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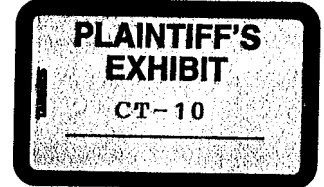
SAINT LUKE'S HOSPITAL

of the Methodist Church

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December 20, 1967

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Mr. F. J. Solon, Jr.
Johns-Manville Corporation
22 East Fortieth Street
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Dear Mr. Solon:

You have asked me to submit to you in written form an expression of my opinion with respect to certain questions raised by a letter from Dr. James D. Snell, Jr. addressed to Mr. Robert L. Lawrence of the Metro Water Department in Nashville, Tennessee.

If I interpret Dr. Snell's concern correctly, it is based in part on an overinterpretation of incomplete information with respect to the gastrointestinal system plus some generalizations gleaned from the literature regarding respiratory system cancer and asbestos exposure which he is assuming are applicable to the gastrointestinal system.

He sets forth the reason for his apprehension in his second paragraph of the letter dated November 14, 1967. My response to these follows.

While it is generally accepted by those who have looked into the matter that there is a relationship between the inhalation of "asbestos" fiber and the frequency of occurrence of bronchogenic lung cancer in the population occupationally exposed to the fiber the precise mechanism whereby this relationship is mediated is certainly still moot. The fact that such a relationship seemed to hold in Great Britain as shown by Merriweather in 1955 but did not appear to hold in a pure chrysotile exposure as shown by Truhan and Braun some years later made it apparent that one could not use the word asbestos in a generic way but would have to take sufficient care to know what kind of asbestos might be implicated. At the present moment crocidolite seems to be the form of fiber most strongly implicated. Further information concerning the mechanism of the relationship was presented by Selikoff and Hammond at the American Medical Association Meeting in Atlantic City in June of 1967. They demonstrated that in their careful

F. J. Solon, Jr.

December 20, 1967

prospective study of a group of insulation workers all of their cases of lung cancer developed in men who were moderate to heavy cigarette smokers and not a single case has developed thus far in a non-smoker. This data strongly suggests that the role of asbestos fiber is as a co-carcinogen and not a carcinogen in its own right. Dr. Snell infers that asbestos causes a high incidence of cancer in the lung but it should be pointed out that this relationship even when taken together with cigarette smoking seems to pertain most strongly to insulation workers and there is no supporting evidence to indicate that such a high incidence occurs in all of the other form of occupational exposure. The frequency from the textile mills of Great Britain does not appear to be as high as in the insulation workers reported by Selikoff. The frequency as reported by Enterline more recently in the building products, friction materials, and the U.S.A. textile plants appears to be lower than in the insulation workers thus far reported. I cite this because it seems to me unwarranted to make the inference that asbestos fiber in and of itself causes a high incidence of cancer in the lung and from this make the inference that it is a strong carcinogen and must therefore in very small amounts do the same thing to the gastrointestinal system if swallowed. To summarize this part; in my opinion the current evidence does support the contention that in occupational exposures to asbestos fiber there is a higher incidence of bronchogenic cancer than in non-occupational exposures; the fiber acts as a co-carcinogen; there is no reliable evidence at this time that asbestos by itself acts as an agent to cause bronchogenic cancer; the most likely offending form of fiber is crocidolite; and most importantly, the effect appears to be dose related as well as related to a long latent period between the onset of exposure and the development of the neoplasm. I believe it important to indicate that knowledge of what happens in the lung per se can be transferred to what might happen in the gastrointestinal tract only with the greatest caution, if indeed it can be extrapolated at all to any other organ system.

In the second paragraph Dr. Snell also indicates his belief that there is a high incidence of cancer in the gastrointestinal tract as a result of swallowing asbestos fiber. I have difficulty in knowing what he means by the statement "even in amounts small enough to be visible only under a microscope." Fibers small enough to remain airborne and be

F. J. Solon, Jr.

December 20, 1967

inhaled or ingested are of necessity visible only under a microscope because they are the order of 40 or less microns in length and less than 5 microns in diameter. As to total amounts swallowed over a period of years I don't know what the microscope would do in the way of playing a role in estimating this. Be that as it may, one wonders what evidence he is quoting to indicate a proven high incidence of cancer of the gastrointestinal tract in persons occupationally exposed to fiber. Most likely he is referring to a paper forming part of the symposium on "biological effects of asbestos" held in October of 1964 and published at the end of 1965. This paper by Hammond, Selikoff and Churg indicated a frequency of cancer of the stomach, small intestine and colon about three times as high as the expected whereas even at that date they were quite careful to indicate that the primary source of their information was not entirely reliable since they say and I quote, "taken at face value it would appear that asbestos workers have an abnormally high risk of dying of gastrointestinal cancer. However, we will refrain from drawing conclusions on this matter at the present time." It is of importance that in their most recent paper concerning this general subject and referred to in this letter previously as having been presented at the American Medical Association Meeting in June, 1967 they continued to be just as cautious. They again report that the observed rate of cancer of the stomach, colon, and rectum in their groups under intensive study was three times the expected but they state and I quote, "Although this bears out our earlier findings, the number of deaths from these causes was so small that we still refrain from drawing any conclusions at this time." Certainly Dr. Snell's apprehensions nurtured by his belief that a high incidence of gastrointestinal cancer has been proven to occur as a result of the ingestion of asbestos fibers would seem unwarranted.

Since the relationship to bronchogenic cancer appears to be rather clearly a dose related one and the same is true for all known carcinogens, I would think that if any association between asbestos fiber and gastrointestinal cancer exists, it should be dose related. The insulation workers that are constantly under study by Selikoff et al are obviously a quite heavily exposed group. According to various reports emanating from that laboratory as much as 25 per cent of the population under study has asbestosis and this means a heavy exposure. It can be accepted that a very large per cent of

F. J. Solon, Jr.

December 20, 1967

the fibers deposited in the tracheo-bronchial tree of such workers is brought back up and some of this must of necessity be swallowed. In addition, some fiber deposited in the oral and nasal cavities will ultimately find its way into the intestinal tract. I would reason from this, therefore, that in the insulation workers the gastrointestinal exposure to fiber would be high and therefore if there was a strong relationship of fiber ingestion to gastrointestinal cancer it should not be difficult to demonstrate it.

There are some other data in humans bearing on this. Enterline has recently published a study of the death certificates of a large number of workers who manufacture building materials, friction products and textiles utilizing asbestos fiber. He compared the causes of death in these workers to those of a cotton textile processing group. Looking at these data one sees no relationship suggesting an inordinately high frequency of gastrointestinal cancer even when one takes into consideration the factor of dilution caused by including rather large numbers of fairly young and short-term exposed people. Taking all things into consideration, I do not believe there is substantial evidence at this time to support the contention that even the highest intensity of exposures that we know of in industry lead to clear cut increased frequency of gastrointestinal cancer.

There is abundant animal experimentation along these lines. There have been large scale animal experiments studying the effects of asbestos fibers of various kinds and sizes on the pulmonary systems by exposing the animals to airborne fiber. In many of these experiments the intensity of exposure and duration was well over two years and sufficient to produce well developed pulmonary fibrosis. Such studies carried out in Saranac Lake were to my own knowledge always characterized by careful gross examination of the entire body of these animals and this included the intra-abdominal contents. Since receiving information concerning the apprehensions of Dr. Snell I have checked on this matter with the Saranac Lake group and in addition with Dr. Forde McIver at the University of South Carolina. Utilizing all manner of animals including dogs and with observations going up to two and more years in the mouse and on to four or more years in the dog none of the investigators involved in these studies has ever seen anything whatsoever to suggest a relationship between fiber exposure and gastrointestinal or liver cancer in the exposed animals. In fact,

F. J. Solon, Jr.

December 20, 1967

to their best knowledge, they have never seen a tumor of the gastrointestinal tract in these experimental animals. I cite this data because such animals do not cough and spit and of necessity swallow the fibers that are brought back up from the lungs. In addition, the food, especially of the small animals is covered by the settled-out asbestos fibers in the experimental chambers. These experiments are as a rule conducted with exposures for six to eight hours a day, five days a week and the food in general is simply added to that which is already in the feeding boxes. When fresh vegetables are fed, they are placed in the cages in the morning and cleaned out only with the general cleaning of the cages the next day. I would estimate that the ingested fiber in these experimental animals far exceeds that of workers in industry. In mice, the observations were carried out over the lifetime of the animal and for 75 percent or more the expected lifetime in most of the other animals. Although it is difficult to extrapolate from animals to man, the total lack of any evidence whatsoever that in the experimental animal the ingestion of asbestos fiber causes any sort of malignancy in the intestinal tract would seem to me to be important. In fact, it is this total lack of finding of tumors in the gastrointestinal tract in this type of experiment that has obviated the necessity of setting up a full-fledged feeding type of experiment. I understand that one or two investigators are embarking on this kind of study at the present time, although I personally do not see the need for it.

It seems to me, therefore, that Dr. Snell's apprehensions are based on an erroneous impression that a high incidence of gastrointestinal cancer has been proven to exist in persons occupationally exposed. There is evidence that such a relationship does not exist. This is both with respect to humans and experimental animals. In this context I think it should be re-emphasized that the intensity of exposure in all of the circumstances alluded to is far higher than one could conceivably expect in the drinking of water from asbestos cement pipe.

A third type of neoplasm has been implicated recently with the inhalation and consequent ingestion of asbestos fiber. Although Dr. Snell did not mention mesothelioma I presume he may have had this tumor in mind also. This tumor arises from the lining of the pleura space and abdominal cavity or peritoneum. In 1960 Dr. Wagner and his co-workers, at

F. J. Solon, Jr.

December 20, 1967

that time working in a hospital that serviced a rather dispersed population, noted an unusual frequency of occurrence of mesothelioma in the patients admitted to their hospital. In the general population, as will be indicated later, this tumor is one of the exceedingly rare ones and hence the occurrence of only a few cases in a single hospital within a short period of time was rather dramatic and required further investigation. Wagner and his co-workers learned that a factor common to all of their cases was either a history of having worked for a long period of time in the production of asbestos fiber or having had rather intimate contact with it over many years. The non-industrial contact being a strong one in that such individuals had picked short fiber from the tailings heap, had walked or ridden on roads constructed of asbestos-bearing rock, or had washed the clothes of asbestos workers in the mines and mills frequently over many years. Subsequent investigations in the South African asbestos producing regions indicates quite clearly that this unusual frequency of mesothelioma occurred only in those areas producing crocidolite and the chrysotile producing areas failed to show this unusual frequency of mesothelioma. It was of some interest, too, that not all crocidolite producing areas showed a high frequency of mesothelioma. Subsequent to this disclosure, an unusual frequency of mesothelioma has been unearthed in Great Britain where at the present time I am told a total of 276 cases of mesothelioma in the entire British Isles have been located. I do not know over how many years this series of cases were accumulated. Even at this number it continues to be a rare tumor. Retrospective exploration of the life experiences in these identified cases of mesothelioma has shown a bona fide exposure to the inhalation of asbestos fiber such as employment in the asbestos textile industry, the unloading of fiber at the docks or handling of the fiber en route to the mills, etc., in a majority of the cases. In some instances direct employment in such a way has not been demonstrated but a greater than casual contact with fiber has been disclosed such as living in the immediate neighborhood of industrial operations known to disperse fiber into the general environment or washing of clothes of a member of the family employed in the asbestos industry. In the few remaining cases, in the light of the great difficulty of disclosing asbestos fiber exposure by retrospective methods involving questioning of relatives, etc., it is highly probable that an actual greater than casual contact with fiber did occur in all. More recently, a greater than anticipated frequency of occurrence of mesothelioma has been disclosed in insulation workers and there

F. J. Solon, Jr.

December 20, 1967

is some evidence rather strongly suggesting the same is true in at least some of the asbestos textile employees of the U.S.A. In all of these exposures, crocidolite is again to be found. As was true in the chrysotile exposures of South Africa, a study of similar asbestos exposures in the milling of this type of fiber in the Canadian production area has failed to disclose any unusual frequency of mesothelioma. A careful study of the Finnish population exposed to anthopholite also has failed to disclose a single case of mesothelioma.

In addition to a strong suggestion that crocidolite is the agent implicated in some way with the occurrence of mesothelioma, there is evidence to suggest that this tumor likewise is dose related. In all of those situations where the exposure can be relatively well documented, the occurrence of mesothelioma has been in persons not only exposed to crocidolite, but also the exposure has been greater than casual even though this tumor apparently has occurred in the absence of sufficient exposure to cause actual pulmonary asbestosis. It would appear that the total exposure may be somewhat less than that needed to relate strongly to bronchogenic carcinoma, nevertheless the exposure is still one that is much greater than casual. By casual exposure I mean the kind of exposure which might occur in persons not working or living daily in contact with known sources of asbestos fiber dissemination. The finding of ferruginous bodies in the majority of the adult population whose lungs come to necropsy examinations suggests rather strongly that the entire population of the civilized world has some--though casual--exposure to the inhalation of fibers amongst which one can reasonably assume asbestos should be included. The finding of these fibers in the lungs indicates that such fibers most assuredly have been swallowed and hence enter the gastrointestinal tract in some as yet unknown numbers. In spite of this probable uniform type of casual exposure to asbestos fiber, Selikoff, Churg and Hammond report in the New England Journal of Medicine, Volume 272, page 560 in 1965 that of the 31,652 persons who were known to have died between the ages of 30 and 89 years and who were members of a follow-up of 1,048,183 persons only three had died of mesothelioma of the pleura and none of mesothelioma of the peritoneum. In the light of what we now know, it can be assumed that 50 per cent or more of these 31,652 persons who died must have had at least enough exposure to fibers,

F. J. Solon, Jr.

December 20, 1967

some of which were doubtless asbestos, to cause ferruginous bodies. It can be further assumed that some unknown quantities of asbestos fiber were ingested during their entire lifetime, beginning with the application of body dusting powder. Since only three subsequently developed mesothelioma it is clear that some quantity of asbestos fiber ingestion is well tolerated, even for life.

There is further evidence along this line which will be presented next spring by Dr. William E. Smith and his co-workers. Pleural mesotheliomata have been produced by the injection of asbestos fiber and other non-asbestos materials in the pleural space of experimental animals. Smith's group have shown that a progressive attenuation of the amount of asbestos fiber placed in the pleura leads to the development of fewer and fewer mesotheliomata and at the one milligram dose no mesotheliomata developed.

With this background of information, what can be said in a direct fashion about the actual problem which raised Dr. Snell's apprehensions. There is some useful information in this regard. One can inquire into the evidence that asbestos fibers are released from asbestos cement pipe. It is my understanding that in predeterminable circumstances asbestos cement pipe may develop an inner lining of carbonates completely shielding the original pipe from contact with the water flowing through it. In other circumstances, the pipe does not in any way disintegrate and therefore releases no fibers. You would know better than I as to the possibilities that repair of pipe might at the time release some fibers but I cannot conceive that this occasional type of fiber release if it did occur could be anything other than a casual type of exposure. In some circumstances I am told that asbestos cement pipe might slowly lose substance from its inner surface and thus release some asbestos fiber. This kind of weathering must be very slow--if rapid, it would be economically unwise to use this pipe under such circumstances. With information concerning the volume of water transiting the system, the area of the inner surface of the pipe and the rate of weathering it should be possible to make some rough calculations of the total fiber dispersal. I would anticipate that the amount ingested would be so low as to be in the casual exposure range where mesothelioma has not developed with an unusual frequency.

F. J. Solon, Jr.

December 20, 1967

Even more meaningful to me is the fact that asbestos cement pipe has been in use in water systems throughout the U.S.A. for twenty-five to thirty years in a rather large number of major urban locations. These geographic areas, as for example the Los Angeles Department of Water and Power in California, have medical facilities which are not likely to have overlooked a frequent occurrence of this exceedingly rare tumor.

In this connection some data are available in regard to cancer of the digestive organs which include the gastrointestinal tract. Data from the National Office of Vital Statistics of the U. S. Public Health Service indicates that from 1947 to 1966 the rate of occurrence of tumor of this body system has dropped from 55.2 per hundred thousand population to 48.4. Substantial amounts of asbestos fiber have been used in various ways from 1930 on in the U.S.A. and one would anticipate that if this fiber was playing a role in the causation of gastrointestinal tumors, it might be expected to have led to an increase in tumor rather than the observed decrease.

For the U.S.A. as a whole, and from the same statistical source, cancer of the digestive organs is reported in 1964 to have been responsible for 5.1 per cent of all deaths. In Los Angeles, California where asbestos cement pipe has been used in very substantial amounts from 1936 on, the reported figure for cancer of digestive organs as the cause of death is 5.1 per cent in 1964. In other cities where asbestos cement pipe has been utilized in the water system for twenty-five or more years, as for example Knoxville, Tennessee; San Antonio, Texas; San Diego, California; Lubbock, Texas; and New Orleans, Louisiana, the per cent is less than the average for the U.S.A. and in Providence, Rhode Island and Miami, Florida, it is slightly above the average namely 5.7 per cent.

I find it difficult to understand the reasoning upon which Dr. Snell bases the last sentence of his third paragraph to the effect that "If any particles were released, current medical knowledge suggests that a rise in certain types of cancer could be expected about twenty to fifty years among the population." I wonder if Dr. Snell might provide us with the information on which he bases his inference that medical knowledge suggests such a development

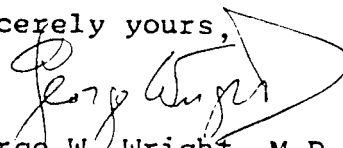
F. J. Solon, Jr.

December 20, 1967

following the release of a few or some determined number of particles into a water system. All of the information that I and others have strongly indicates that the relationship between neoplasia and asbestos fibers is a dose related one and to believe that a single fiber can cause a cancer seems incredible. The medical literature contains ample evidence that the kind of exposure to fiber experienced by those using the fiber in an occupational way is manyfold that of the general population. In the lungs received from persons with several years or more of continuous industrial exposure to asbestos fiber the number of ferruginous bodies can only be described by the word "myriads" whereas in the casually exposed lungs it is necessary to digest large parts of the lung or squeeze the juice from large volumes of lung in order to find one or two such ferruginous bodies. In those instances where bronchogenic cancer or mesothelioma appear to occur with greater frequency on a population basis, the number of ferruginous bodies also appears to be much larger than in those casually exposed. I do not believe that Dr. Snell can offer any substantial scientific evidence to indicate that the ingestion of one or a hundred or a thousand asbestos fibers on one or more instances is causally related to the development of mesothelioma. Most assuredly so few fibers cannot be related to gastrointestinal cancer, which appears to be his major worry, since in individuals known to be exposed far more heavily daily over a period of many years there is no acceptable evidence of a higher than anticipated frequency of cancer of this system. If Dr. Snell does have such evidence, we and others would welcome knowing about it.

With best wishes.

Sincerely yours,



George W. Wright, M.D.
Head, Medical Research
Department

GWW:kal