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TAKEN FROM PAGE 111.

BY DOCTOR HATCH:

Gentlemen, to continue our discussion now on the newer problems, with a report by Doctor Pratt of the

Laboratory staff on their studies on some of the new synthetic silicas. Doctor Pratt.

BY DOCTOR PRATT:

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

BY DOCTOR HATCH:

Ladies and gentlemen, we have heard now about many different kinds of materials ranging all the way from our old friend Silica, as it occurs in nature, to problems that develop with the synthetic silicas, and these other curious dusts in between.

We go now to a little departure, perhaps, from the processes that have been followed this afternoon, the discussion of the behavior of particulate matter, without special reference to the nature of the material, in the course of inhalation and certainly the way in which particulates are handled in the course of inhalation and their receipt, and the amount of retention, and the understanding of those things is fundamental to the building up an understanding of the whole problem of dust diseases.

Merril Eisenbud of the New York Operations Office of the Atomic Energy Commission will report to us now on the Fate of Inhaled Particulates. Mr. Eisenbud.

BY MR. EISENBUD:

(Mr. Eisenbud read prepared paper which is on file

UNITED STATES
ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE

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October 15, 1952

Dr. Arthur J. Vorwald
Director of Research
Saranac Laboratory and The Trudeau Foundation
7 Church Street
Saranac Lake, New York

Dear Dr. Vorwald:

As you probably know, Mr. Eisenbud is at present abroad for a period of about 8 weeks, and therefore, I am taking the liberty of forwarding to you a copy of the talk he gave at Saranac recently which he indicated you would need for your records.

Sincerely,

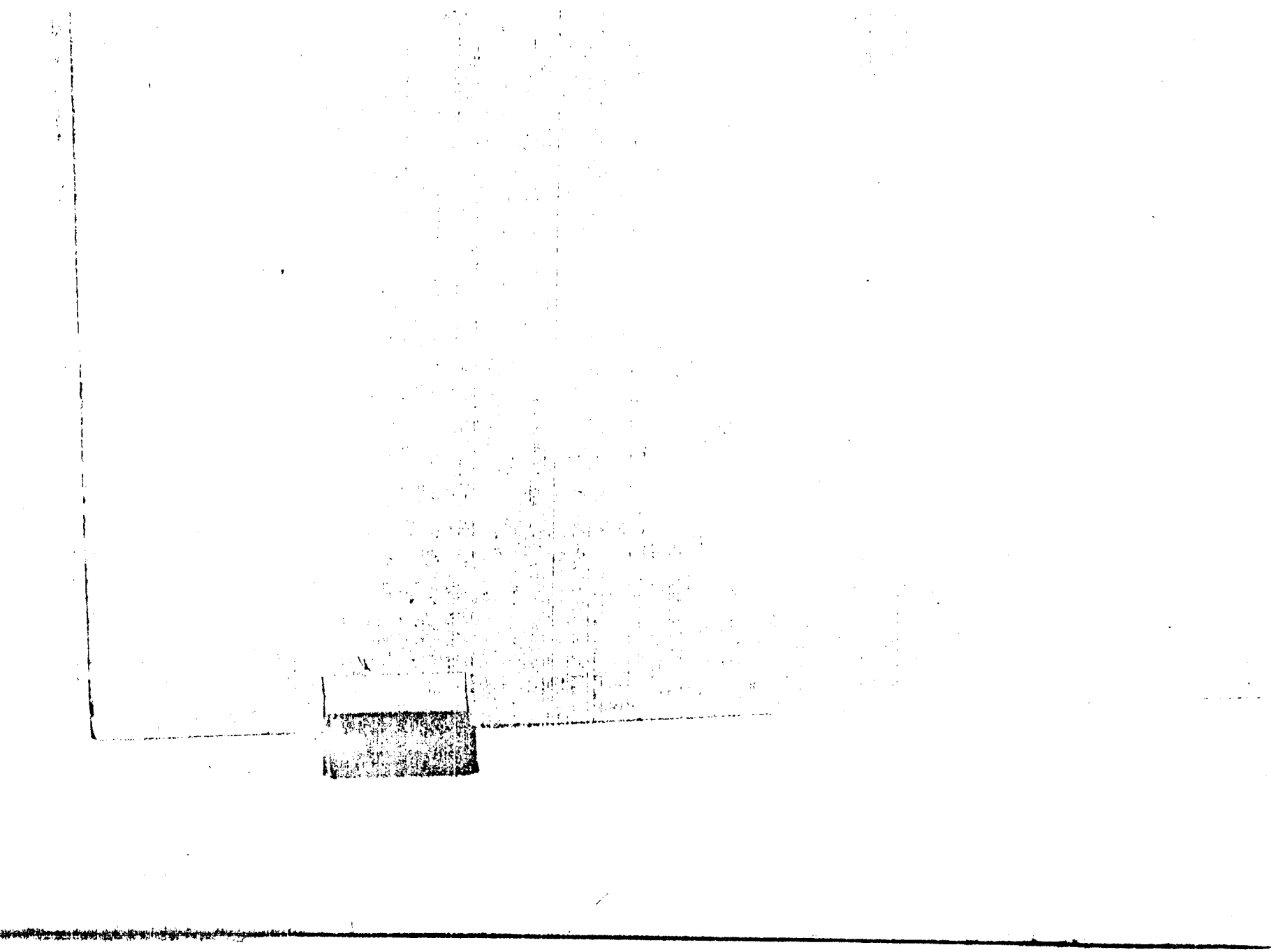
S. Hulstein
Secy. to Mr. M. Eisenbud

Enclosure:
"The Fate of Inhaled Particulates"

12-3-52

For Mr Eisenhood's
original paper -
refer to Symp. file
his folder

LBB



in the Saranac Laboratory).

BY DOCTOR HATCH:

I think you will all agree with me that we have had a very concentrated afternoon and I'm not sure how much time you're going to feel like taking now for discussion, but I am certain that whether you feel like it or not, you all have many questions that you'd like to raise for such discussion.

I should like to emphasize at this point, the chairman's privilege of opening the discussion and to make one or two comments which pertain particularly to the last presentation of Mr. Eisenbud's, and having to do with the fate of inhaled particulates. First of all, I'd like to suggest, whereas there has been a good deal of attention paid to initial retention of particulate matter in relation to particle size or the - over the last few years, I'm not at all sure in my own mind that it's the most important factor compared with the subsequent clearance of particulate matter from the entire lung structure. I remember how impressed I was many years ago when I made a very crude little calculation with some of the data from South Africa comparing the amounts of materials found in matching of silicotic lungs with some rough calculations on my own among the material that the individual had probably inhaled and retained, and while the essence is necessarily very crude, nevertheless

the order of magnitude was not far off, and the amount retained or the amount accounted for in the silicotic lung was in the order of one tenth to one percent of the amount which they had inhaled over the years.

Now, then to whatever degree that residue represented the material that it produced in them, it's pretty clear that we're talking about a highly selected portion of the total material inhaled, and so when we try to relate the composition and the physicial characteristics and so on, of the material in the atmosphere, among them it seems to me pretty evident, that there is an awful lot of information - an awful lot of things happen from time of inhalation to the development, full development of the effects, so I suspect that the - one of the biggest gaps in our understanding, one of the things in which there is the greatest need for research, is the research into the way partifulate material is handled, the rates, relative rates of clearance and the relative ways in which the particulate matter is disposed of within the lungs and in that connection, I'd like to make two points which will amplify, add perhaps a little bit, to what Mr. Eisenbud has just had to say about the retention.

First of all, if you will permit me to make a very diagramatic sketch here, of a primary molecule, and this is very diagramatic, but I want to use this way of making my

point. Considering the primary lobule, beginning with the respiratory bronchiole, we have -- I warned you this is going to be very diagramatic -- we have some kind of vestibule beyond the respiratory bronchiole connected to that in various air sacs. Now, I won't go beyond that in trying to picture it, but I make this point that down to this point here, concerned with known respiratory air passage ways, the volume of which air got through something like 140 c.c.'s of atypical, and this pass in here adds up to something of that order, and the alveolar spaces to something of that order; now, in the course of inhalation, these are figures representing a relaxed lung. In the course of inhalation, there is expansion down here, and I presume some expansion in this volume also, but even under the most rapid rate of inhalation, the air velocity down in here and out into this space is of the order of, well, at best, one or two feet per minute or one or two centimeters per second.

According to the very elementary view of the thing, from the standpoint of fluid flow, we have to accept the notion that the flow of air into this space is completely slow. There is no turbulence in it, so that as these spaces expand, the air that was in here at the beginning of the inhalation simply recedes quietly out in these spaces here and the new air comes in on top, so that active mechanical

ventilation - by active mechanical ventilation, I mean active change of gasses, takes place only down into this particular space, since at least under conditions of normal quiet breathing, the tidal volume will not any more than see that and even under heavy breathing of exercise as it goes up, it will still just fall in on top of the receding air.

Now, there is an important point here. The ventilation is all right so far as exchanging is concerned, because the exchange of oxygen and Co_2 across this face, takes place by rapid molecular diffusion, a pretty well accepted notion in respiratory physiology, but the philosophy of diffusion of particles of the order of one or two microns is so slow that we can expect no exchange of particles out into the true alveolar spaces in any way comparable to the exchange of gas out into them, so that these figures that we're talking about here represent deep lung deposition, but not necessarily mean the same for all different sizes, as to the ultimate site.

As particle size goes down, the gravitational defect which is a primary one in causing the sedimenting out of particles, the gravitation effect goes down in size and the diffusion velocity goes up, decreasing size in that fashion, and for simple sedimentation, this is about a quarter of a micron, so it seems to me that basic to our considerations this afternoon, which we have heard so much about

the peculiar behavior of some of these sub-microscopic materials, basic to that may be a deeper understanding than we now have of the actual site of the position and the way that those particles are handled by this total structure, since it seems clear to me at any rate, that a particle that does get out of here by diffusion is going to be - well, say we depend on different mechanisms for its removal, and that is true of particles settled out in the earlier part.

One more point which I'd like to make: If this represents the respiratory cycle with this inhalation and expiration, we know that these early stages of inhalation as a relatively rapid intake which peters off with the end of the inhalation and then there is a rapid beginning of exhalation which tapers off. Current thinking, from recent experimental work, suggests anyway, that the volume of air which is breathed in at this time is represented by this volume of air exhaled, and this volume of air inhaled represented by that volume exhaled and so on, and the so-called sequential ventilation of the first air in, the last air out, which is another way of saying that the different parts of the lungs are expanded at different times in the course of inhalation and exhalation.

Now, the function, among other things, is the time it saves down in the lungs in this volume of air that's being actively exchanged, so that along with this question,

we have also to consider the parts of the lungs that are most actively ventilated during the early phase of inhalation, that they are being last out, as against the air that comes in during the last ventilation and that is the last air out, so that where this air goes to in the lung compared with where this air goes to, is important in your understanding of the site of deposition, and again your point of clearance, so I would like to suggest that more important than our understanding of retention, is a better understanding than we now have of the clearance of the material from the lung and the way in which that is related to the nature, both chemical and physical, of the material.

Now, I had to get my say in. At this point, I should like to open the meeting for discussion from the floor.

BY DOCTOR VORWALD:

Ted, how do you know all this, that is how do you know there is no turbulence of air way out in this microscope?

BY DOCTOR HATCH:

Well, obviously, we can't know it from any experimental work. We can only know it from analysis. We know this, that in the normal typical lung, there are, and we have a pretty good idea, how many, respiratory bronchioles there and we know from anatomical measurements, the cross-section

of air in the anatomical bronchiole, and in one of - one set of data that I have in mind, total air of a whole set of bronchioles, cross-section adds up to one eight eight square bronchioles. Respiratory - yes, there are one and a fifth times ten respiratory bronchioles, and that relates to this velocity per second and so on down. This is Landau's chart I think.

These are typical dimensions and reported for the respiratory system. I'm sure they're not exactly right, but they are good enough for our purposes.

Now, one thing we know in fluid mechanics, in the understanding of fluids and flow, and we can draw a sharp distinction between so-called laminal flow and so-called turbulent flow, and determining in advance in any given situation when we're going to have one and when we're going to have the other. The index is the so-called Reynolds number which I won't burden you with, but say this, if a Reynolds number is less than two thousand, you can be sure you have laminal flow.

These calculations here would indicate that in the lungs even under the deepest inhalation at an instantaneous rate of sixty liters a minute, the Reynolds number is tremendous to be compared with two thousand, as a dividing line between laminal and turbulent flow so it's only my faith in the Reynolds number and fluid mechanics that would

tell me that this is so.

I think there is some physiological evidence to indicate that it is so in this case, that after exchange, it's ventilated by diffusion. Does that answer your question?

BY DOCTOR MACHLE:

Mr. Chairman, I'd like to compliment Doctor Hardy on a very excellent summary of the beryllium problem. I would like also to ask if she would elaborate on the cases presumably exposed to low beryllium phosphor. We have been following data on several thousand people exposed to low beryllium phosphors since 1945. From our experience, from the data we have now pooled together, we have yet to find any cases of exposure to beryllium encountered in the low phosphor, at least in one manufacturing operation in this country, and in another manufacturing operation, there have been several hundred including - several hundred thousand man hours of exposure to low beryllium phosphors, the percentage was less than three years.

BY DOCTOR VORWALD:

The percentage was less than what?

BY DOCTOR MACHLE:

Beryllium.

BY DOCTOR HARDY:

My data is a mixture of material that I have by

the courtesy of Doctor Kline, on General Electric phosphor which, I understand, is always below four percent, and he reports about eleven cases, and we have two cases in Massachusetts in or from subsidiary companies in that same phosphor. (NOTE: Doctor Hardy requested following the closing of the session that the reference to General Electric be deleted from her remarks. However, as the reporter understood the response, the reference is made in such a manner that it is felt Doctor Hardy should make the deletion in such a way as not to confuse her statement).

I have reports from Nash in England, reporting six cases of chronic beryllium poisoning, three of these from low beryllium phosphor manufacturing. I used the term 'roughly' advisedly, because I didn't have the precise data as to the total number of these, but it was something of the order of fifteen which is on the low side, of individuals with an unknown number, doubtless in the thousands, exposed to phosphor below four percent. Is that what you want?

BY DOCTOR MACHLE:

May I ask again - yes, that's a very significant observation, but there are several various significances in beryllium phosphor quite apart from what Doctor Pratt mentioned, characteristic, so to speak, of exposure. By the characterization of phosphor, the total amount of beryllium

present is an important consideration because of the limitation in the limit of the solution which you can make of beryllium in material.

The second variable is the completeness of the reaction which, of course, is determined by the time, temperature and repetition in firing, together with the use or non-use of flexes. In situations where we have encountered cases which seemingly occurred from exposure to low beryllium phosphor only, it has been possible in at least two of the situations to establish that there have been unusual practices in the preparation of phosphor by - in the direction of lessening firing, experimentation with flexing methods, and so forth, which lead one to believe that it was an anomalous situation and it could not be included in the general epidemiological consideration which, obviously, you are bound by, to have a certainty as to the nature of the exposure.

BY DOCTOR HARDY:

That is why I quoted you, Doctor Machle, as one of the more studied of physical characteristics of state of aggravation, and so forth, and so forth, but it seemed to me in reviewing the evidence in my own personal experience, we had to say that the low beryllium phosphor used in that manufacture before May 1949 had caused the death of a number of cases of beryllium poisoning and I think, as you do,

this is a very crucial point in studying the epidemiology of the disease.

BY DOCTOR VORWALD:

Mr. Chairman, it may be interesting for you to know, I think we have in recent years, or last year, succeeded in reproducing a lesion in the lung of animals which simulates, at least, the lesion which we see in the human cases exposed to beryllium, and certainly the simulation is as comparable in that instance as is the simulation between silicotic produced and the silicotic natural subjects. We have succeeded in doing that after many months of exposure to pure beryllium oxide at extremely low levels of concentration, and also to a beryllium sulphate at extremely low levels of concentration.

There is - in my own mind, however, there is one difficulty which I can not explain and that is that we have not as yet succeeded in reproducing the number of lesions that we see in human cases. Now, I must admit that the lesions that we have reproduced experimentally are very few and far between, but we will be reporting some of our other observations on Wednesday when we discuss the pulmonary cancer and its relationship to some of our exposures in experimental animals.

I should like to ask, if I may, just one more moment, Mr. Chairman. Doctor Solandt - we may have not given

him sufficient time, and if he could merely tell us very briefly, what he is doing then as the agent that is producing this change in the group - in these experimental animals, and also related to human subjects in the abrasive bauxite industry. Is Doctor Solandt still here? (No response). Doctor Shaver, could you - he's not here. We may have stopped him too short; I'm not quite clear as to his final conclusion. Perhaps while Doctor Shaver is asking for that, some others might have a question.

BY DOCTOR GREENBURG:

Mr. Vorwald, I'd like to ask Mr. Hatch a question. In that diagram, you've got there for the inhalation and the exhalation, you say the material can be fractionated to different parts of the cycle, but as I remember it, you said that the total retention was about one tenth of a percent up to one percent.

BY DOCTOR HATCH:

The ultimate retention.

BY DOCTOR GREENBURG:

Yes, the ultimate retention. Now, if the ultimate retention is one tenth to one percent and the concentration to which the animal is exposed is approximately uniform, for any given duration of time, wouldn't the amount retained in the various parts of the cycle be approximately the same in the last analysis?

BY DOCTOR HATCH:

Well, I think somebody who knows more about the lungs than I do would have to answer that. The picture I have is that there are - there is relative ease in ventilation of certain parts of the lungs compared with others and you would expect, therefore, over a period of time to find a disease and, therefore, there would be a higher deposition in such areas.

BY DOCTOR GREENBURG:

No, that isn't the thing I was talking about; the first thing I'm quite in agreement with.

BY DOCTOR HATCH:

You're speaking about this chart on the right?

BY DOCTOR GREENBURG:

That's right.

BY DOCTOR HATCH:

This is inhalation-exhalation-ventilation curve for the lungs.

BY DOCTOR GREENBURG:

Right. Now, it seems to me that the retention in all parts of that cycle, in all parts of the inhalation cycle would be approximately the same.

BY DOCTOR HATCH:

Well, I was suggesting -- no, I can't say that is so. I was just suggesting it. You say this, the subject

breathing fifteen respirations a minute, then this is four seconds from here to here. The average duration of stay of this air in the lungs will approach four seconds. The average duration of stay of this air in the lungs will be one second or less. Now, the amount that's deposited out of that air is going to be in proportion to the duration of stay in this actively ventilated space so that in certain portions of the lung, favorably receiving this air, then they're going to get more dust.

UNIDENTIFIED SPEAKER:

Gentlemen, I suggest that you're talking about two different things; he is talking about retention in respiration and you're talking about ultimate retention in the tissues after the elimination process.

BY DOCTOR HATCH:

Maybe I'm a little confused.

UNIDENTIFIED SPEAKER:

You can get particles of this order, magnitude, something of the order or magnitude of two to three microns; you can get upwards of thirty-five or more percentage retention in the lung during the respiratory cycle. How much you'll find there six months later is a totally different story.

BY DOCTOR HATCH:

But with respect to that, that average figure is

made up of higher percentages in the lungs and lower percentages in others depending on the activity of ventilation.

BY DOCTOR VORWALD:

Ted, are you sure that the first air in is the last air out?

BY DOCTOR HATCH:

I think the most - the best evidence we have on that is a paper by Fowler, remember, down in Pennsylvania, in which he determined that was so by the ingenious trick of splitting up the inhalation for a moment and then suddenly completing the exhalation with a mixture, and then he analyzed the exhaled air in the same way and then he found that that same mixture going in was found in the air coming out. Now, we have some other indirect evidence and we have a little bit of evidence that agrees with Fowler.

BY DOCTOR VORWALD:

Doctor Shaver?

BY DOCTOR SHAVER:

Rather than hash what Doctor Solandt had to say, I will just read part of his summary and conclusions.

(Doctor Shaver reads from Doctor Solandt's paper, which has been filed with the Saranac Laboratory.)

UNIDENTIFIED SPEAKER:

I wanted to ask Doctor Hardy a couple of questions. One is what is the longest period of time for treatment of

these patients you have referred to?

BY DOCTOR HARDY:

One recently reported by Kennedy in the Journal of the American Medical Association, I have continued to treat that same case up until now.

UNIDENTIFIED SPEAKER:

The second question, one of your patients showed here, looks like a hyperthyroid; is there any indication toxicity stimulates the hyperthyroid, or is it because of hyperacidity of the bone?

BY DOCTOR HARDY:

We don't know; there has been a lot of speculation about that. We had two cases of thyroid tumors that sort of disappeared. They had high m. p. r.'s. No one every explored their lungs to know. Hypercalcemias were present. Our feeling is that, in some mysterious way, the behavior of beryllium in the body, particularly its disposition and modus operandi must be related, but at present I have no knowledge except those early tracer studies of Doctor Hamilton Berkeley, except that when he gave beryllium, the material went in the animals' body and was in the liver and kidney for a while but it never left the bones for the duration of his study. That's been true in autopsy cases, where beryllium was present. Doctor Fuller Albright thinks that the renal calculi and perhaps the other phenomena that I have

enumerated are related, just as he thinks they are in sarcoidosis to a protean binding, that is protean will bind calcium in certain diseases, but as far as I'm concerned, that's a description, not an explanation. I don't know.

UNIDENTIFIED SPEAKER:

What is the dosage of your ACTG for that treatment?

BY DOCTOR HARDY:

Well, it varys a great deal. In general, we have given him 200 milligrams a day, ACTH embodied into fifty milligrams every six hours, for a few days; then down to a hundred milligrams spread out, then shift to the oral cortisone, keep him there one or two weeks until you're sure that you have what would be the best possible benefit from the symptomatic standpoint, and in various cases, we have tested this by pulmonary function study and cardiac catherization study and then we do what Doctor George Dorn calls titrate the dose, meaning let him go down to the point below which he is still comfortable and then keep him there.

I'm a great deal older than I was when I talked about this in 1950 and I have patients that have been on 75 milligrams of cortisone, 25 milligrams every eight hours for a year, and I can't see where I've done any harm, and I've taken symptomatic patients from a complete chair patient back to forty hours a day - four hours a day, and this is very impressive even though in all honesty, I don't

think I'm curing them.

UNIDENTIFIED SPEAKER:

The only reason I'm asking, Jerry Kane of Michigan seems to think that the use of cortisone may lead to sporadic sclerosis; I don't know.

BY DOCTOR HARDY:

Well, I think it might easily be true, but I think in the case of beryllium poisoning, you have to sort of take the choice and play your cards as you go.

BY DOCTOR VORWALD:

Is that a general tendency in cortisone?

BY DOCTOR HARDY:

Yes, it's been my experience in talking with Doctor Max Michel, who has treated very many of these, that you may get brilliant results in treatment of sarcoidosis with ACTH or cortisone, but as I pointed out in that swift-running survey summary, just given you, I have seen cases of sarcoidosis that simply will not respond in any way to ACTH and cortisone, and I have seen - I have even seen cases recently -- two are very fresh in my mind -- that have definitely been made worse, and have proven this by pulmonary function studies and a clinical downhill course of obviously increasing replacement of the granular tissue. This I have not seen in beryllium poisoning except for my remarks that one or two cases I have watched appear to be getting, from the

laboratory standpoint, worse though they're systematically better.

BY DOCTOR TABRUCK:

I'd like to state that our experience in the treatment of chronic beryllium poisoning with cortisone parallels that of Doctor Hardy. We have seen several dose cases under cortisone therapy and we find we have been able to do a great deal for these patients, but we find very definitely we're not curing anything. We find the patients go downhill and the best we can offer them is to give them a more protracted period of disability but a more practical period of disability if you can use that word. In other words, they are sleeping much more comfortably during this period of disability, which becomes longer, but the end results are about the same.

I'd like to ask Doctor Hardy what, in her opinion is the activating factor in her precipitate mechanism? Is it a matter of true allergy or is it a matter of physiochemical changes within the system that precipitates the instance of disease in beryllium poisoning?

BY DOCTOR HARDY:

Well, I see I didn't make myself clear or talked too fast. I think the beryllium is in the body very often in happy equilibrium, stored for excretion, and then something happens to the patient -- maybe it's a respiratory

tradt infection or this very fascinating business of the woman having a baby and getting along quite well, and then when the baby is four or five months, she begins to go downhill in induced weight loss. I have seen this very strikingly, or in unusual exercise, the soldier, you remember a very small but definite group, after experience in combat; or I have young girls in cases where, or cases where a lazy 190 pound man went and was put through boot training and lost thirty pounds and he became a clinically active case of beryllium disease.

In fadt, in practically all of the cases in which I have been able to make a good clinical hunt, I have been able to find something that happened to that man or woman after he or she stopped inhaling beryllium or perhaps still is in the situation that is an added insult or added physiological burden, that if you like, makes it possible for the beryllium to become pathogenic.

I suspect you're referring to the very fascinating work of the boys, showing that beryllium in the test tube and in small animals will inhibit magnesia, will take the place of magnesia in certain enzyme systems and, by pressing out the phosphatase, set up a whole chain reaction so to speak, and it's very, very seductive to consider that this may be the means by which to say your response takes place, that later on you'll have fibrosis and so on, symptom

producing. The cortisone that is used in test tubes on small animals compared to the human of this particular set-up, makes it a little difficult to translate it from the test tube to humans, but there it is possible for later use.

I haven't seen any evidence there that the clinically active disease is an allergic type of response, although I think Doctor Sterner has a very good basic broad isdea that may explain a lot of things about goiter response to toxic insult, not just beryllium, but also infection.

BY DOCTOR HATCH:

I think at this hour I'd like to call the meeting to a close, and I'd like to make one comment in closing. We have heard, this afternoon, of the action of different dusts in the lungs, the relative importance of different factors in the dust, that go to determine the nature and magnitude of the action. Very illuminating, I believe, in the light of this morning's discussion in which we had great difficulty in arriving at definitions to a high degree because there were so many gaps in our knowledge. I should like to leave with you this thought, will the day ever come when we will be able to anticipate difficulties associated with the inhalation of particulate matter and not have to wait until the difficulty has developed before becoming concerned with it. It's going to the question or the degree of which we can reduce our understanding to the fundamentalities, the common

denominators that go to make up the problem, whether it's the problem of asbestos or bauxite or whatever, to whatever degree we can meet those fundamentals and extract out of them a common denominator.

Is it going to be possible for us to anticipate and predict, from basic studies of new dusts, the possibility of toxic infection? I, for one, would be pretty discouraged if I thought that day would never come. I don't want to suggest that one day we'll be able to explain everything, but I certainly hope we will be able to do a better job than we have in the past in anticipating this trouble.

The other comment I want to make is one I think Doctor Fletcher spoke in particular about this morning, that in our understanding of these problems we have to depend as much on epidemiological findings from the field as we do on the findings from the laboratory. One compliments and supplements the other.

I think, with that, we'll call the afternoon meeting to a close.

-oOo-

(Session adjourned at 5:45 P. M.).

REPORTER'S NOTE: Throughout the transcript, unless names were specifically spelled at the time given, all proper names will be subject to change or correction.