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BY DEBORAH HIGGINS:

Are there further questions on the chrome questions:

(No response). If not, we will pass to the last paper, that of
our host, Doctor Townsend, who will discuss his

studies on pulmonary cancer in the experimental exposure to beryllium.

BY DOCTOR VORWALD:

I'm sorry to say the report I'm about to give emanates from the work of my colleagues, particularly Doctor Pratt, and Mr. Durkan, Mr. Delehant and Mr. Urban of the Sarsnac Laboratory. Also, the second remark is that the hour is late and as host to this conference, I'm sure that they will agree with me when I cut my paper drastically, so that I will not be longer than ten minutes, if that. Third, I am not going to bow to those who champion the human experimentation versus animal experimentation because these observations are purely accidental. They weren't planned. The animals performed the experiment for us, and we have relatively little to do with it, except to place them in an environment for other purposes.

Briefly then, the report involves, this pilot or tentative report involves an experiment where we were exposing large groups of white rats to inhalation of atmospheres contaminated with beryllium in the form of pure beryllium sulphate, in one instance, and in the form of pure beryllium oxide in another. The animals, the white rats, and I call attention to that, that these animals are not mice, were bred in our own stock and they came originally or are descendants about 1935 from the Worcester Institute,

and no attempt has been made to inbreed or to select the strain and the strain is subject to lymphosarcoma at a low incidence rate which is not precisely known by us, because large enough groups of animals have never been kept in a duration of life experiment.

All rats under this observation were fed ad lib with a standard diet of prepared dog chow and water. The rats were exposed to pure beryllium sulphate in an atmospheric concentration of 0.011 milligrams per cubic foot of air. The rats were kept there under exposure for usually six and a half to seven hours daily for five days a week and the animals which I will report on, one of the observations made or the observations which I will report upon are made upon animals that have had that exposure continuously for approximately thirteen months.

The first slide, Jim. And, I will, rather than to show you all of the epithelial changes that have gone on in the bronchial tree of these white rats during the course of their exposure, namely, at one month, at three months, six months, nine months, ten months and twelve months, I take you immediately to the fourteen month animals. At that time, there were only four white rats left in the experiment in the large group of - well, in the group of fifteen female white rats being exposed to beryllium sulphate in the concentrations which I have given. At thirteen and three quarters

months, it was observed that one animal was ill, and so as is our custom, that animal was sacrificed rather than to allow it to die, and we, on killing the animal, we observed a very strange lesion which we had never heretofore observed in our rat colony, and here is the gross lung of that rat, and we see that there are para-broncholar foci of reaction to the beryllium that has become beryllium sulphate, that has become localized in these areas in the lung and in addition, we see also rather consolidated areas, and here is one, and we can pick some out.

Here is another, and in this area here, and also this large tumor mass at this point. That is one area.

The next slide. And, the second animal, now, subsequently then, having made the observation, killed all three remaining animals, remaining in that particular experiment, and I shall now show you the lungs of the three remaining animals and we have here the lung of a rat at fourteen months of exposure, the gross lung. We see the tumor localized in the apex. We can see the small lesion there. We can see it in the lugs, we can see a small lesion at that point. We can see a small lesion here and here and here. I merely take pains in pointing them out to show that the tumors are multiple within the lung tissue, and here is a larger tumor which was one - a one of the lobes which is not included in this section, and we see it - there

is a serial section and we see the tumor in the lowest portion of that lobe. This is the mark where I have taken the photomicrograph.

The next slide. The third and again, the fourth animal. Mind you, all four animals having been exposed for fourteen months to beryllium sulphate, 0.11 milligrams per cubic foot of air. At twelve months, we do see pronounced epithelial hyperplasia and I haven't bothered to show you those sections, but we did not believe at the time nor do we believe now that that epithelial hyperplasia had become cancerous but at fourteen months, it has. That again is another gross section.

We show you one of the larger tumors. Here is another tumor implanted on the pleura. Here is another tumor implanted on the pleura. Here is three tumors implanted on the pleura and we question whether this tumor is not infiltrated and replaced by the tracheo-bronchial lymph node which ordinarily occupies the proliferation of the lobe at this point. We're not sure about that, but we believe it has happened, because there is no evidence of lymph node tissue at this site which is common to both human subjects and in animal subjects, namely the trifurcation of the bronchi.

I will proceed briefly to show you the microscopic of these sections. Now, this then is a section photomicro-

graph from the major bronchial tree, and I call your attention to the epithelium lining the major bronchial tree, columnar in type, slightly hyperplastic and at some points the submucosa lymphoid tissue has apparently broken through which may be a normal observation, and here we see that lymphoid tissue exposed. I won't discuss that further. There is a problem here which I do not think pertains at the moment, to our immediate problem.

The next slide. And, as we go further down into the bronchial tree, we do find foci where a cross-section of a respiratory bronchial made up of epithelial cells, thick at the mucosa, evident hyperplasia, but in addition, we also find the adjacent alveolar spaces which are distorted by reason of the fibrous tissue or the cellular reaction of the alveolar walls, and we find these alveolar spaces lying with a very well defined epithelium which in instances is columnar, but in most instances is of the flat colloidal type. This is common, a common finding in the lung, subject to chronic diseases which give rise especially to fibrosis.

It is seen in human, in the lungs of human subjects, as well as it is seen in the lungs of experimental animals. Here is the type of lesion which we think simulates the lesion seen in human subjects, which characterizes that lesion due to the composition of beryllium. Made up of large mono-nuclear cells and very exact. I only

point that out in passing. That is the lesion which we are attempting to reproduce and we believe that we have reproduced it in these animal subjects, the rats, but not in any other animal have we produced a reaction. We have produced a reaction after intravenous injection in the rabbits.

Doctor Gardner first showed this with zinc beryllium sulphate, a BeO content of 13.8 percent and subsequent to that time, we have carried on a large number of experiments with various beryllium compounds, and we have reproduced the similar type of osteogenic sarcoma with metastases to the lungs with various beryllium compounds.

In passing, I might say that we were unsuccessful in producing these lesions with beryllium stearate, with beryllium carbonate, with - I want to get the list here so beryllium stearate, beryllium carbonate was too toxic, it wasn't tolerated by the rabbits intravenously. Beryllium hydroxide and beryllium metal, we have not succeeded in reproducing this tumor in the bones of rabbits, but we have done so with zinc beryllium silicate, a 13.6 percent BeO, 18 percent BeO, 2.3 percent BeO. We have done the same thing with pure BeO delivered intravenously in rabbits, in lower doses, the lowest dose was 650 milligrams. The same thing was accomplished with beryllium phosphate, in a dose of a hundred and two, 102.2 milligrams. I say that only because some of you are interested in the dosage factor.

So that this epithelial hyperplasia lining alveolar spaces is a common finding, and I am not going to enter the debate at the moment as to whether this re-epithelialization represents a hyperplasia of epithelial to epithelium which normally lines the alveolar space or whether it represents growth of epithelium from the adjoining respiratory passage which we know is lined with epithelia.

This then is the slide of the tumors. Now, and it is a deposit of all these four animals, and we find here two different types of tumor, one which is distinctly adenoidous in type and one part of the same tumor which is more alveolar in type, tending to reproduce at times at the alveolar architecture. Well, let us go on, and examine some of these tumors.

And we'll concentrate, first, upon the adenomatous type of tumor, that is the adeno-carcinoma seen in these lines and here we have a high-power magnification. It demonstrates the heterogeneous growth of this tumor tissue, a tendency to form spaces adenomatous in type. Certainly, there are many cells which are antiplastic, they are large, they are hypertrophic. We can discover here many hypertrophic figures.

The next slide, and taking you to a higher magnification because my attempt here will be to show that this cellular change, this tumor is, we believe, a truly

malignant, and it has been submitted to other pathologists who have reviewed the section. Again, a higher magnification, you can see the cell structure.

The next slide, and still a higher magnification to show you the differences in size and staining capacity of these cells. No reproduction really of a specific pulmonary tissue growing in the tissue and also producing implants or metastases go to the pleural surface and metastases also going to the tracheo-bronchial lymph node.

The next slide, as to the alveolar structure, the alveolar type, indeed, this has been called by some in contrast to the respiratory bronchio-carcinoma, the alveolar type carcinoma and here we see a reproduction of the pulmonary alveolae lined with the malignant cells. And here a higher magnification to show you the character of that cellular growth.

The next slide, and still a higher magnification of this alveolar type of structure and we see a multitude of cells. This is now lining an alveolar space and hyper-traumatic, there is not myotic figure, except possibly that may be one, I don't remember the particular detail of this section.

The next slide is a section from the pulmonary implant tumor, and here it is tending to reproduce the major tumor in the - within the pulmonary branch. The next

slide, and here is the high powered magnification of that tumor on the implant, the megalocytic lesion, and here we have obvious metastases going on, extreme activity. Again note the difference in size and shape of the cells and the hypertraumatic richness of the nuclei, and the large size of the nucleoli, all of which is characteristic for a true cancer.

The next slide, and this then is the area of the tracheo-bronchial lymph node, this is the large mass bound at the bifurcation of the trachea and these merely represent serial sections because we were looking for differences in the growth of this tumor.

The next slide shows you now the tumor which has apparently replaced the metastases too and replaced the entire tracheo-bronchial lymph node and here again we see the character of the cell structure reproducing the primary tumors occurring within the pulmonary trachea, and this tumor is highly vascularized in the tracheo-bronchial lymph node.

With that then, we have now with BeO, we have subjected animals to BeO, pure beryllium oxide exposure, the concentration there was approximately 12 milligrams per cubic foot of air and the animals at that experiment were carried along for only eleven and one third months, not long enough to reproduce the same type of tumor as we have observed

with beryllium sulphate.

However, at this time, we saw similar epithelial hyperplasia in the bronchi as demonstrated in rats under exposure to beryllium sulphate, but we can point out that intra-tracheal injection of beryllium oxide, we have reproduced the same kind of tumor on intra-tracheal injection of beryllium oxide as we have with the beryllium sulphate, and also the beryllium sulphate on intra-tracheal injection, those animals have gone for only eight months, but the animal killed at eight months also shows a similar epithelial hyperplasia and lining of the alveolar spaces, and we suspect that these animals with longer periods of time, when they approach the fourteen month period, will show comparable changes.

So, with that then, we believe that we have produced in the white rat pulmonary cancer of the adenocarcinomatous type, with metastases to the pleural surface and to the tracheo-bronchial lymph node. We have not as yet observed distant metastases. This, as I mentioned, is only pilot experiment. The observation is only tentative. It involves only four animals, but all four animals, all the animals remaining in that inhalation experiment, so we have set up a very large experiment in order to reproduce and to validate these observations.

We have abandoned the sacrificing period so that

at the conclusion of the exposure, we will have an adequate number of animals which will give validity to our observations. I should like to point out here also that this is a pilot experiment, that this has been produced in white rats, that this does not mean that beryllium will produce pulmonary cancer in human subjects. Thank you.

(Applause).

BY DOCTOR MUDER:

Doctor Rhoads has delegates his authority to me, finding it necessary to go back to New York. It would seem unequivocal that Doctor Vorwald and his colleagues have produced real lung neoplasms in an animal with which all of us are familiar, and a species in which the spontaneous occurrence of neoplasms seems to be excessively rare. He and his colleagues are to be congratulated for this most timely report. May we have some discussion? Are there any questions which someone would like to ask?

BY DOCTOR MCCORMICK:

Would you repeat again, Doctor Vorwald, the concentration of beryllium used?

BY DOCTOR VORWALD:

0.1 per cubic milligram of air.

BY DOCTOR BARTLER:

May I ask about the intra-tracheal?

BY DOCTOR VORWALD:

The intra-tracheal was an injection over a period of four weeks consisting totally of 2.5 milligrams or 2.5 c.c.'s of a five percent suspension.

BY DOCTOR MILLER:

Any other questions?

BY DOCTOR VORWALD:

I will check that, Doctor Baetjer, I want to be sure of that, I have it here.

BY DOCTOR MILLER:

Are there further questions?

BY DOCTOR FAROX:

Ignore a clinician's ignorance for me to ask how old in a man's life a fourteen month old rat is, how long do rats live?

BY DOCTOR VORWALD:

Our rats seldom live beyond two years, so we believe this animal at fourteen months, and that may be a factor that they're approaching, this age period, when they may develop pulmonary cancer.

BY DOCTOR FAROX:

I was trying to translate it into the number of years that humans have carried a body burden of beryllium.

BY DOCTOR VORWALD:

Well, I suppose fourteen months in a rat, to that exposure, might be equivalent to twenty-five years in a human.