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EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST., PHILADELPHIA, PA 19104

Teratology Literature and the Thalidomide Controversy

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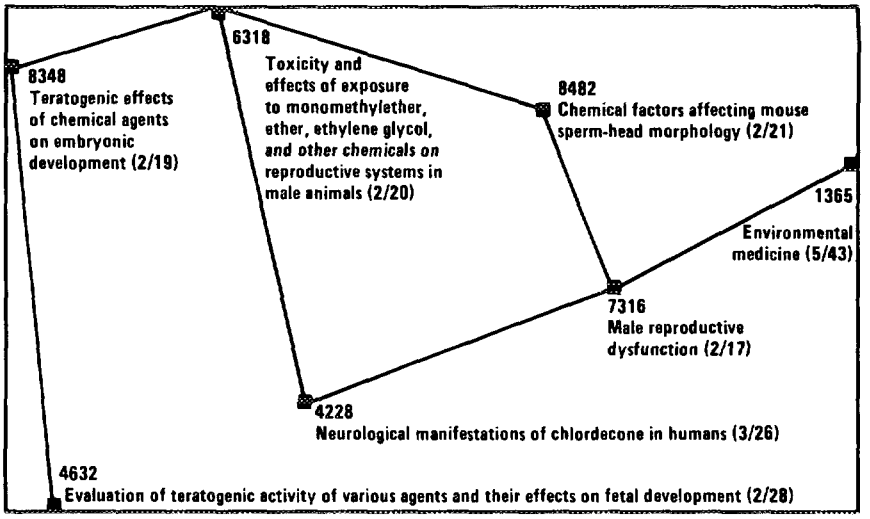
The prospect of bearing an abnormal or deformed child has long been a chilling fear of all expectant mothers. Of the estimated 130 million children born each year worldwide,[1] at least 2 to 3 percent are born with some type of birth defect.[2] It has only been within the last 150 years that doctors have attempted to interpret birth defects, or congenital malformations, in a scientific manner. The term "teratology" was first coined in 1832 by the French physician Isidore Geoffroy Saint-Hilaire to define a field of science dedicated to studying developmental anomalies. The term is derived from the Greek term "terato," meaning monster. He also described and classified the known abnormalities of his day.[3]

While teratology had its origins in the descriptive anatomy of congenital malformations, Richard W. Smithells, Department of Pediatrics and Child Health, University of Leeds, UK, points out that today teratology includes any birth defect—morphological, biochemical, or behavioral—induced by an embryotoxic agent at any stage of gestation.[4] This wider definition inevitably includes the involvement of many disciplines. For example, teratology is considered an offshoot of developmental biology. While developmental biology is the study of the overall development of the individual during gestation, teratology is primarily concerned with factors that interfere with developmental differentiation. These factors are often considered embryotoxins requiring the expertise of a toxicologist who studies the action, detection, and treatment of toxins. Although interrelated, each of these disciplines has its own language. In the near future we will study the developmental biology journals.

A major challenge to teratologists, therefore, is to establish and expand links with the varied disciplines contributing to the field. The multidisciplinary aspect of teratology makes it an excellent field to demonstrate the value of citation analysis. The cognitive and social ties between scientific papers and authors can be determined by analyzing direct citation links, co-citation, or bibliographic coupling. The relationships between teratology and other areas can then be ascertained. ISI® is using similar procedures in a project concerning toxicology for the National Library of Medicine. We are using bibliometric methods to determine how well the current TOXLINE database covers the relevant literature.

Figure 1 is a map showing how research fronts from the various fields of teratology are related. The higher-level front on "Teratogenic activity of various chemicals" (#85-0540) shows the links between smaller fronts on environmental medicine, the effects of chemicals on fetal development, and the neurological effects of chemicals. Table 1 is a list of six 1985 research fronts directly concerning teratology. We will review some of these research fronts, pointing out those areas that have made the most impact in the science community. We will also discuss some of the established principles of

Figure 1: Higher-level map for C2 research front #85-0540, "Teratogenic activity of various chemicals," showing links between C1 research fronts. The numbers of core/citing items are given in parentheses following the research-front name on the map.



teratology as well as the obstacles preventing certain questions from being answered.

In addition, to show the complexities involved in the mechanisms of teratogenesis, we will discuss the drug thalidomide. This drug was taken off the market 25 years ago after it was established as a cause of congenital malformations. Controversy still exists concerning this tragedy—which allegedly caused over 10,000 children to be born with severe physical defects—and whether it could have been averted.

Early Teratology Studies

The earliest scientific human teratology studies are found in a wide range of journals, such as the *American Journal of Ophthalmology*, the *American Journal of Roentgenology*, and the *Biochemical Journal*. This is an indication of the diverse fields contributing to the origin of modern teratology. Table 2 is a selected list of the current journals publishing articles on teratology. These journals cover many disciplines, including gynecology, obstetrics, embryology, and mutagenesis.

A preliminary journal list was developed using keywords, concepts, and prominent authors in an online and manual literature search. We also examined the *Journal Citation Reports*® for journal titles. The journals that appeared most often from these sources were added to the preliminary list. The final list was reviewed by subject specialists to provide an inclusive representation of all facets of teratogenesis.

The earliest teratology studies began appearing in the late 1800s, when the emphasis shifted from classifying malformations to experimentally inducing them in animals. In 1855 Camille Dareste applied heat, cold, shaking, and chemicals to chicken eggs. These treatments artificially induced developmental abnormalities in chicks and provided the first proof that extrinsic factors could cause abnormal embryonic development.[5]

The first report of experimentally induced congenital malformations in mammals was in 1921. Sylvester S. Zilva, Biochemical Department, Lister Institute, London, UK, and colleagues fed a pregnant sow a fat-deficient diet. Eight piglets were stillborn

Table 1: The 1985 *SCI®/SSCI®* research fronts on teratology and thalidomide. A = research-front number. B = research-front name. C = number of core items. D = number of citing items.

A	B	C	D
85-1803	Use of thalidomide therapy in leprosy	2	14
85-2250	Teratogenicity of retinoic acid and vitamin A analogs	4	35
85-4632	Evaluation of teratogenic activity of various agents and their effects on fetal development	2	28
85-6306	Maternal drug use in early pregnancy and birth defects	9	75
85-7692	Intrauterine factors affecting normal fetal growth and development	2	18
85-8348	Teratogenic effects of chemical agents on embryonic development	2	19

Table 2: Selected list of journals reporting on teratology and embryology. A = title and first year of publication. B = 1985 impact factor.

A	B
American Journal of Obstetrics and Gynecology (1920)	1.78
Anatomy and Embryology (1892)	1.62
Arzneimittel-Forschung/Drug Research (1951)	0.87
Cell Differentiation (1972)	1.39
Development, Growth & Differentiation (1950)	0.98
Developmental Biology (1959)	3.58
Differentiation (1973)	1.79
Journal of Embryology and Experimental Morphology (1953)	2.46
Mutation Research (1964)	2.28
Teratogenesis, Carcinogenesis, and Mutagenesis (1980)	0.99
Teratology (1968)	1.76
Toxicology (1973)	1.03
Toxicology and Applied Pharmacology (1959)	1.93
Toxicology Letters (1977)	0.76
Rouxs Archives of Developmental Biology (1894)	1.93

or died very soon after birth. Four of these piglets were born with rudimentary limbs.[6] In 1929 Leopold Goldstein and Douglas P. Murphy, Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania, Philadelphia, showed that X rays can affect human embryonic development.[7] And in 1941 Sir Norman M. Gregg, Royal Alexandra Hospital, Sydney, Australia, determined that the dreaded virus of rubella, or German measles, is a teratogen.[8] James G. Wilson, Children's Hospital Research Foundation and Department of Pediatrics, University of Cincinnati, Ohio, observed that an interest in the teratogenic potential of drugs and other biologically active chemicals virtually exploded during the 1950s. But despite the notoriety associated with the thalidomide experience, Wilson noted that teratology research continued to grow at a steady, rather than startling, rate after 1960 and 1961.[9]

Etiology of Congenital Malformations

Wilson estimated that about 20 to 25 percent of all birth defects are the result of genetic transmission and chromosomal abnormalities, while 5 to 10 percent have been attributed to known environmental factors. The remaining 65 to 75 percent of birth defects arise from unknown causes but may be caused by an interplay of multiple environmental agents with genetic factors.[10]

Alcohol is an example of an environmental factor acting as a teratogen. There is evidence that habitual or even occasional drinking by an expectant mother can endanger the health of the fetus. A baby of a heavy drinker may be born with fetal alcohol syndrome (FAS), characterized by a small head, defective joints in the hands and feet, a cleft palate, heart abnormalities, or mental impairment.[11] There is a large literature on FAS that will not be reviewed here, but the research fronts have been identified in the historiograph (see Figure 2).

Determinants of Drug Teratogenicity

Our review focuses on the mechanisms involved in drug-induced malformations since this is the topic involved with thalidomide. The potential for drug teratogenicity is dependent upon at least four variables, according to Marcus A. Klingberg and colleagues, Department of Preventive and Social Medicine, Sackler School of Medicine, Tel-Aviv University, Israel. The first of these is the nature of the drug. Some embryonic tissues are more sensitive to specific chemical structures, modes of action, or biochemical peculiarities of certain compounds. A second factor concerns dosage, timing, and

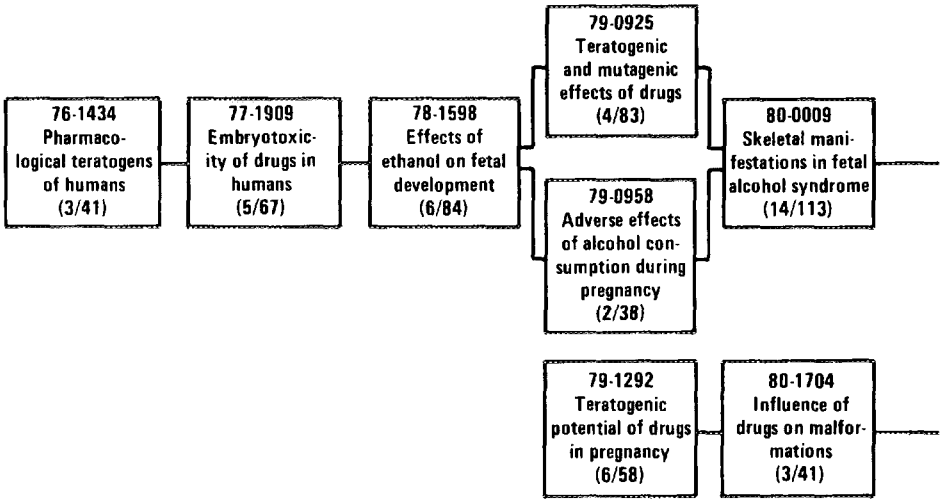


Figure 2: Historiograph of drug teratogenesis research. The numbers given in parentheses following the research-front titles refer to the numbers of core/citing items for each research front. If the same core documents are cited at the required thresholds year after year, linkages develop between research fronts and a historiograph is established.

mode of drug administration. The critical teratogenic period in humans is between the 3d and 12th weeks of pregnancy. Some drugs are teratogenic if given in low doses over an extended period of time, while others are damaging at higher doses for a short period of time; certain drugs, like thalidomide, have produced malformations after only a single exposure.[12]

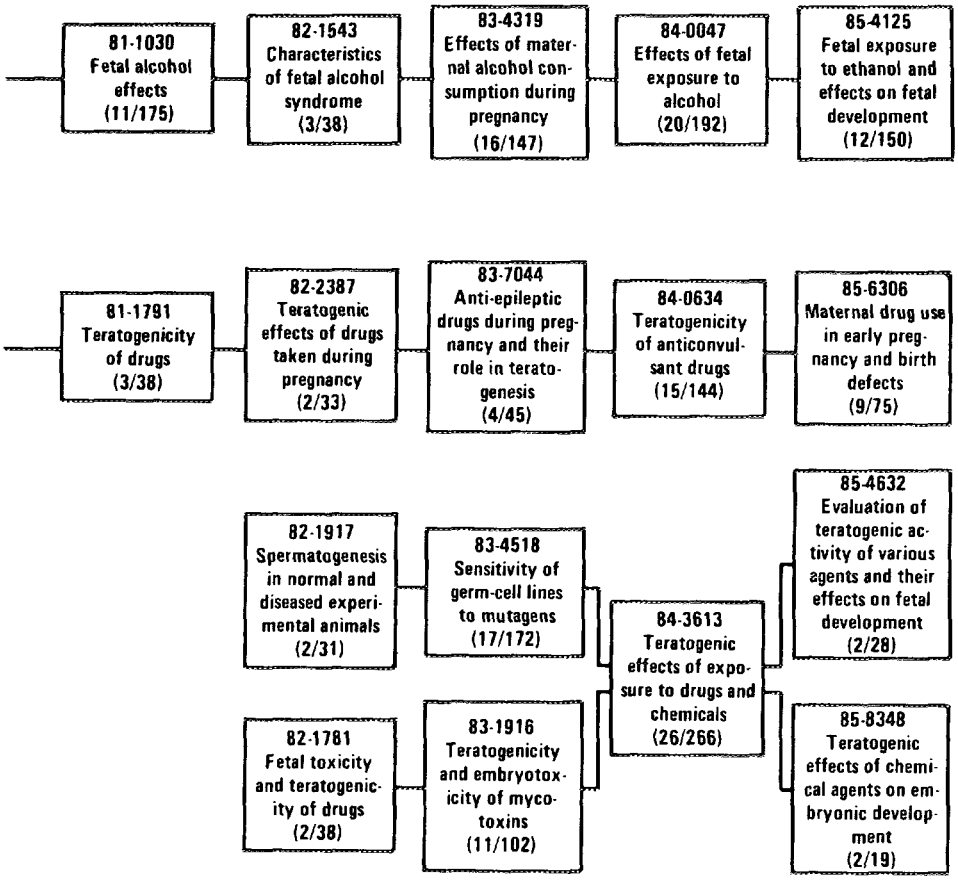
A third determinant in drug teratogenicity is the interaction resulting when more than one drug is taken at a time. This interplay may cause four possible effects ranging from antagonistic, to additive, to synergistic, to no effect at all. Klingberg and colleagues state that a fourth factor deals with genetic susceptibility. Not all fetuses exposed to a specific drug develop malformations. This implies that there is an inherent, or genetic, susceptibility to drugs.[12]

These four determinants have made it difficult to identify more than a few drugs as teratogenic. In addition, a major obstacle in identifying a teratogen is finding a suitable experimental animal. Robert L. Brent, Department of Pediatrics, Jefferson Medical College, Philadelphia, states that transferring animal teratologic data to the human situation is often unreliable for many reasons. One problem is that the structure and function of the placenta differ in animals and humans. Therefore a drug may affect an animal differently than humans.[13]

In a recent article in *Nature*, Heinz Nau, Institute for Toxicology and Embryopharmacology, Free University of Berlin, Federal Republic of Germany (FRG), and William J. Scott, Division of Basic Science Research, Children's Hospital Research Foundation, Cincinnati, Ohio, have found that the acidic property of drugs may also be an important determinant of teratogenicity. Nau and Scott tested 11 drugs that have been shown to be teratogenic. Eight of these are weak acids, whereas none is a weak base. The authors also studied the pH level inside the cells of mouse and rat embryos at various stages of gestation. Embryos are considerably more basic than their mothers, suggesting that the lower acidity of the embryo causes acids to accumulate there.[14]

Thalidomide

The drug thalidomide provides an example of the unreliability of transferring animal



results to humans. Synthesized by Chemie Grünenthal, Stolberg, FRG, thalidomide was first marketed in 1957 as a hypnotic causing a deep sleep with no hangover effects. Before Grünenthal put thalidomide on the market, Wilhelm Kunz, then head of chemical research at the firm, and colleagues produced a study in 1956 showing that increased doses of thalidomide depressed the central nervous system in animals but did not produce any toxic effects. The animals, although sleeping or sedated, could easily be roused. Kunz and his coworkers were unable to determine a minimum lethal dose.[15]

In 1959 D.M. Burley, Medical Registrar, Westminster Hospital, London, and colleagues confirmed that thalidomide was an effective hypnotic with few side effects, comparing well with a barbiturate as a means for inducing sleep in 83 hospital inpatients.[16]

The drug was subsequently sold in 46 countries, including the UK, Japan, Sweden, Australia, and Canada. Soon, however, it became apparent that some patients who used thalidomide regularly for six months or more developed a neurological disorder called peripheral neuropathy, which causes

numbness, cramps, and weakness in the limbs. It was also later discovered that some pregnant mothers who took the drug in the first trimester, the time when limb buds of the fetus are formed, produced children with distinctive deformities. These types of deformities are called phocomelia, derived from the Greek words *phokos*, meaning "seal," and *melos*, meaning "extremities." Some children with phocomelia are born without arms and have just flippers attached at the shoulders; others have no legs, just toes sprouting from the hips; some simply have no limbs at all.[17] (p. 88)

Evidence for the toxicity of thalidomide began to accumulate. In December 1961, Australian physician W.G. McBride wrote a letter to *Lancet* describing "the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide during pregnancy."[18] About a month later, in January 1962, W. Lenz, Pediatric Clinic, University of Hamburg, FRG, wrote of his own experiences with women who had taken thalidomide during pregnancy.[19] The drug was soon taken off the world market. (These letters have become classics; there are over 180 cites to McBride's letter and about 140 to Lenz's. In the near future I intend to examine the impact of letters in the scientific and medical literature.)

It had become obvious that animal testing needed to be reconsidered. Animal studies performed after thalidomide was removed from the market showed that thalidomide is very species specific. While G. Pliess, Pathological Institute, University of Hamburg,[20] and G.F. Somers, Distillers Company, Liverpool, UK,[21] failed to produce malformations with thalidomide in pregnant rats, pharmacologist Valdemar Larsen, Dumex Ltd., Copenhagen, Denmark, found that thalidomide given to selected strains of white rabbits between the 8th and 16th days of gestation caused typical limb malformations in the offspring.[22] Giorgio Bignami and colleagues, Department of Therapeutic Chemistry, Institute of Health, Rome, Italy, were finally able to prove that rats were sensitive to thalidomide after all, but only at the 12th day of gestation.[23]

Fortunately, thalidomide was never sold in the US, due to a combination of the strict US drug laws and the diligence of pharmacologist-physician Frances O. Kelsey, the medical officer at the Food and Drug Administration who was in charge of the thalidomide application. Kelsey received the Distinguished Federal Civilian Service Award in 1962 from President Kennedy for her efforts in preventing the marketing of thalidomide by the Richardson-Merrell pharmaceutical company.[17] (p. 81) Although Kelsey successfully kept the drug off the US market, thalidomide was distributed to over 1,000 US physicians under an "investigational program" by Richardson-Merrell.[24]

Controversy

Many people consider the thalidomide tragedy as inevitable because they believe that the drug was tested to the best standards of the time. This opinion is considered a popular fallacy by a team of journalists from the *Sunday Times of London*, led by Phillip Knightley. In *Suffer the Children: The Story of Thalidomide*, these reporters argue that "the knowledge and scientific procedures to give protection [from thalidomide] were available. The disaster might well have been averted everywhere."[17] (p. 4) Knightley and his coauthors claim that although the animal tests necessary to prove thalidomide teratogenic were not in general practice before the disaster, it was not unusual for drug reproductive studies to be performed in the days before thalidomide. The authors describe how the drug Daraprim, developed in 1950 as an antimalarial, underwent extensive reproductive studies in many animals before it was marketed. Yet in the studies

by Kunz and Burley, no mention was made as to the effects of thalidomide on the fetus.

In the 1972 book *Thalidomide and the Power of the Drug Companies*, Henning Sjöström, a Swedish attorney, and Robert Nilsson, a Swedish physician, argue that there was substantial literature available on the subject of the effect of drugs on the fetus prior to the development of thalidomide. They quote John B. Thiersch, Department of Pathology, University of Washington Medical School, Seattle, who stated, "in the ten years preceding the appearance of thalidomide, that is by 1959, not less than 25 compounds were shown by investigators ranging from Japan to the US, to England and France to affect the foetus *in utero*, either killing many foetuses or inducing malformations.... The findings by the various investigators were published in scientific journals and distributed internationally."[25]

Thiersch published a paper studying the effect of the drug aminopterin on the fetus.[26] Cited over 230 times since 1955, this paper was the subject of a 1984 *Citation Classic*® commentary published originally in *Current Contents*® and more recently in *Contemporary Classics in Clinical Medicine*.[27] Thiersch wrote, "I believe this publication is so highly cited because it opened up a new field—the effect of drugs on the fetus *in utero*."[27]

In an April 1968 letter in *New Scientist*, M.A. Phillips, a pharmacologist from Upminster, UK, also argued that before thalidomide was marketed, the knowledge was available that many drugs may cause fetal malformations if administered to pregnant women. Phillips cited many studies showing the adverse effects of drugs on the mammalian fetus published prior to 1958.[28]

G.E. Paget, of Smith, Kline and French, Hertsford, UK, criticized the argument presented by Phillips as misleading. Paget noted that one of the articles Phillips cited dealt with a diet deficiency study as opposed to a drug teratogenic study. Another article Phillips cited studied chick embryos and not the effects on the mammalian fetus. Paget contends that "the thalidomide tragedy did not occur because a known risk was ignored. It occurred because an unknown risk was not deduced."[29]

Literature Study

The scientific literature on thalidomide dates back to 1956, when Kunz and his coworkers first published on their newly synthesized compound in the journal *Arzneimittel-Forschung/Drug Research*.[15] By now, over 2,000 papers and books concerning thalidomide have been indexed since 1955. These include technical studies of the teratology and metabolism of thalidomide as well as editorial comment in medical journals.

A current area of thalidomide literature concerns its use in dermatological clinical investigations. Raymond L. Barnhill and A. Colin McDougall, Department of Dermatology, Slade Hospital, Oxford, UK, have found that thalidomide is effective in treating patients with lepromatous leprosy.[30] (See my earlier discussion of leprosy.[31]) Barnhill and McDougall's paper, published in the *Journal of the American Academy of Dermatology* in 1982, is one of two core papers in the research front entitled "Use of thalidomide therapy in leprosy" (#85-1803), which includes 14 citing papers published in 1985 alone.

Those who are not familiar with its history frequently believe that modern teratology had its inception as a consequence of the thalidomide tragedy. However, as we have indicated, there have been experimental teratology studies since the turn of the century. This is confirmed in a paper describing the organization of the Teratology Society by Wilson, mentioned earlier, and Josef Warkany, Department of Pediatrics, University of Cincinnati College of Medicine. The authors state that "it is incorrect to say that thalidomide was the impetus that gave tera-

Table 3: Selected list of associations engaged in research or providing information on teratology.

American College of Toxicology
9650 Rockville Pike
Bethesda, MD 20814

American Board of Obstetrics and Gynecology
4507 University Way, NE
Seattle, WA 98105

European Teratology Society
c/o Laboratory of Teratology
Karolinska Institute
S-104 01 Stockholm 60
Sweden

Japanese Teratology Society
Kinki University School of Medicine
Sayama-Cho, Osaka 589
Japan

Latin American Association of Environmental Mutagen, Carcinogen and Teratogen Societies
c/o International Association of Environmental Mutagen Societies
Institute of General Genetics
University of Oslo
P.O. Box 1031
Blindern, Oslo 3
Norway

Teratology Society
c/o Carol Kimmel
Reproductive Effects Assessment Group
US Environmental Protection Agency
RD-689
401 M Street, SW
Washington, DC 20460

tological science its beginning, but it is certainly equally incorrect to deny that thalidomide was a strong stimulus to both the experimental and clinical aspects of the field."[32]

Wilson and Warkany are two of the founders of the Teratology Society, organized in 1960. This association established the journal *Teratology* in 1968. Table 3 lists other organizations that engage in research or provide information on teratology.

Both Wilson and Warkany have had a significant impact on the field of teratology. Their 1965 book *Teratology: Principles and Techniques* is considered a cornerstone of teratology literature.[33] Cited in about 700 papers since its publication, chapters of this *Citation Classic* are core to two fronts from Table 1: "Evaluation of teratogenic activity of various agents and their effects on fetal development" (#85-4632) and "Teratogenic effects of chemical agents on embryonic development" (#85-8348). Both of these research fronts are included in Figure 2, a historiograph showing the development of the field of teratology from 1976 to 1985.

Conclusion

It is not possible to determine whether the thalidomide tragedy could have been avoided using the concepts and technologies available in the late 1950s. My purpose is not to report allegations of blame, but to focus on learning from experience. As Paget noted in 1968, "The important thing is to remind ourselves that there may be other unknown risks. We must be constantly vigilant in our efforts to deduce their existence and to detect them before they do harm."[29]

As a personal footnote to this study, I can well recall the complacent attitude of many organizations toward the literature problem. I was asked to testify on this by Senator Hubert Humphrey.[34] Whether literature searching would have prevented the tragedy is debatable. But in those days, it was often cavalierly assumed that we had little to learn from the literature. Sometimes in our rush to find new solutions, we forget that we have much to learn from the past.

* * * * *

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