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September 13, 1949

CONFIDENTIAL

To: Dr. Warren
From: Dr. Hardy
Subject: Recent trip to Cleveland and Rochester

Schenectady

An extraordinary case seen with Dr. Rozendaal at the Ellis Hospital, of a 25 year old woman surely suffering from chronic beryllium intoxication, with a very poor prognosis after a clinical course of nearly two years. The beryllium exposure rests at present on $3\frac{1}{2}$ hours of cleaning insulators made in General Electric ceramics department of BeO. Patient had worked 3 years before her illness on floor below ceramics department directly concerned with porcelain work. It is my opinion after visiting this ceramics department that more work with BeO was done in years gone by than at present and that this patient may ultimately qualify as a "neighborhood case." Clinically this patient seems very similar to those in Massachusetts series. (Saranac Laboratory concurs in this following a period of study there in 1948.) By X-ray this worker-patient had atypical involvement of both lower lobes until March, 1949, when all lobes showed X-ray densities suddenly with coincidental exacerbation of clinical symptoms. Patient is on O_2 therapy continually.

Cleveland

Plant visit - Trip to Clifton Products made on August 30, 1949, accompanied by Mr. Schorrmiller, general manager. I was impressed by the following:

(1) Absolutely first-rate housekeeping and worker protection provided.

(2) Correlation of cases of acute beryllium intoxication with breakdown of equipment or failure of workers to use protection provided.

(3) Certainty of Mr. Schorrmiller that BeO is "probably" nontoxic. (I noticed, however, that low fired BeO was handled exclusively in completely enclosed "dry boxes".)

(4) Dogmatic belief of Mr. Schorrmiller that $BeSO_4$ is the main offender, with $BeCl_2$ as a surprising to him but proven second offender. This in contradistinction to Dr. DeNardi's assertion that at Brush $BeSO_4$ may be important, but the fluoride compounds of beryllium are certainly harmful.

Cleveland Clinic - Through the courtesy of Drs. VanOrdstrand, Hughes, Carmody, DeNardi, especially Dr. VanOrdstrand, I had a chance to study records and X-ray evidence of disease in the beryllium industry in the Cleveland area. This covers chiefly extraction, of course, but also some research work. Since most of this has been reviewed, I will only record here the points of greatest clinical interest to me.

(1) Fifteen per cent incidence of illness in beryllium workers in three plants - this compares with present figure of about 5 to 6 per cent incidence in Sylvania, Salem exposure. G. E. Nela Park Lamp Department reports 12 cases of chronic beryllium disease August 1949 (compared to denial of any October 1947). Word of four neon sign workers suffering with chronic beryllium poisoning in Ohio and Wisconsin added to one reported from California in 1946. One case seen by H.L.H. but not examined of chronic beryllium poisoning in an engineer who supervised grinding of BeO for jet engine parts at Batelle in 1945. Twelve cases of chronic disease in Lorain area - six of these workers in beryllium extraction without previously detected acute disease.

(2) Striking fact that acute beryllium poisoning and chronic beryllium poisoning have certain biochemical findings in common. Changes in B.S.R. test and Tiselius pattern are instances of this. No evidence of hypercalcemia (renal stones) seen in the series of acute cases.

(3) Study of pathology of both series with Dr. Hazard at Cleveland Clinic shows certain cellular reactions in common.

(4) Study of X-ray changes shows nonspecificity of the densities in beryllium disease.

(5) Renewed feeling on my part that there may be several factors operating in the onset of clinical disease after beryllium exposure not unlike the elusive factors of bacterial immunology or vulnerability. For instance, in one of Dr. VanOrdstrand's cases, the worker had inhaled a small but definite amount of phosgene (one recalls the case of Rodrique's exposure history) prior to a sudden BeO_2 exposure when the airline respirator failed to function while the patient was repairing a hot furnace.

(6) Out of ten cases reported by DeNardi et al, in an article entitled, "Chronic Pulmonary Granulomatosis," accepted for publication in the "American Journal of Medicine," there are two cases (Cases 9 and 10) with the following pertinent history. Case 9 - quoted only in part:

> A white man aged 26 complained of exertional dyspnea and a persistent cough which had been present from January, 1946 to May 20, 1947. In January, 1946 he had the "flu" with accompanying cough, shortness of breath, and arthralgia....
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> This patient had worked in the fluoride process department of a beryllium plant during the last eight weeks of 1941. His reason for leaving this work was the development of a cough and shortness of breath. However, he has not experienced chemical or occupational exposure since that time.

Case 10 - also quoted in part.

> A white man 48 years old at the time of examination on April 26, 1948 complained of a persistent spasmodic productive

cough, anorexia with weight loss and progressive exertional dyspnea beginning in early October, 1947...

The patient was employed in a beryllium plant on April 30, 1945 and first worked for seven days handling beryllium fluoride until transferred to the crystallizing sulfating department for a period of nine days previous to onset of symptoms on May 30, 1945, when he developed exertional dyspnea and a productive spasmodic cough. The clinical and roentgenologic diagnosis at that time was acute chemical bronchitis, probably due to beryllium salts. He recovered from this initial attack and returned to work in the same plant on July 9, 1945, in the ore grinding mill. After an additional ten days of work, he developed a second attack of acute bronchitis; and following complete recovery, he was given a medical release from the industry on September 11, 1945, because of his illness.

From these two cases, it will be seen that chronic beryllium disease follows acute beryllium effect in a few instances in the Cleveland area, although for some reason this interpretation is not put on the above quoted material by Drs. DeNardi and VanOrdstrand. I plan to ask them about this at an appropriate time.

From studying the neighborhood case material at hand in Cleveland, I am frankly not convinced that all the cases at present so diagnosed really qualify. Certain variations in the X-ray pattern and discrepancies between the amount of beryllium found in tissue at postmortem between these cases (one especially) and worker cases make me raise the question. Subsequent knowledge may easily prove me wrong in this skepticism.

(7) Only two cases of acute beryllium poisoning resulting in chronic disease may be evaluated as follows.

(a) Since Mr. Windecker's death in 1943 and second attack of acute beryllium poisoning soon after, no worker has been returned to beryllium atmosphere.

(b) Turnover has been great in Brush and Clifton following deaths and disease in these companies.

(c) Since the episodes mentioned, housekeeping has dramatically improved, first at Clifton and secondly at Brush.

(d) Further, since the above, there has been a natural avoidance of unnecessary risk by all except a few die-hards in the staff and executive levels of these two companies.

Reactions of Interest to AEC Division of Biology and Medicine

There is marked increase of respect for the toxic possibilities of small amounts of beryllium (compounds not always or necessarily designated) on the parts of medical and nonmedical individuals with whom I talked in the Cleveland area.

There is real anxiety on the part of Dr. Sawyer of Brush Beryllium Company that the proposed recommendations of removing those who have shown "any" evidence of acute beryllium effect from beryllium work will upset his highly skilled staff and executive group. I have the following to suggest.

(1) The basis of decision as to whether or not these men have had acute beryllium disease has been largely lay, subjective opinion. I think a review of the evidence for such diagnoses might well reduce the list from 12 men to three or four. Dr. VanOrdstrand, in my opinion, would be best qualified for such clinical decision.

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(2) Due to markedly improved engineering, the "beryllium background" to which such men would be exposed would doubtless be below the tentative figure now used of 1 to 2 micrograms beryllium per cubic meter for steady exposure. I believe Dr. Zelinski at Brush, Mr. Windecker at Clifton in consultation with Drs. VanOrdstrand and DeNardi, could impose certain reasonable restrictions on the activities of such key men compatible with wise medical preventative measures. If deemed important, such restriction could under the present attitude toward beryllium toxicity easily be made mandatory.

(3) In view of the evidence at hand, I believe that no one who has had acute beryllium poisoning (except for local eye and skin reaction) should be permitted access to beryllium operations.

Rochester

Clinical Studies - You are probably aware of the details of the studies done by Drs. Waterhouse and Bruce and their colleagues on eight cases of chronic beryllium disease. My reactions are as follows:

(1) Justification for such studies at present appears to me to rest on therapeutic implication.

(2) The mechanism of beryllium action in the body is more basic to discovery of therapy than simply the knowledge of etiology, as say in bacterial disease where one may develop anti-bacterial agents.

(3) There appear to be two promising therapeutic leads:

A. The metabolic studies of Dr. Waterhouse taken with the suggestive work of Dr. Bois et al. in Chicago give promise of attack on the disease by means of counteraction of beryllium effect on certain enzyme systems. This comment is mine alone and doubtless premature.

B. The pulmonary physiology studies of Dr. Bruce give immediately important leads in suggesting that the use of oxygen intermittently and under pressure may be remarkably beneficial, whereas the use of constant O_2 may actually be harmful. If this is true, there is a great deal of mismanagement of O_2 therapy in chronic beryllium disease in the country over.

Animal Studies - I am not qualified by training or experience to be critical of animal experimentation. My reactions are as follows:

(1) There is an unfortunate lack of mutual exchange of data and experience between those with clinical experience and those engaged in animal work. (This, of course, in not unique with Rochester.) It seems to me this could be easily remedied to good effect. I thought of speaking to Dr. Howland about it, but did not, chiefly because I did not see him alone.

(2) One wonders at the usefulness of getting acute beryllium intoxication in experimental animals over and over unless, of course, as stated above, understanding of mechanism of beryllium poisoning might lead to therapeutic leads. Species differences already demonstrated (i.e., hematologic changes in certain animals not seen in man) make this questionable.

(3) The chronic disease is certainly our most pressing problem, and at present the whole weight of the Rochester work, if I understood Dr. Hodge, is on the acute manifestations. Perhaps this is necessary.

(4) I cannot understand the defeatist attitude about producing chronic changes in animals with beryllium compounds sufficiently approximate to the human pathology to enable investigators to study biochemistry, etc. Dr. Gardner produced certain granulomatous changes in guinea pigs, rats and rabbits with a variety of beryllium compounds and reported them in private correspondence in December, 1944. The attitude I speak of appears to emanate from Saranac and is, I believe, most unfortunate--causing confusion and delay in initiating work on the chronic disease.

(5) Perhaps I have omitted crucial points that may be discovered by animal experimentation. I refer especially to knowledge of which compounds at what levels are disease producing. Again, data at hand suggest that extrapolation from animal work to human reaction is uncertain because of species differences.

In summary, then, my trip August 29 to September 3, leads me to the chief points here listed:

(1) Due to acceptance of beryllium as toxic and consequent engineering control, acute beryllium poisoning will appear as benzol or mercury poisoning do on rare occasions, from ignorance or a breakdown in equipment (mechanical or deliberate human).

(2) Cases of chronic beryllium poisoning are being uncovered daily from a variety of remote and apparently slight beryllium exposures.

(3) Merging of clinical aspects of subacute and chronic cases of beryllium is striking. All cases of beryllium disease have certain clinical and biochemical features in common.

(4) There is dire need for studies leading to treatment of the chronic disease. With this in mind, it is perhaps unfortunate that the work by Drs. Waterhouse and Bruce has stopped. I believe consideration should be given to opening this work. Dr. Howland tells me the request would have to come from Washington. Perhaps some other group could be found to do this work.

(5) I continue to encounter, as I did in 1948, seeming lack of open-mindedness on the part of the Saranac group as to etiology of disease seen in those exposed to beryllium compounds. This is reflected in their reports, conversation and correspondence. I don't understand the reason for it.

(6) I believe that those responsible for the medico-legal affairs of the AEC should consider the problem of the disability involved in the growing group of individuals with chronic beryllium disease. This group is small in workers exposed in AEC installations at present, but I suspect it will, unfortunately, grow.

Harriet L. Hardy, M.D.

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