and an incidence of eighteen per hundred thousand would give you an expected case incidence of eighteen cases, in this period, which again would be a ratio of five to one.

Now, I'd like to call your attention to the fact that if this particular case method were done on half the number of cases, if instead of getting all nine hundred and nine cases, you had gotten half of those, then these two observations would not be significantly different from each other from the standpoint of chance variations. That is they would be the kind of difference that would occur often by chance alone, so that one couldn't be sure that that was

a real difference, so that the actual magnitude, the actual number of cases that you'd study in an industry or that you'd study of this kind, is as important as the selection of the cases themselves.

Now, let us assume, however, that we have done this study in this way and we do find a significant difference, in other words, we find that there are five times as many cases in Industry A as in the general population, all factors being held constant. Does that mean necessarily that Industry A, there is something in Industry A which causes lung cancer?

Now, in my view that does not necessarily mean that. I think that one of the important principals, philosophical principals, to remember in studies of this kind is that data do not tell you any more than what they actually signify. They tell you that, for some reason, people in Industry A have developed five times as much lung cancer as people in the general population. That may be due to the fact that there is something in Industry A which causes lung cancer. It may be due to something else, for instance, if we were studying a factor such as the presence of six fingers on one hand rather than five, and found that one industry had five times as many people like that as would be expected in the general population, I think one would think twice before one attributed that to something in the

industry. One might, normally, if that is a genetic trait, one might wonder whether the owner of the industry had six fingers and whether he had many members of his family working for him.

The point is that one can not automatically jump from association of this kind to causation. Causation may be the factor or it may not. Whether or not it's causation depends on other evidence, depends on what else we know about the disease. If we did not know that various dusts can produce lung pathology, that it is possible to produce lung cancer in animals by the application of certain chemicals, I think we would be less apt to suspect that an observation like this actually indicated a cause of the effect.

Now, actually, there are only a few ways in man that I know of, whether - or that I can think of, in one connection, that can actually prove causation to one's satisfaction. One is by this second method here which I have called experimental induction. I mean if one suspected a certain substance in this industry and one applied it either to man, which, of course, is extremely improbably although it has been suggested, and as a matter of fact, we are making tentative plans along that direction, if one applied to man or animals and actually got the disease in question, I think one would have some additional evidence

that that was an etiological agent.

However, I'd like to call your attention to the fact that if one didn't do that, one wouldn't have evidence that it wasn't an etiological agent, because unfortunately, there are many things or at least there are some things which will cause cancer in man that will not cause it in animals, so the negative evidence is not conclusive negatively.

The other way you can test it is by the protective test, by actual prevention. I mean if we actually made some element in Industry A which was a factor and then studied the incidence later on, the protective incidence and found out it had dropped, I think we would have some additional evidence to the etiological relationship, but it seems to me that one or the other of those tests has got to be applied in all of our presumed data regarding etiologic - etiology in pulmonary cancer, environmental etiology, before we are absolutely certain that what we think is etiology is or actually is.

Now, I don't know whether I'm running too much over my time. I had some data which, from the philosophical point of view seemed to me to be interesting as to how important environmental, especially occupational cancer might be in America, but we might keep that, perhaps, for the discussion, Mr. Chairman.

BY DOCTOR RHOADS:

You have three minutes.

BY DOCTOR LEVIN:

I do have three minutes? Well, may I have the next slide? These are some - some of our data regarding the relationship between cigarette smoking and cancer, two forms of cancer, cancer of the lung and cancer of the larynx. This is simply the proportion of cases of cancer of the lung and cancer of the larynx who were cigarette smokers, by age, compared with two types of controls, in the same hospital populations.

This is our - the Buffalo Hospital, the two controls were patients who had no malignant tumor and patients who have other types of cancer than lung or larynx. You will note one thing which apparently has not been emphasized very much, but which we have confirmed by further study of the same phenomenon. That is apparently there is much relationship between cigarette smoking and larynx cancer as between cigarette smoking and lung cancer.

You will notice, also, the interesting thing is that the cigarette smoker is one of the things which drops off with increasing age. You were caused - one of the things we would probably have to find to explain the age curve in cancer is something which dropped off with increasing age. For some reason, at least at present, the older

a man is, the less likely he is to be a cigarette smoker.

Now, that's a very interesting observation. That is, again, as Doctor Rhoads indicated, and I think we will all agree, this does not necessarily mean that cigarette smoking causes lung cancer, though that may be simply an added effect or factor. It simply means there is more lung cancer among cigarette smokers than there is among non-cigarette smokers.

The interesting question is what does that actually mean from the standpoint of numbers, quantitatively? And there are various ways of doing that, and I won't try to go into the arithmetic of it, but on the next slide, I have jotted down some conclusions which arise from our data. They do not arise, incidentally, from the data such as has been induced by Winter and Graham, because if their data is right, practically all - practically only cigarette smokers get lung cancer and that isn't true according to our data at all.

Thirty-five percent of lung cancer cases are not cigarette smokers according to our figures. If our data are correct, throughout life, this is the incidence of lung cancer. In non-smokers, five per thousand, this is throughout life, mind you. In heavy smokers, that is not just cigarette smokers, that's people who smoke one to two packs a day, it's six times as much or thirty per thousand, that's

three percent. You will recall that the lieftime expectancy in the general male population is one percent and this is three times as much.

Now, according to a recent paper in Public Health Reports by Britain, Frasier and Coven, it's is my opinion that that agrees at least in general with the data of Machle and Gregorius on chromate worker cancer; these are not the figures given by Britain, Frasier and Coven, they are simply my interpretation of them, as to how much lung cancer those workers may be expected to develop in twenty-five years if their data are correct, per thousand.

Among white males, there should be sixty-five cases in twenty-five years in chromate workers and among non-whites, two hundred and thirty-five. Now, unless my arithmetic is very, very far off, this means one thing, possibly two, certainly that cigarette smoking, if it is a carcinogen is a pretty mild one, since it increases the general incidence throughout life only by a factor of three, and if such an occupational factor as chromate dust is a carcinogen, it apparently, when it does work, is a pretty strong one, since it may increase it by a very much higher factor. That is, twenty-three percent of all the male workers, in twenty-five years, may be expected to develop lung cancer if the data published by these workers stand up and are representative of the true picture.

So that we have apparently, assuming that the facts we have at our disposal, we can rely on, two chief types of carcinogen, which are environmental, among others, because I hadn't considered general environmental dust, one which is heavy smoking, which is apparently very weak, and one of this type whose incidence we don't know since we don't know all the occupational carcinogens, but which when it does occur, is perhaps very strong.

I think I have more - one more slide, which perhaps puts this in numbers. Applying the one percent throughout life figure to the seventy-five, approximately seventy-five million males in the United States, throughout their lifetime, seven hundred and fifty thousand of them will develop lung cancer. Of those, a little less than half or rather something like a third, two hundred twenty-five thousand, will be non-smokers. The rest will be smokers, but since there is no reason to suppose that smokers are immune to the same influences as the non-smokers, we can only attribute three hundred and thirty-seven thousand of those cases to smoking per se, so that what this leads us in substance, to is this, that even if smoking gets full credit, we have got to account for about four hundred thousand cases of lung cancer to other causes which, if they're environmental and if they occupational, means that we've got to find a lot more occupational causes of lung

cancer than we have up to the present.

The one thing which makes that likely is the fact that one, when occupational causes do occur, they apparently are quite strong as compared to such a mild agent as tobacco seems to be. (Applause).

BY DOCTOR RHOADS:

I know Doctor Levin's presentation will arouse a great deal of discussion. I would like to open the discussion by just one question, Mort. I assume that the drop-off with age is just for the number of individuals in that age group population?

BY DOCTOR LEVIN:

Yes, that's the case.

BY DOCTOR RHOADS:

And I also assume that when you refer to the high incidence in individuals born in 1885, that is continuing high as the years go on and similar studies are being made; it isn't that year, but that period after?

BY DOCTOR LEVIN:

Yes.

BY DOCTOR KING:

I'm very much interested to hear Doctor Levin indicate his acceptance of smoking as a possible etiological or participating agent, because this, in view of the importance of the problem, its extent would justify one perhaps

in considering whether that subject should lend itself to experimental work designed to prove or disprove the case more adequately, provide more adequate statistics on the subject.

Now, may we have discussion? Doctor Lanza, would you care to make any comment at all?

BY DOCTOR LANZA:

No, I have no comment.

BY DOCTOR RHOADS:

Is there no one who inclined to smoke cigarettes, who wants to ask questions?

BY DOCTOR FLETCHER:

According to Doctor Levin, he supposes that chromate is a much more powerful carcinogen than tobacco, but how did he measure the intake of chromate as compared to tobacco in these two groups?

BY DOCTOR RHOADS:

Doctor Levin, would you care to answer that question of Doctor Fletcher's?

BY DOCTOR LEVIN:

Well, I think it's a very good question. In other words, it refers to the relative dosage. I wasn't trying to be as fine as that. I was simply referring to chromate as the net experience of a chromate worker, wherever they're involved. The net experience of a chromate worker, if the

data that we have available act or are correct, I have no reason to suppose they're not, because they seem to have been very carefully done. The net experience, whatever that is, is apparently much more powerful than the net experience of heavy smoking. Now, your question is what would happen if we took those chromate workers and gave them one tenth as much dust as they did get? I don't know. I'm simply referring to the actual facts as they were observed in actual life.

BY DOCTOR RHOADS:

Does that answer the question? I'm surprised no one has commented on the possibility of air pollution. Doctor Smith, you must have some feelings on this point. I saw Doctor Joe Smith in back here a few minutes ago. Would you care to comment on air pollution in view of Stott's report, as a complimentary factor of environmental nature?

BY DOCTOR SMITH:

I have yet to see Doctor Stott's report. It certainly opens up a very different problem. I think I'm in a fortunate position here in that most people who are really familiar with this subject and who told me what little I've been able to gather about it, are in this room and I can pass the problem on to them.

BY DOCTOR RHOADS:

Well, there are other facts bearing on this

question in one report, the incidence of lung cancer in individuals in cities of over one hundred thousand, is much greater than in rural communities. I don't know how valid these hints are, but they justify further discussion. Are there further comments on Doctor Levin's paper?

(No response).

If not, we'll proceed to the next paper. Doctor Hueper needs no introduction. You know his long continued contributions to the field of environmental cancer. My acquaintance with him dates over many years. It has always been most stimulating. He is one who has stuck to his guns in this important problem, and I happen to know, in some instances, under difficult circumstances, and has given us much knowledge of this important field. Doctor Hueper.

BY DOCTOR HUEPER:

(Doctor Hueper read a prepared paper, which is on file at the Saranac Laboratory).

BY DOCTOR RHOADS:

I'd like to congratulate both of the speakers on completing their presentations on time. I hope their precedents can be observed for the rest of the day.

I would like to raise one or two questions to initiate the further discussions. Doctor Hueper, you referred several times to the presence of benzpyrene in suspected material as supporting the view that these materials

were carcinogenic in the lung of man. I do not know of the evidence that pure benzpyrene, per se, will produce cancer in the primate. Does such evidence exist?

BY DOCTOR HUEPER:

No, that evidence does not exist. There is only some circumstantial evidence available. There are two cases on record among laboratory workers which, by accident, came in contact with benzpyrene. One was the screen of the skin while later on a cancer developed, but whether that is conclusive evidence, I would - I am not quite certain, but we have to consider one fact, that benzpyrene is only one of the carcinogenic chemicals in these materials. For instance, Falk and Steiner isolated three or four, and they are all shale oils available which do not contain the pyrene, but which are carcinogenic, so we should not - it isn't the material as such, the crude material as such, which we should consider as carcinogenic, and we should not take the presence of one carcinogen as authentic, but should take into account that such materials are carcinogenic.

BY DOCTOR REDDISH:

This was one of the things I hoped the doctor would bring out. If benzpyrene is present, it suggests the presence of possibly stronger carcinogenic agents, or a whole series.

BY DOCTOR HUEPER:

A whole spectre of carcinogens.

BY DOCTOR RHOADS:

Doctor Hueper made also a very interesting point in John, that was the disposition of the point that the sun might be prophyllactic. I think one can not wholly ignore the endocrine system in cancer, in view of McCann, Tannenbaum's and other worker's surveys. There are surveys as yet unpublished, but they suggest very strongly indeed that hypoxectomy (?) will render inactive, inert compounds which, otherwise, are active, exceedingly carcinogenic, and it's not entirely inconceivable that the sun might play some role.

BY DOCTOR HUEPER:

Various surveys have been made by Pellet, who studied the incidence of cancer of internal organs among Canadian - among the natives, and he suggests that persons who develop cancer of the skin would become partially immune to cancer of the internal organs. I don't think the occupational evidence shows that. If you are exposed to an occupational agent that causes cancer of the skin, you have, in fact, a higher liability to develop cancer of the internal organs. That's the general evidence offered from a general epidemiological viewpoint.

The pathologists of the University of Richmond - his name escapes me right now, he makes very similar claims.

I don't think they are justified on the basis of the factual evidence we have. One can speculate a lot but I think it's our feeling we have to stick quite strictly to what we actually observe, the factual evidence, and not speculate too much.

BY DOCTOR RHOADS:

Now, I'd like to ask Doctor Levin to comment on the statistical validity of the evidence regarding occupation, where the incidence is comparatively low. Many of those figures are from Kenilway series, of course; do you want to comment on the validity of those observations of the engineers, the tobaccionists, the barroom workers, other happy occupations?

BY DOCTOR LEVIN:

I don't think I have recently examined that data to - sufficiently to be at all critical. One of the things which impressed me about the type of information that Doctor Kuepper presented and which is, I think, good literature is that, in general, even at the - with a few exceptions, the lung cancers of Schnaberg, seems to be one of those, even with the high dosage of exposure and the majority of people exposed, apparently do not develop a disease, which strongly suggests that we are over-stressing the situation if we confine attention entirely to the ventilation and ignore the intrinsic constitutional agent. I think that perhaps - I

don't mean to say that we should do the other thing and throw overboard the evidence regarding these things, but I think we should study just as carefully why it is that some people just as exposed to the concentration of the agent, do not develop the disease. I think we may get clues to the development of the disease in others which may be more useful or certainly as useful as the preventive aspects of the occupational data.

Some of the published material that Doctor Rhoads referred to is simply of a kind that's very difficult to evaluate because you don't have enough facts. You don't know how many people were in the factory at a certain age for so many years. You don't know whether all the cases were studied. You don't know at what age they were retired. You don't know the difference between the people that you did have information about, and the people that you did not have information about, but from the standpoint of a state official, which I am, and from the standpoint of what all this sort of thing leads to, from the standpoint or question of actual action, official action, I would say - and since this is an industrial group, I'd like very much your reaction to this proposal - I would say that the evidence is sufficiently strong to at least justify one proposal and that is that industry be required to keep much better records than it does regarding both its workers and what

happens to them without any bias as to what conclusions will be reached and perhaps with every preservation of the confidentiality of that information.

I think the information is there that will answer many of these questions beyond a shadow of a doubt; we simply are not getting the information in such a way so that we can analyze it and really be sure of some of these things. I think, however, that could very readily be done.

BY DOCTOR RHOADS:

Thank you, Doctor Levin. I hope that point will come out and I think I would like to emphasize another point Doctor Levin made previously, and that is it is perhaps the obligation of industry to consider the setting up of the so-called preventive experiments with control groups, which, after all, will provide perhaps the most final data, I take it, from your feelings about it.

Like to have your further discussion. Yes, sir.

BY DOCTOR PRATT:

In reference to carcinoma in asbestosis cases, we see the hyperplasia of the bronchial epithelia and its extention into the alveolar spaces in areas of the lung that show fibrosis, but if we look at the epidemiology of bronchi, it seems to me it looks quite normal; yet in the cases that do have carcinoma together with their asbestosis, the cases that I've seen, in the main give every evidence of

being primary in the major bronchil It seems to me that if there is a connection between asbestosis and cancer, it must be considerably more devious than simply hyperplasia, metaplasia and neoplasia. I'd like very much to hear Doctor Hueper's comments on that point.

BY DOCTOR HUEPER:

I'm glad you brought up that question, because it's been a long time in my heart, but I'm glad you brought up that question because it's been a long time on my heart, and I would like to shoot it off.

The carcinogens are really misnomers. If you study the - an atomic reaction of carcinogens, you see first hyperplasia, you see lots of benign tumors and then finally you may see carcinomas, you may see that some of the benign tumors become malignant or you may see, in the prepared soil carcinomas, originating primarily.

I personally place a great deal of significance upon seeing the development or history of carcinomas in the slides I have studied in the cases I have studied. I think they give us the life history of the carcinogen and the life history of the cancer. To me, the changes in asbestosis are typical of that. I have seen them in the cancers which we produce in dogs. I have seen them in cancers which we produce in mice with the various hydrocarbons; it's always the same story; to me those progressive changes are

significant.

BY DOCTOR RHOADS:

I think this is a very interesting point that comes up frequently in discussions of the histo-pathologic development of neoplastic change, and always puzzled by the group of cells presumably equally in contact with others become exposed to a rapid shift in mortality, and I presume there are unknown factors regarding concentration. Next question?

BY DOCTOR [redacted]:

I was the instigator of two of the surveys Doctor Hueper mentioned, the one of Lombardo's on arsenic and the one of Ingall's on carbon black, so I have an interest, more than a casual one, in Doctor Hueper's remarks. Today the big arsenic producer is Sweden, with Mexico second and the United States third. We will continue to produce arsenic for the indefinite future, because of the fact that the copper comes contaminated by arsenic.

The industrial experience of the smelters dates back now in the United States for about forty to fifty years, so that as experience goes in health matters, they probably have as good as there is. The Mexican experience is a little briefer and so is the Swedish experience. The survey in the arsenic works was instigated because we were a little apprehensive after what was found in the

chromate industry to which we may have some slight analogy.

That is, the chromate workers get the perforated scepta, and then they were shown to get lung cancers, so we wondered if perhaps the same kind of thing did not occur in the arsenic business.

Doctor Hueper remarked that Lombard, and Lombard and Schnager, from an interpretation of their statistics, the interpretation was curious. I can't say I agree. I will admit that half of something is - startles you, and - but half of four or half of ten is not very startling, and I rather think that the explanation in the smelter in the west in which Hueper takes them to task for not making more of the arsenical cancer is due to the fact that the figures are too low, the amount of numbers of workers are too low and they concluded that it might just as well have been the other way, on a pure chance basis.

They took for a control a smelter in the arsenic business that had no arsenical exposure and, in that case, the lung cancer, I regret to state, was a little more alarming than that of the community at large, and there was no arsenic exposure whatever. The smelter handled no arsenic.

I think that the doctor's plea for better statistics in industry is an extremely good one and I know that the smelting business, all of the big smelters now, I'm familiar with what they're doing about this, are more than

anxious to get their figures straight and will keep records. Their records, in the past, are very fragmentary. Hueper did not mention the fact that there was a good arsenical survey in Utah by Neal and others, in which they found no evidence of lung cancer.

BY DOCTOR RHOADS:

Well, here information comes from another angle, perhaps alluding to a point brought up before, and that is the tendency is to incriminate pure compounds of known activity when one is considering the possible carcinogenic action of a most confusing and complex mess of materials coming out of a smelter or coming out of a complex organic mixture, and perhaps the evidence, I take it the evidence is good for the problem involved, in contamination and pollution, but not so good for a single pure constituent of the polluted material. Yes, sir?

BY DOCTOR SAMUELSON:

On that point, in reference to carbon black, I'd like to correct the record. The Steiner work showed that 3:4 benzpyrene and 1:2 benzpyrene, a very mild carcinogen was present in the extract of carbon black, and no evidence of carcinogen to follow.

BY DOCTOR RHOADS:

Thank you. Will you give your name please?

BY DOCTOR SAMUELSON:

Doctor Samuelson.

BY DOCTOR RHOADS:

Very interesting point, yes.

BY DOCTOR HEMPE:

I would follow up the question of Doctor Pratt. Did I hear it right that you were commenting on the fact that in asbestos carcinoma or carcinoma with asbestosis, you did not find the so-called hyperplasia, metaplasia and so on, of the carcinoma? Was that what you said?

BY DOCTOR PRATT:

That's what I said.

BY DOCTOR HEMPE:

May I show one slide? I come from Holland and there were only two cases up to now, of asbestos in Holland, one with carcinoma, one without. It was by chance I got them; it was a chance I got the case with hyperplasia and metaplasia. I don't know how you use those words, hyperplasia, metaplasia, I can only say that I tried to differentiate between the kind of hyperplasia, as you see it in tuberculosis. I tried to differentiate between the types, as you see it in tuberculosis, so-called metaplasia and the type you see ordinarily in carcinoma, bronchial carcinoma of the lung, as you can study it in specimens, and then I must say that in the same type of bronchi, the middle lot, not only the small ones, but the greatest ones,

as you will get the specimens, but in the middle grades bronchi, you will find a certain type of metaplasia, that certainly is related to carcinoma.

I do not say that carcinoma does come from a type of metaplasia, but you do find them together, as you do not find the metaplasia in bronchiectasis or tuberculosis, and this is the slide I got here. Our slides are not as beautiful and our micrographs are not as beautiful as you normally see them here, but I hope you will see the point in what I am trying to show.

Here you see the bronchi epithelia, and you see - the comment will come that is not an entire cross-section, but you will see the typbal metaplasia, the hyperchromatosis of it, and you will see entirely how this bronchial epithelium is out of order.

This is one of the greater bronchi; it is not a small one, and the next please. Here you see the contents of the middle lobe bronchus, mucous cells, mucocytes. Here you must imagine the basal membrane and here you see the so-called typical metaplasia, perhaps leading to hyperplasia, I don't know.

These are of the greater bronchi too, and the next please? Here you see the same, that thick mucous that is coughed up so diffi tly in asbestosis, the thickened basal membrane, and here the very typical kind of epitheliu