Individual Susceptibility to Genotoxic Agents in the Human Population

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PREFACE

As a result of the industrial revolution, man's technological achievements have been truly great, increasing the quality of life to almost unimagined proportions; but all this progress has not been accomplished without equally unimagined health risks. Sufficiently diagnostic short-term assay procedures have been developed in recent years for us to determine that there are mutagenic agents among thousands of chemicals to which the human population is exposed today. These chemicals were not significantly present prior to the industrial revolution. As of today, there are no procedures available which have been adequately demonstrated to assess individual susceptibility to genotoxic exposures, and as a result we have had to rely on extrapolating toxicological data from animal model systems. The question is can we afford to allow such an increased environmental selection pressure via mutagenic exposures to occur without expecting adverse long-term effects on our health. It is apparent from this line of reasoning that what is lacking and immediately needed are test procedures that can be applied to humans to assess genotoxic exposure as well as individual susceptibility to it.

There have already been two conferences which have focused attention on this research area. "Guidelines for studies of human populations exposed to mutagenic and reproductive hazards" (A. D. Bloom, ed., March of Dimes Birth Defects Foundation, White Plains, New York, 1981) and "Indicators of genotoxic exposure in humans" (Banbury Report 13, B. A. Bridges, B. E. Butterworth, and I. B. Weinstein, eds., Cold Spring Harbor Laboratory, 1982) were important beginnings in approaching the need for examining this field. During this same period, The Swedish Council for Planning and Coordination of Research established a program entitled "Chemical Health Risks in our Environment" to stimulate a better organization of research in this area for Sweden.

In May 1982 we organized the first American-Swedish Workshop dealing with "Individual Susceptibility to Genotoxic Agents in the Human Population" at the National Institute of Environmental Health Sciences in the Research Triangle Park, North Carolina. Our intentions were to pick up the momentum produced by the two earlier con-

ferences, by focusing more directly on the "State-of-the-Art" assay procedures already being developed or planned in the United States and Sweden for use on humans. It is hoped that publication of these proceedings will emphasize the importance of international collaboration and place into a better perspective the biochemical and genetic methods that can be developed and assessed in the near future as epidemiological tools for the determination of mutagenic risk to man.

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There is a paradox in discussing the use of occupational experience in relation to individual susceptibility to genotoxic agents. First, disease that is seen occurs in individuals, and reflects their individual susceptibility. The research that is done, however, is focused on populations. Therefore, in this presentation I will move from one foot to the other. Secondly, there's long been a curious dichotomy with regard to reproductive experience and occupational and environmental health matters. Curious, because there's been a concordance in many ways. In each, both somatic and genetic material are included, many species can be affected, many different organs, different tissues, and both are very selective within populations. A large variety of agents can affect individuals in each, both males and females can be involved. Yet this dichotomy has continued.

Several recent examples may be given. For instance, when it became clear a decade ago that bis-chloromethyl ether was capable of producing lung cancer and nasal cancer in humans, there were no studies started among the populations involved to see whether there might also be adverse reproductive experience. Our own laboratory was very much involved in 1974 in vinyl chloride research [1] and it was clear that this chemical could produce a good deal of cancer. There were some 6000 to 10,000 heavily exposed polymerization workers and probably more than a million people involved in chronic exposure at much lower levels. There have been few studies with regard to reproductive experience, even though the occupational experience was very clear and even though chromosome aberrations had been demonstrated [2]. I am not aware of concurrent studies with regard to aflotoxins in East Africa and there isn't a single nickel smelter to

my knowledge in which the workers are followed for lung cancer and the offspring simultaneously considered in relation to adverse reproductive experience. This discordance has lasted for many decades. In part, perhaps it's been structural. There's been compartmentalization of research. Geneticists, pediatricians, and obstetricians have been very much involved in one area, and environmental scientists, pathologists and biostatisticians in another. This is beginning to change. Not only is this meeting an example, but also the perspectives of NIEHS, where such interdigitation is very much encouraged.

It may be useful to review how we came upon many of our current concepts in environmental and occupational disease, to see whether some guidance might be provided for an increase in such interdigitation and joint studies.

We both began with description in our earliest decades, and also enumeration. Perhaps immediately postwar, we began to somewhat diverge in our approaches. In occupational and environmental health, we began to have a much greater focus with regard to etiology.

How did this come about? [3]. In environmental and occupational disease (and cancer is a good example) data collection was primarily in terms of registries, very much as were reproductive experience studies. This was just before, during and after World War II. Data began to come in from cancer registries; data of different quality from different parts of the world. Variations in incidence were found. Stomach cancer was high in Chile, Iceland, and Japan, low in the United States, Roumania, etc. For cancer of the esophagus, very much the opposite; low in the United States and high in France and China. Colon-rectum cancer was high in Scotland and the United States, and low in Roumania. Explanation was needed for these differences. One that was quite obvious was that people were genetically different, that people in France were different from those in Egypt, etc. That was a possibility.

However, when geographical pathologists examined what happened when people moved from one country to another, they found that when people in Japan, who had high stomach cancer risk, moved to the United States, their children here had the low rates of other Americans. In contrast, the low colon cancer rates in their home country changed to the high colon cancer rates of all other Americans when they came to this country. It was surely unlikely that there was enough genetic drift in one generation to account for this.

Secondly, even within one country, it was noticed that rates were changing. For example, there's been a sharp decrease in stomach cancer in the United States. We don't know why, although we are very thankful. But it hasn't been equally true for all people in the

United States. It's true for whites, but not so much for black people. With regard to colon cancer, the rates have stayed the same from 1930 to 1980 among whites. However, they have been increasing for our black population. Cancer of the esophagus has very much remained the same for whites, although it has been sharply rising for blacks. Genetic differences seemed an incomplete explanation.

Explanations were sought. Hints were available. One came from radiation studies. Beginning in the Schneeburg area a century ago, it was observed that what was then thought to be sarcoma of the lung (now known to be lung cancer) was very common among the miners [4]. Fifty years later the same was found in Joachimstal, on the Czech side of the mountains, with autopsies of the miners showing 50% with lung cancer. The explanation that the cancers might be exogenous in origin was suggested by a young woman journalist, who opined that it could be due to radiation since these were the mines from which the Curies obtained pitchblende for their radium studies.

The second thread that has been woven into our current understanding came from our greatest public health error, our failure in the 1920s, 1930s, and 1940s to predict what was going to happen in the 1960s, 1970s, and 1980s, as a result of the extraordinary increase in cigarette smoking that began at that time. Fortunately, this met with new advances that were being made in chronic disease epidemiology and population studies. The American Cancer Society, for example, registered one million people in one-third of the counties of the United States 1959-1960. A vast amount of data were collected. People were asked, "Where were you born?", "Where was your father born?", "How much fried food do you eat?", "How many hours do you sleep at night?", "How much schooling have you had?", "How far down do you smoke your cigarettes?", and a wide variety of other questions. All were then followed prospectively. Within five years, by the mid-60s, the results were clear. In two groups of more than 37,000 men each, carefully matched for many variables except for cigarette smoking, it was found that people who smoked cigarettes had much more lung cancer than those who did not. This was true for a number of neoplasms and, of course, for a number of other diseases, as well [5].

The use of large scale population studies was obviously very valuable. This was true in identifying not only a direct effect on the lung in cigarette smoking, but for such diseases as cancer of the bladder and cancer of the pancreas, which were not the result of a direct effect but a diffuse chemical influence. Individuals who smoked cigarettes had much greater risk of developing cancer of the bladder, compared to those who did not.

The third thread that allowed us to reach our present understanding came from a series of unnatural, unwanted, unplanned cir-

cumstances in which human beings were exposed to a variety of toxic agents. This began about 200 years ago, with Percivall Pott's original description of cancer of the scrotum in chimney sweeps, in 1775 [6]. One hundred or so years later, Dr. Rehn reported cancer of the bladder in aniline dye workers [7]. Yamagiwa (1915) followed and produced experimental cancer of skin in rabbits with coal tar eventually leading to the chemical studies of Ernest Kennaway and the isolation of a variety of carcinogenic chemicals. Rehn's work was germinally important. He described three cases of bladder cancer in 1895 and suggested that the three workers he studied, since they worked in the same plant making fuchsin, might have gotten their bladder cancer because of the chemical in their environment. This was lésè majesté since Connheim had noted decades before that it was due to epithelial cell rests in the bladder mucosa. Yet Rehn proposed exogenous etiology. Scientists soon published additional case reports. Once again population studies were utilized. In Basel, for example, of the twelve deaths of cancer of the bladder in the first decade of this century, six were in the dye workers of the city, although only 2% of the males worked in the dye industry. The same was true in Frankfurt, where approximately 25% of all bladder cancers recorded at the turn of the century were in dye workers. Thus, the use of population studies, albeit primitive, allowed us to define an association between a specific exposure and disease.

Our failure in the United States to appreciate this led to a tragedy. When in the first World War we could no longer import aniline dyes from Switzerland and Germany, the duPont Company set up its own works in Salem County, New Jersey, the great Chambers Works. By 1931, the first cases of bladder cancer were seen. Dr. Gehrman, the Medical Director of duPont, did a magnificent study, cystoscoping 532 men. Even at that early time, 4-1/2% had bladder tumors, and he was able to define that some had been exposed to β-naphthylamine, to benzidine or to both chemicals [8].

Another agent that has been very well studied - asbestos - has again given evidence in this regard. In 1898, Dr. Montague Murray, a physician at the Charing Cross Hospital in London, saw a man who was very short of breath. He was told that the man worked in a local asbestos factory that had opened up only 10 years or so before. When the man died the following year, an autopsy was done. Diffuse interstitial fibrosis was found with what we now know as asbestos bodies.

Since then, we have learned a good deal [9]. First, during the 30s, 40s, and 50s, we learned that, unlike other dusts (coal, silica, diatomaceous earth, aluminum), with asbestos the pleura was often involved, although the mechanism is still not clear. This might be simply discrete plaques, with no particular signs or symptoms, or more diffuse, sometimes causing pulmonary insufficiency.

In the mid-30s, Dr. Kenneth Lynch, at that time Professor of Pathology at the Medical University of South Carolina, described a man who had both interstitial fibrosis (asbestosis) and cancer of the lung. He proposed there might be an association [10]. Ten years after that, Dr. Weiss in Germany reported another unusual event. A man who had worked with asbestos was found to have a malignancy of the mesothelial lining of the chest (mesothelium). Since a primary tumor of the mesothelium is termed a mesothelioma, this was the first case of mesothelioma related to asbestos work. The description then was very much like what we have been seeing since - diffuse, malignant, often fatal within six months or a year. The following decade saw other people who have been exposed to asbestos suffer malignancy in the lining of the abdomen. Again the mesothelial lining, therefore, mesothelioma. And again diffuse and invariably fatal. Such cases began to increase so much that scientists began to urgently study the problem. This included studies of insulation workers. Population studies were once more used.

In the New York-New Jersey metropolitan area, where there were a total of 1249 insulation workers on January 1, 1963, 1117 were X-rayed. It was found that about half had abnormal X-rays. But it was also found that of the 725 with less than 20 years from onset of exposure, most had normal X-rays. It was only after that point that the X-rays tended to become abnormal (Table 1). This demonstrated that we were dealing with an important time factor [11].

In the same area, in 1943, there had been 632 men on the rolls of this union. Nine died before 20 years and 623 were still alive, 20 years or more after the onset of their work. It was found, examining their mortality experience as a population from January 1, 1943 to January 1, 1963, that there was an extraordinary increase in the number of deaths observed compared to the number expected. Twelve were due to asbestosis. That was no surprise. What was unusual was that instead of 32 deaths of cancer, 95 had occurred (Table 2) [12]. Instead of 6 deaths of cancer of the lung, there

TABLE 1. X-Ray Changes in Asbestos Insulation Workers [11]

Onset of exposure (yrs.)	No.	% Normal	% Abnormal	Asbestosis (grade) 1	2	3
40+	121	5.8	94.2	35	51	28
30-39	194	12.9	87.1	102	49	18
20-29	77	27.2	72.8	35	17	4
10-19	379	55.9	44.1	158	9	0
0-9	346	89.6	10.4	36	0	0
	1,117	51.5	48.5	366	126	50

TABLE 2. Observed and Expected Number of Deaths Among 632 Asbestos Workers Exposed to Asbestos Dust 20 Years or Longer [12]

Cause of death	Years				Total, 1943-1962
	1943-1947	1948-1952	1953-1957	1958-1962	
Total, all causes	28	54	85	88	255
Observed (asbestos workers)					
Expected (US white males)	39.7	50.8	56.6	54.4	203.5
Total cancer, all sites	13	17	26	39	95
Observed (asbestos workers)					
Expected (US white males	5.7	8.1	13.0	9.7	36.5
Cancer of lung and pleura	6	8	13	18	45
Observed (asbestos workers)					
Expected (US white males)	0.8	1.4	2.0	2.4	6.6
Cancer of stomach, colon, and rectum	4	4	7	14	29
Observed (asbestos workers)					
Expected (US white males)	2.0	2.5	2.6	2.3	9.4
Cancer of all other sites combined	3	5	6	7	21
Observed (asbestos workers)					
Expected (US white males)	2.9	4.2	8.4	5.0	20.5
Asbestosis	0	1	4	7	12
Observed (asbestos workers)					

were 42. Dr. Lynch at the postmorten table in 1935 had been correct.

Mesothelioma in the past had been found, in general, in approximately 1 out of 10,000 deaths, in autopsy series. Here it was almost 1 of 10. There was also increased cancer at a number of other sites.

This cohort has now almost reached extinction, giving virtually their total experience. By 1977, instead of 329 expected deaths, there were 478. Once again, some were due to asbestosis. However, the majority of excess deaths were due to cancer where instead of 57, there were 210. Instead of 13 deaths of lung cancer, there were 93. One out of very 5 of these people died of cancer of the lung. Instead of no deaths of mesothelioma, there were 38. And increases were seen in cancer of the gastrointestinal tract and at a number of other sites.

Therefore, with radiation studies, chemical studies, studies of particles, with smoking studies, a very important advance was made. It was demonstrated that we can identify things that are carcinogenic to humans. This has been coupled with the understanding that "every cancer has a cause," and the causes are generally exogeneous - itself a remarkable step forward. If you hear of a person with cancer of