

## The History of Organized Teratology in North America

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### FIRST HALF OF THE 20th CENTURY

The first half of this century saw several developments that proved to be of major significance in the later flowering of teratology as a true science. These early events, mainly in the areas of research, have been amply documented in the published literature by Warkany ('53), Russell ('50), Landauer ('41), Wilson ('73), and others, and aside from noting their historical importance, need no further description here. The emphasis instead will be on organized efforts to exchange ideas about research and to promote understanding within this emerging field by people engaged in it, through the medium of the conferences, symposia, and other scientific meetings that were held. Many will be surprised to learn that there were some ten such efforts between 1952 and the organization of the Teratology Society in 1960.

### TERATOLOGY MEETINGS PRIOR TO ORGANIZATION OF THE SOCIETY IN 1960

These early meetings are described only in sparse detail below; but if readers wish to know more about particular gatherings, they are invited to communicate with one or both of the present authors, who may be able to provide additional information.

In June, 1952, at New York, NY, a meeting designated by its organizers as the First Scientific Conference consisted of a small number of invited participants who discussed basic research on congenital malformations, birth injuries, and prematurity. The proceedings under the title "Prematurity, Congenital Malformations and Birth Injury," edited by L.E. Holt, T.H. Ingalls, and L.B. Hellman, were circulated mainly to the participants and consequently made little impact. The conference was sponsored by the Association for the Aid of Crippled Children.

On April 20-21, 1953, at Oak Ridge, TN, a symposium entitled "Effects of Radiation and Other Deleterious Agents on Embryonic Development" was organized by Dr. Alexander Hollaender and sponsored by The Biology Division, Oak Ridge National Laboratory.

Eleven scientists were asked to present comprehensive reviews of experimental studies in their own and related fields. Major emphasis was on the teratogenic effects of radiations, but other possible causative agents such as nutritional deficiency, drugs, and chemicals were also discussed. No record of attendance is available but it is estimated that approximately 50 scientists representing several research institutions and universities were present. The proceedings were published as Supplement 1 in *J. Cell. Comp. Physiol.* 43, 1954.

During April and May, 1954, at Cincinnati, OH, several informal talks about the best ways to promote activity in the reawakening science of teratology, particularly in its experimental aspects, were held by Drs. Josef Warkany and James G. Wilson at the University of Cincinnati College of Medicine. It was decided to send a questionnaire to 21 scientists in North America thought to share this objective. The following letter and questionnaire were mailed on May 10.

This letter is being sent to a number of persons known to be interested in the general subject of teratology. In talks with friends and acquaintances at scientific meetings, we find that increasing numbers of people are again concerning themselves with problems relating to the causation, mechanisms and manifestations of abnormal embryonic development. Teratology, although once a flourishing science in its own right, received only sporadic attention during the first half of this century. Research in the subject was carried on at the fringes of some of the well established branches of biology, but there was little direct communication between the scattered investigators. The recent revival of interest in both experimental and clinical aspects of the subject has increased the need for coopera-

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tion and interchange of ideas among teratologists. One way of meeting this need would be the organization of a society for the specific purpose of planning and conducting annual conferences of persons interested in the subject.

We are thinking of arranging for a small preparatory meeting to consider the organization of a society. On the accompanying sheet are a few questions which if answered and returned will give us an indication of how you feel about the matter. We welcome any suggestions or comments you may care to make.

The enclosed list includes the names of the persons to whom this letter is being sent. You will doubtless think of others who are interested in teratology and who might also wish to join a society of the sort proposed. It is felt, however, that the initial discussions and preparations might best be carried out by a relatively small group of individuals known to be directly concerned with the field. If you know of additional persons who you feel should be included in the preliminary discussions, please send us their names and addresses.

The following questions were asked:

1. Do you think the organization of a society of persons interested in teratology would serve to advance the subject?
2. Would you care to join and support such a society?
3. Would you be willing (aside from financial considerations) to attend a meeting to consider the organization of a society?

Eighteen of the 21 persons contacted returned the questionnaire and of the replies 14 answered all questions affirmatively and four were either undecided or were negative about a society and/or a meeting. Nine additional names were suggested. This favorable response encouraged the initiators to proceed with plans for a meeting which would include a modest scientific program but would also provide opportunity to discuss the possibility of organizing a society. The search for financial support was successful but a meet-

ing was not scheduled until January 12-13, 1956 (see below).

On June 15-16, 1954, at New York, NY, a Second Scientific Conference was attended by 43 invited participants (ten from Europe) of which 13 presented papers of variable length and previous preparation. Only one paper, by Dr. Theodore H. Ingalls, entitled "Epidemiology of Congenital Malformations," dealt with teratological subjects. The remainder concerned obstetrics, placental transport, and fetal physiology. The proceedings, under the title "Mechanisms of Congenital Malformations" (ed. H. Wolff), published by the Association for the Aid of Crippled Children, 1955, were obviously misnamed since little was said about malformations and less about mechanisms. The Association for the Aid of Crippled Children sponsored the conference, which was organized by Dr. S.R.M. Reynolds.

On January 12-13, 1956, at Cincinnati, OH, a Teratologic Conference, which was a direct consequence of the 1954 questionnaire (see above), was held. The newly established Human Embryology and Development Study Section of the National Institutes of Health together with the Association for the Aid of Crippled Children provided funds sufficient to pay the travel expenses of approximately 50 scientists from a number of medical disciplines, including 15 members from the Study Section. The scientific program, organized and chaired by Dr. Warkany, consisted of 11 papers on various aspects of experimental and clinical teratology and most of these were later published as a supplement in *Pediatrics* 19, Part II, pp. 725-792, 1957. During a general discussion period which followed the consensus was reached that future teratologic meetings of this type should be held at 1- or 2-year intervals. A majority of those in attendance, however, felt that the time had not arrived to attempt to organize a society with a commitment to hold annual meetings.

On August 2-4, 1956, at Bar Harbor, ME, a loosely organized conference on the subject of "Environmental Influences on Prenatal Development" was held. No formal papers were presented but several of the 20 invited participants had been alerted to lead discussions on various teratological and embryological subjects. The conference was sponsored by the National Academy of Sciences, National Research Council and was held under the general chairmanship of Dr. Paul Weiss. Dr. Beatrice Mintz edited the proceedings, which were published by University of

Chicago Press in book form in 1958 under the same title as the conference.

On April 15–16, 1957, at Bethesda, MD, a Second Teratology Conference was held at the National Institutes of Health, and like its lineal predecessor in Cincinnati, was supported by the Human Embryology and Development Study Section of National Institutes of Health (NIH) and by the Association for the Aid of Crippled Children. Of the 78 persons who registered, 16 were NIH personnel or were from other nearby governmental agencies. The program consisted of twelve 30-minute papers dealing mainly with experimental and epidemiologic aspects of teratology. The organizational committee was James G. Wilson (chairman), Bradley M. Patten, and Josef Warkany. Six of the papers were published as a special supplement to *Pediatrics* 23, Part II, 1959.

On March 30–31, 1959, at Portland, OR, a Third Teratology Conference was held, sponsored by the University of Oregon Medical School and organized by Dr. David L. Gunberg. A program of fifteen 30-minute papers was devoted largely to mammalian experimental teratology. (The present writers have no record of the number of scientists in attendance but estimate that there were about 50.) The proceedings were not published.

On April 5, 1959, at Palm Beach, FL, the National Foundation Conference on Congenital Malformations publicly marked the Foundation's transition from support of research and medical care, largely in the area of poliomyelitis, to similar activities in other areas, including teratology. In attendance were mainly members of the Scientific Advisory Board and the staff of the National Foundation, since the meeting was intended to acquaint these people with current knowledge and activities in teratology. Dr. Thomas M. Rivers organized a program of five 1-hour position papers as follows: "Congenital Malformations in the Past" by Dr. Josef Warkany, "Causes of Malformations" by Dr. F. Clarke Fraser, "Experimental Studies on Congenital Malformations" by Dr. James G. Wilson, "Surgical Treatment of Birth Defects of the Nervous System" by Dr. Donald D. Matson, and "The Problem of Congenital Malformations" by Dr. Rustin McIntosh. The proceedings were published in *J. Chronic Diseases* 10, 1959.

Of equal or possibly greater importance for the future of teratology was the incidental fact that on the evening following the above scientific program, Drs. Fraser, Warkany,

and Wilson went for a long walk on the beach. Conversation naturally centered around recent advances and future prospects in teratology. The suggestion was made by someone that the time had probably come to organize a society to promote and coordinate research within the field through the medium of annual meetings. The others agreed and to expedite matters the three conversants assumed the role of an organizational committee with the immediate objective of holding a meeting to organize a society within 1 year. Dr. Fraser was asked to serve as chairman to make arrangements for a Fourth Teratology Conference.

On April 9–10, 1960, at New York, NY, a Fourth Teratology Conference was held at Memorial-Sloan-Kettering Auditorium in New York City at the invitation of Dr. Lois Murphy. A program, organized by Dr. Wilson and consisting of 17 scientific papers on experimental and clinical teratology, was presented during the first day and a half, but the main focus of attention was the business session scheduled for the second afternoon. Ninety-three persons from the United States, Canada, England, France, and Germany were invited to the conference and 62 of these chose to attend the business session and thereby to become charter members of the society.

The business meeting was declared in session for the purpose of organizing the proposed society, with Dr. Wilson serving as chairman. In due course a name, The Teratology Society, was chosen, a constitution was adopted, and the following officers were elected by acclamation: President, Josef Warkany; President-Elect, James G. Wilson; Secretary-Treasurer, Marjorie M. Nelson; Recorder, Sidney Q. Cohan; Council Members: M. Lois Murphy, David Gunberg, and F. Clarke Fraser. It was decided to attempt to hold annual scientific meetings beginning in 1961.

This Fourth Teratology Conference, which became the Organizational Meeting of the Society, was supported by the Association for the Aid of Crippled Children and the Human Embryology and Development Study Section of the National Institutes of Health, as were several of the earlier conferences. The newly formed Teratology Society made as its first official act a unanimous vote of gratitude to these and many other agencies which had lent their facilities, personnel, and other resources to insuring the success of the various prior meetings which had culminated in formation of the Teratology Society.

Acknowledgment is made to Mr. Aaron T. Grad, Esquire, for his expert assistance in effecting the incorporation of the society in 1961 in the state of Ohio, and in obtaining tax exempt status from the U.S. Treasury Department. Gratitude is also due to Mr. Stephen V. Ryan, Vice President and General Counsel of the National Foundation, for preparing the initial version of the constitution.

SUMMARY OF THE EARLY MEETINGS OF THE  
TERATOLOGY SOCIETY—PRIOR TO PUBLICATION  
OF THE JOURNAL *TERATOLOGY*

The lack of an appropriate journal from 1961 until 1968 for the publication of programs and abstracts of the annual meetings made it necessary that these items be privately printed, usually at the home institution of the current president. This meant that distribution was largely limited to the membership of the society, since no existing journal had agreed to publish them. The programs and abstracts did not find their way into libraries or other permanent repositories and consequently are not now readily available.

In the interest of preserving at least some of the facts relating to the first seven meetings of the Teratology Society, summaries including the time, place, incumbent officers, and brief comments about the program are given here.

The First Annual Meeting took place on May 26–27, 1961, at the Children's Hospital Research Foundation in Cincinnati at the invitation of the President, Josef Warkany. This meeting had been preceded in February by announcements in several scientific journals, both in this country and abroad, telling of the formation of the society and requesting titles and abstracts of papers. Early in March the president became understandably uneasy when only a few responses had arrived, but by the end of the month enough abstracts had come in to make a respectably full program. On the evening before the first day of scientific sessions the officers which had been elected a year earlier assembled for a council meeting to discuss and act upon the policies and problems of the society, thereby initiating a long-standing tradition. This meeting was supported by grants from the National Science Foundation, The Association for the Aid of Crippled Children, and The National Foundation.

Because of its landmark importance the 2-day program is reprinted here *verbatim* and needs no further comment.

It is worthy of mention here that almost concurrent with the first meeting of the Teratology Society the officers were in touch with the founders of the Anomalies Research Association of Japan, which was established in 1961 and has maintained communications with the Teratology Society from that date onward.

The Second Annual Meeting was held on March 16–17, 1962, at the College of Medicine of the University of Florida in Gainesville, at the invitation of the President, James G. Wilson. The program consisted of four half-day sessions at which a total of 19 papers were presented from the platform, including two special sessions, with seven papers read by title.

The first special session, titled "Some Aspects of Developmental Genetics," a program organized and chaired by Edgar Zwilling, consisted of three 30-minute papers by Max Hamburger, Edgar Zwilling and John W. Saunders. A second special session, organized and chaired by F. Clarke Fraser under the title "Chromosomes and Congenital Malformations," was an updating and further exploration of the subject introduced under the same title at the First Annual Meeting in Cincinnati. The speakers were Josef Warkany, David L. Carr, Klaus Patau, and Kurt Hirschhorn, whose informal discussions constituted a workshop which was sponsored by the Human Embryology and Development Study Section of NIH.

Aside from the special sessions the subject matter of presented papers was varied, with several on such topics as the teratogenic potential of various antimetabolites, of antibiotics, of malnutrition, and of trypan blue. Facial clefts were considered from a number of points of view. At least four papers in addition to those in the special session on chromosomes dealt with human teratology. It is interesting to note that no participants were yet ready to talk about thalidomide, although the causal association between this drug and birth defects was known and the impact of this new human teratogen was beginning to be discussed.

In addition to the president, other officers serving at this meeting were President-Elect F. Clarke Fraser; Secretary-Treasurer Marjorie M. Nelson; and council members David L. Gunberg, Meredith N. Runner, and David A. Karnofsky. At the annual banquet Dr. Warkany spoke on "Congenital Malformations Through the Ages." In 1961–1962 there were 121 members of the society and 17 new

## PROGRAM

THE TERATOLOGY SOCIETY  
FIRST ANNUAL MEETING  
Children's Hospital Research Foundation Auditorium  
Clinic Building, Elland Avenue, Cincinnati 29, Ohio  
May 26 - 27, 1961

Auditorium

(Members Only) 4:00 P.M.

## BUSINESS MEETING

President  
President-Elect  
Secretary-Treasurer  
Recorder  
Council Members

Dr. Josef Warkany  
Dr. James G. Wilson  
Dr. Marjorie M. Nelson  
Dr. Sidney Q. Cohlman  
Dr. M. Lois Murphy  
Dr. David Gunberg  
Dr. F. Clarke Fraser

REGISTRATION: 8:30 - 9:30 A.M. Auditorium  
MORNING SESSION: May 26 9:30 A.M. - 12:20 P.M. Auditorium

*Presidential Address:* Josef Warkany  
Children's Hospital Research Foundation  
Cincinnati, Ohio

1. The production of congenital malformations using tissue antibodies — Robert L. Brent and Elaine Averich, Department of Pediatrics, Jefferson Medical College, Philadelphia.
2. The effects of physiological purines on the development of the chick embryo — David A. Karnofsky and Cortinne R. Lacon, Memorial Sloan-Kettering Cancer Center, New York City.
3. Some aspects of protein and amino acid metabolism in the chick embryo — Norman W. Klein and Heinz Herrmann, Department of Zoology, University of Connecticut, Storrs.

## INTERMISSION 10:40 A.M.

4. Distribution of flavin nucleotides in rat embryos and fetuses from normal and riboflavin-deficient mothers — Zelma Miller, Inna Poncet and Eva Takacs, (introduced by Harold Kalter) Christ Hospital Institute of Medical Research and Children's Hospital Research Foundation, Cincinnati.
5. The effect of trypan blue on oxygen uptake of the rat yolk sac in vitro — David L. Gunberg and Frederick D. Wade, Department of Anatomy, University of Oregon Medical School, Portland.
6. Changes during teratogenic action of tolbutamide in fish—Morris Smithberg and Padmakar Dixit, Department of Anatomy, University of Minnesota, Minneapolis.
7. Teratogenic effects of 5-fluorodeoxyuridine and fluorodeoxycytidine in inbred strains of mice — M. Lois Murphy, Charles P. Dagg and Charles C. Runner, Memorial Sloan-Kettering Cancer Center, New York City, and Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

LUNCH 12:20 P.M.

MORNING SESSION: May 27 9:00 A.M. — 12:30 P.M. Auditorium

SYMPOSIUM: *Chromosomes and Congenital Malformations*

Moderator: F. Clarke Fraser,  
Department of Genetics, McGill University, Montreal.

Participants:

Murray L. Barr, Department of Microscopic Anatomy,  
University of Western Ontario, London, Ontario.  
Curt Hirschhorn, Department of Medicine, New York  
University Medical School, New York City.  
Klaus Patau, Department of Medical Genetics,  
University of Wisconsin, Madison.  
Arthur Robinson, Departments of Biophysics and  
Pediatrics, University of Colorado, Denver.  
Liane B. Russell, Biology Division, Oak Ridge  
National Laboratory, Oak Ridge, Tennessee.

LUNCH 12:30 P.M.

AFTERNOON SESSION: May 27 1:40 — 3:20 P.M. Auditorium

16. Teratogenic effects of x-irradiation as compared to other agents —  
Meredith N. Runner and Karl-Heinz Degenhardt, National Science Founda-  
tion, Washington, D.C. and Roscoe B. Jackson Memorial Laboratory,  
Bar Harbor, Maine.
17. The production of congenital malformations in guinea pigs by adrenal-  
ectomy — Richard M. Hoar, Department of Anatomy, University of Cin-  
cinnati, Cincinnati.
18. Histochemical changes associated with teratogenesis in the rat embryo  
— E. Marshall Johnson, Department of Anatomy, College of Medicine,  
University of Florida, Gainesville.
19. Effect of feeding N, N'Diphenyl-p-phenylene diamine (DPPD) and N,  
Propyl gallate (NPG) on teratogeny in vitamin E deficient rats —  
Dorothy Wei Cheng, S. Subbammal and David M. McCoy, Department of  
Anatomy, State University of Iowa, College of Medicine, Iowa City.
20. The teratogenic action of SK 21,778 on the rat fetus — Shakuntala  
Chaube and M. Lois Murphy, Memorial Sloan-Kettering Cancer Center,  
New York City.
21. Uterine vascular clamping in the rat: days 6 — 14 — John B. Franklin,  
Robert L. Brent and Elaine Averich, Department of Pediatrics, Jeffer-  
son Medical College, Philadelphia.

INTERMISSION 3:40 P.M.

AFTERNOON SESSION May 26 1:40 — 4:40 P.M. Auditorium

8. Hydrocephalus and other abnormalities in rat young resulting from ma-  
ternal pteroylglutamic acid deficiency from the 8th to 10th days of  
pregnancy — Ian W. Monie, Rosa M. Armstrong and Marjorie M. Nelson,  
Department of Anatomy, University of California Medical Center, San  
Francisco.
9. Vernicomelia; its bearing on theories of genesis of the Arnold-Chiari  
complex — Benjamin H. Landing, Edmund B. Jacobs and William  
Thomas, Department of Pathology and Pediatrics, Children's Hospital,  
Children's Hospital Research Foundation and University of Cincinnati,  
College of Medicine, Cincinnati.
10. Effects of two cleft palate - producing teratogens on palate morpho-  
genesis — Bruce E. Walker, Department of Anatomy, University of Ge-  
Texas Medical Branch, Galveston.
11. Role of the tongue in producing cleft of the secondary palate in mice  
with spontaneous cleft lip — Daphne G. Trasler, Department of Ge-  
netics, McGill University, Montreal.

INTERMISSION 3:00 P.M.

12. The effect of adenosine triphosphate on the teratogenic action of cor-  
tisonic acid in mice — Harry W. Gordon, Walter Tkaczyk, Lyndon A. Peer  
and William Bernhard, Research Department, St. Barnabas Medical  
Center, Newark, New Jersey.
13. Teratogenic effects of a two-hour inactivation of nicotinamide activity  
in the mouse — Marc Goldstein, Merrille F. Pinsky and F. Clarke  
Fraser, Department of Genetics, McGill University, Montreal.
14. Localized epiphyseal dysplasia in offspring of manganese-deficient  
rats — Lucille S. Hurlley, C. Willet Asling, and Eloise Wooten, Depart-  
ment of Home Economics and Anatomy, University of California, Davis  
and Berkeley.
15. Furfurylthiocarbamide non-tasting among congenital athyrotic cretins:  
further studies in an attempt to explain the increased incidence —  
Thomas H. Shepard, II, Department of Pediatrics, University of Wash-  
ington, Seattle.

**BANQUET** Netherland-Hilton Hotel Restaurant Continental 7:00 p.m.  
*Guest Speaker:* Dr. Gustav Eckstein, Professor of Physiology  
University of Cincinnati Medical College  
*Author of "Noguchi," "Canary," "Everyday  
Miracle," et cetera*

"1 to 1,000,000,000,000"

members were elected at the business meeting.

The Third Annual Meeting was held May 31–June 1, 1963, at the Chantecler Lodge in Ste. Adele, Quebec, at the invitation of the President, F. Clarke Fraser. Twenty-three papers were presented from the platform and five read by title. A symposium entitled "Thalidomide and the Embryo" consisted of five 30-minute papers by F. Degenhardt, R.E. Staples et al., J.D. McColl, and H.M. Wuest. The society thereby recognized the fact that this drug had introduced a large and very troublesome new facet into the subject of teratogenic causation in man.

Invited lectures were given by D. Bennett and L.C. Dunn on "Developmental Genetics and Population Effects of a Chromosome Locus in the Mouse." Teratogenic interactions, infections, antibiotics, and a variety of other chemical agents were given etiologic consideration by speakers in other sessions. Facial clefts and chromosomes continued to be popular subjects.

In addition to the president, other officers serving at this meeting were Secretary-Treasurer Charles P. Dagg and council members Meredith N. Runner, David A. Karnofsky, and Bruce E. Walker. Marjorie M. Nelson, who had been made president-elect at the last meeting, was unable to attend because of severe illness and the society suffered great loss at her death prior to her installation as president. The council elected Dr. David A. Karnofsky to the presidency.

The Fourth Annual Meeting consisted of two consecutive meetings, the first on June 9–11, 1964, at Arden House, Harriman, NY, and the second on June 12 at Sloan-Kettering Institute for Cancer Research in New York City, both at the invitation of the President, David A. Karnofsky. The program at Arden House began with an evening symposium organized and moderated by Dr. Gilbert W. Mellin under the general title "Epidemiology of Human Teratology," with papers presented by Josef Warkany, Gilbert W. Mellin, John Futig, and Robert Miller. The following day a symposium that was organized and chaired by Dr. Paul Weiss, entitled "Cellular Basis of development," and also held at Arden House, consisted of 45-minute papers by Paul Weiss, A. Glucksmann, and Alfred J. Coulombre. A third symposium on "Examination of Agents Capable of Producing Teratogenic Activity," organized and moderated by Dr. Lois M. Murphy, was held at Sloan-Kettering Institute and consisted of four 30-

minute papers by J.B. Thiersch; C.P. Dagg and Lois Murphy; M.M. Grumbach; and Charles H. Barron.

The growth of the society was evident in the increased numbers of papers presented, 42 from the platform and seven read by title, and expansion of teratology as a discipline was manifested in the great diversity of subjects discussed. The principal speaker at the banquet was Dr. Robert A. Aldrich, director of the National Institute of Child Health and Human Development. In addition to the president the officers were President-Elect Ian W. Monie; Recorder Sidney Q. Cohlman, Secretary-Treasurer Charles P. Dagg; and the council, Kurt Benirschke, C. Willet Asling, and Bruce Walker. The society now had 161 members.

The Fifth Annual Meeting was held May 26–28, 1965, at the Jack Tar Hotel, San Francisco, CA, at the invitation of the President, Ian W. Monie. The opening session was devoted to a symposium organized and moderated by Earnest W. Page entitled "Membrane Transport," with 40-minute papers presented by Ernest W. Page, Harry Prysztowsky, and Irwin A. Schafer. Two other symposia were organized and chaired by John L. Sever on "Viruses and Congenital Malformations," with John Sever, Gilbert M. Schiff, and Gordon C. Brown as speakers; and another organized and chaired by Robert W. Miller on "Overlap of Teratogenesis and Oncogenesis," with Robert Miller, Joseph A. DiPaolo, and Eugene V. Perrin as speakers. The regular sessions were again diverse in subject matter but nutritional and immunological aspects of teratology and the pathogenesis of craniofacial defects were well represented.

The speaker at the banquet was Dr. Curt Stern, whose subject was "Mendel and Human Genetics." Including symposia, 49 papers were presented from the platform and five were read by title. Other than the president, officers were President-Elect Sidney Q. Cohlman; Recorder Daphne G. Trasler; and the council, Kurt Benirschke, C. Willet Asling, and John B. Thiersch.

The Sixth Annual Meeting was held May 25–27, 1966, at the Robert Driscoll Hotel, Corpus Christi, TX, at the invitation of President Sidney Q. Cohlman. The first session was opened with a symposium organized and moderated by Dr. Thomas Shepard entitled "Possible Mechanisms of Teratogenesis in Riboflavin-Deficient, Galactoflavin-Treated Rats," with papers by Josef Warkany, Ron-

ald Lemire, Thomas Shepard, and Bruce Mackler. An evening symposium was scheduled at the end of the first day on the subject, "The Primate in Experimental Teratology," organized by Dr. Leon Schmidt, but the names of the participants and their subjects were not printed in the program. In addition to such standard subjects as the embryogenesis of cardiac malformations and the teratogenesis of trypan blue, the program included papers on such relatively new subjects as teratogenicity of pesticides and enzyme inhibitors and gene-trace-element interactions.

The banquet speaker was Dr. Bernard B. Brodie, Laboratory of Chemical Pharmacology, National Heart Institute. Certainly a well-remembered occurrence during this meeting was the visit to King Ranch, where after a sizable chuckwagon lunch a lecture on the breeding and genetic problems of range cattle was presented to a group of overfed teratologists in the blazing Texas sun.

Other than the president the officers were President-Elect Meredith N. Runner; Recorder Daphne G. Trasler; Secretary-Treasurer Charles P. Dagg; and the council, Harold Kalter, C. Willet Asling, and John B. Thiersch. The society now had 185 members.

The Seventh Annual Meeting was held May 24-27, 1967, at The Estes Park Chalet, Estes Park, CO, at the invitation of President Meredith N. Runner. The opening session was devoted to lectures by two invited speakers: Dr. Casimer Grabowski, whose subject was "The Fluid Problems of Embryos and Their Relationships to Morphogenesis," and Dr. Ujihiro Murakami, whose subject was "The Immediate Effects of X-Irradiation with Relation to Abnormal Morphogenesis." After a chuckwagon lunch the membership was taken on an afternoon-long tour of the adjacent national forest. Two other invited speakers later in the program were Professor Antoine Giroud, whose subject was "Teratology as an Embryological Tool," and Dr. James R. Gillette, who spoke on "Acylation as a Possible Mechanism of Thalidomide-Produced Teratogenesis." Otherwise the program was made up of 44 contributed papers covering a broad range of subjects from epidemiology to teratogenesis in *in vitro* cultures. Fifteen papers were presented by title.

The officers other than the president were President-Elect Robert L. Brent; Secretary-Treasurer Charles P. Dagg; Recorder Daphne G. Trasler; and the council, Thomas H. She-

pard, Harold Kalter, and David L. Gunberg. The society now consisted of 199 members.

The programs and abstracts of subsequent annual meetings, beginning with the eighth at Buck Hills Falls in 1968, are printed in *Teratology* from volume 1 onward, as are the names and addresses of the members.

#### ORGANIZATION OF THE JOURNAL *TERATOLOGY*

At the business meeting of the 1966 meeting at Corpus Christi the society discussed and voted to explore the matter of sponsorship by the Society of a journal for the purpose of providing compatible and understanding editorial treatment and publication of research and review manuscripts and abstracts in the field of teratology. Toward this end President-Elect Runner appointed an ad hoc committee consisting of Drs. Sidney Q. Cohan, Lucille S. Hurley, and James G. Wilson, chairman, to investigate the feasibility of a journal. The committee was instructed to be prepared to report on pertinent matters relating to the publication of a journal at the annual meeting in 1967.

At the business meeting of the 1967 meeting at Estes Park, CO, President Runner asked the chairman of the journal committee to make its report, from which the following points have been excerpted.

1. The rate of publication in teratology and related fields, measured by annual number of titles published in national and international periodicals, was noted to have increased steadily in the several years preceding.
2. The increase in published titles, notwithstanding, several investigators with whom committee members had talked had experienced or knew others who had experienced having been dealt with in a less-than-satisfactory manner by editorial boards of journals to which manuscripts had been submitted.
3. The committee proceeded to make inquiries about the ways and means used by other scientific societies which were known to sponsor, own, or otherwise publish journals. After considering a number of publishers the committee concluded that the proposal submitted by the Wistar Institute most nearly fitted the needs and expectations of the Teratology Society and, therefore, recommended that the society enter into an agreement with that publisher.
4. The membership voted by a large major-

ity to sponsor the publication of a journal and to accept the committee's recommendation to adopt the proposal of the Wistar Institute as the basis for an agreement.

5. The council of the society concurred with this recommendation and proceeded to make necessary decisions, based on a consensus derived from the discussions of the membership at the business meeting, the detailed recommendations of the journal committee, and discussions with representatives of the Wistar Institute, as follows:
  - a. The name of the journal to be *Teratology: Journal of Abnormal Development*.
  - b. An interim editor to be Dr. Harold Kalter, and an interim editorial board to consist of Drs. Sidney Q. Cohan, F. Clarke Fraser, Lucille S. Hurley, David A. Karnofsky, Robert W. Miller, Meredith N. Runner, Josef Warkany, and James G. Wilson.
  - c. Journal subscription to be a condition of membership in the society.
6. After the first year of publication and appropriate revision of the constitution of the society, the new journal *Teratology* was provided with a permanent editorial staff and was judged to be well on its way to a long and successful career of service to the society. Dr. Harold Kalter was installed as editor-in-chief, a post which he held for 10 years, after which he was succeeded by Dr. Robert L. Brent.

#### THE RISE OF APPLIED AND REGULATORY ASPECTS OF TERATOLOGY

Prior to 1960 teratological studies, much less tests designed to evaluate safety, were rarely undertaken outside of the experimental laboratory. Only occasionally was it acknowledged that the animal studies conducted since 1940 in a few universities and research institutes in North America, Western Europe, and Japan might have some relevance to human congenital diseases. No governmental agency had established guidelines for using animal studies to evaluate human teratological risks from drugs, environmental chemicals, or radiations, and only the relatively crude multigeneration studies were proposed to estimate effects on overall reproduction. Laboratory animal facilities in industry were used for general toxicologic studies in connection with product safety evaluation but this very rarely included detailed examination of the offspring after ex-

posure of pregnant animals. The multigeneration breeding tests that were done did little more than record the number and reproductive capacity of the surviving offspring.

It has been said that industry did not do more meaningful animal tests because such were not required by governmental regulatory agencies. A more accurate statement would be that before 1960 the concept of searching for embryotoxic/fetotoxic effects after in utero exposure and the application of any adverse findings to estimating human teratological risk simply had not evolved. In any event, why should industry or governmental agencies have been overly concerned about congenital disease when the prevailing opinions in medicine and biology generally were that defects present at birth were most likely the expression of a defective genome. The developmental abnormalities that had been associated with radiation earlier in this century and with vitamin deficiencies and rubella during the 1940s could be regarded as exceptions to the general rule that the genes determined all aspects of intrauterine development.

Then in 1960 the far-reaching consequences of thalidomide exposure during early human pregnancy began to unfold! It is frequently said by people not familiar with the history of the science that teratology had its inception in the wake of the thalidomide incident. That this is not the case, however, has been demonstrated in reviews of literature published before and after the event. There was a steady increase in the annual number of experimental studies published beginning in the early 1940s and continuing through the 1950s and early 1960s. The numbers of papers dealing with clinical aspects did show a dramatic increase after 1961, when the thalidomide-birth-defect association was established, but these were mainly retrospective case reports in which questions were raised as to whether this or that drug taken by a pregnant woman was causally related to the birth of a defective infant. Positive causal associations were, and still are, postulated with disproportionate frequency when the malformations include limb reduction defects, whether or not they resemble those seen in the thalidomide incident.

Experimental studies continued to increase at about the previously observed rate until 1963-1965, when the numbers of abstracts at scientific meetings and journal pa-

pers dealing with teratological subjects began to show appreciable increases above previous rates. Thus, it is incorrect to say that thalidomide was the impetus that gave teratological 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. Unquestionably, however, thalidomide was the stimulus that gave rise to previously undeveloped aspects of teratological science—namely: *the safety evaluation and regulatory aspects*.

Not surprisingly even in 1963, after the thalidomide incident but before there had been time for considered action, teratogenicity testing procedures remained crude (Peck, '63). For example, the test material continued to be given mainly in the diet, rather than by the route of human therapy, and to be given continuously throughout much or all of pregnancy, rather than directed at the period of highest embryonic susceptibility. Perhaps of greater detriment to precise teratological evaluation at term was the practice of allowing pregnancies to go to natural delivery, thus precluding accurate observations on numbers of malformed and prenatally and perinatally dead offspring by permitting their destruction by the mother. These and other limitations of the methods employed in animal testing began to be pointed out in research papers of the time (Brent, '64; Cahen, '64), but since these publications lacked any regulatory status, the proposals were not widely adopted until later.

#### *Establishment of official guidelines*

One of the first positive actions toward the setting up of standardized procedures for the testing of drugs for teratogenic potential was taken by the Pharmaceutical Manufacturers Association when in August 1962 it founded and provided financial support for the Commission on Drug Safety. Although the commission did not devote all or even a major share of its effort to the inadequacy of animal tests for teratogenesis, certainly some of its more tangible and long-lasting accomplishments concerned this subject area. One of the first actions of the commission was to establish a subcommittee on teratology, headed by Dr. Josef Warkany, which quickly noted that there was "... urgent need for better animal tests to determine teratogenic effects..." and that "... the present FDA litter test is criticized since it is felt that this test can keep valuable and, in the human, teratogen-

ically innocuous compounds off the market while permitting teratogens to reach the public" (Report of the Commission on Drug Safety, '64). It was also noted that "... minimal standards for animal experimentation cannot be established at the present time" and that "... such inadequate procedures, if officially recommended, could result in a false sense of security."

In view of the recognized inadequacy of then current test procedures, together with the need for careful evaluation of all available information relating to teratogenic induction in laboratory animals before attempting to set up new standards, the commission made the following important recommendation:

Immediate establishment of workshops in which teratologists, pharmacologists, pediatricians, and obstetricians can exchange information is essential. Such workshops will help bridge the gap created by the limited number of teratologists, and these programs will be particularly useful in acquainting pharmacologists, toxicologists, pharmaceutical scientists and others with methods used in experimental work.

This recommendation was promptly implemented by a grant from the Pharmaceutical Manufacturers Association, and Dr. James Wilson was invited to organize a workshop in teratology at the University of Florida College of Medicine in February, 1964. A faculty of 11 recognized teratologists presented a week-long program of lectures and laboratory demonstrations for 41 participants and 18 observers selected from appropriate areas of related interest in pharmaceutical industry, government regulatory agencies, and university medical sciences. The proceedings were published in book form as *Teratology: Principles and Techniques*, edited by J.G. Wilson and J. Warkany, University of Chicago Press, 1965, which was widely distributed as the first comprehensive reference work in the field. Following a similar plan of organization, additional workshops were later held at the University of California, the University of Colorado, and Jefferson Medical College in this country, at the Danish Royal Veterinary College in Copenhagen, and the University of Kyoto, Japan. There is no doubt but that these workshops achieved much of the benefit envisioned by the Com-

mission of Drug Safety in that they disseminated teratological concepts and technology far beyond the relatively few research laboratories where such information had been generated. It is also likely that they contributed the foundation upon which were based the official guidelines later issued by regulatory agencies in various countries.

The United States Food and Drug Administration (FDA) was well represented at the first workshop. At about the same period (1963–1965) the FDA itself conducted a number of small informal conferences with teratologists who had done research on the effects of drugs on mammalian pregnancy, for the purpose of discussing the design of animal tests to evaluate the teratogenic potential of new drugs. These activities culminated in the issuance in January 1966 of the *Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use*, more familiarly known among teratologists as the "FDA Guidelines of 1966." The procedures proposed were soon accepted by many scientists and regulatory officials alike as being both practical and generally sound for the purpose of conducting meaningful tests on the teratogenicity of new drugs prior to human use. With modifications these guidelines have been adapted to the needs of regulatory agencies throughout the free world. Only recently have new regulations and additional concepts in testing made it necessary to introduce modest extensions and changes (Collins, '78), but still the FDA Guidelines of 1966 remain as the prototype for teratological testing procedures.

#### CONCLUDING REMARKS

Experimental studies in mammalian teratology had a faltering beginning in the 1920s, developed modest refinements and control in the 1930s, gained momentum in the 1940s, and grew into a solid field of scientific inquiry during the 1950s. These developments, however, were confined to academic and research laboratories and made little impact on the agencies in medicine, government, and industry which oversaw public health and safety. Then whose is the blame for not having anticipated the risks posed by such drugs as thalidomide prior to 1960, and for not having taken appropriate action to avert these dangers?

Is it reasonable to blame the "ivory-tower" scientists for not more aggressively pronouncing warning that trouble lay ahead, in view of what had been observed about the

vulnerability of mammalian embryos to extraneous chemical and physical agents? Is it appropriate to have expected the policy setters and regulation makers in government to have foreseen or understood that the human embryo may have unpredictable vulnerabilities to certain environmental factors, and that sophisticated tests would be needed even to estimate the risk? Is it fair to ask why manufacturers did not devise special tests to reveal unknown toxic potential in their products before they were marketed, when even today animal tests are known to be inadequate to evaluate all types and degrees of risk? All of these questions must be answered in the negative. Neither the concepts nor the technology used in earlier animal testing had evolved before 1960 to a point where they could have been intelligently applied to the estimation of human teratic risk. Even if appropriate animal tests had been run and the results been available, it is questionable whether they could have been applied in such a manner as to have avoided the thalidomide or a similar occurrence. A catastrophe of considerable magnitude may sometimes be required to bring human attention and efforts effectively to focus on what in retrospect may appear to have been an obvious danger.

Thus we believe that the groups alluded to above cannot rightly be accused of negligence for not earlier undertaking comprehensive tests, when it is considered that the concepts of meaningful teratogenicity testing only began to emerge after 1962 and that standardized guidelines for doing tests that met both scientific and regulatory constraints were available only in 1966. In fact, had it not been for the shocking realization that a presumably innocuous drug taken during pregnancy could cripple several thousand children, it is probable that research scientists, regulatory officials, and drug and chemical manufacturers would have further delayed reaching consensus on what had to be done. To say that thalidomide was a "blessing in disguise" is both callous and simplistic, but to say that such catastrophes could always be predicted is unrealistic. The relatively advanced techniques and regulatory procedures employed today are often recognized by those who try to use them as being inadequate or misleading when applied to the awesome task of guarding human safety. Animal test results still provide only a statement of probability, but the final word on the risk or safety of a given chemical

agent must come from human surveillance after realistic conditions of exposure (Fraser, '64).

The year 1966 may deserve a special footnote in the history of man's response to the dangers imposed on the unborn by the environmental changes which he has wrought. In this year significant efforts were made to minimize the risks to the unborn population from two kinds of extrinsic agents—namely: radiations (by the ICRP Recommendations, '66) and drugs (by the FDA Guidelines). It is also noteworthy that other kinds of threats to human well-being, e.g., social, economic, demographic, etc., were also being recognized about that time. Could this have been one of those times in history when a forward step was taken in general human awareness?

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