The Challenges of Teratology

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ABSTRACT Teratology has its origins in the descriptive anatomy of malformed humans. Although the term now has much wider connotations, the first challenge of teratology is to recognise its purpose as a science related to a human problem. The wider connotations inevitably mean the involvement of increasing numbers of disciplines, each with its own language and limitations, but each with a unique contribution to make. The second challenge of teratology is therefore to establish and expand communications between these disciplines. The third challenge is teratogenesis, which requires a rather more profound consideration of the nature of causation than a simple cause-and-effect relationship. At the same time as looking back from consequences to causes, we must look forward from the causes to alternative consequences. The affinity of teratogenesis, carcinogenesis, and mutagenesis constitutes the fourth challenge. The fifth challenge brings us back to humans, and lies in the relationships between scientists working within the field of teratology, and industry, the law, the media, and the public at large.

"Geoffroy de St. Hilaire appears to have been the first to apply the term teratology to the study of monsters and disorders in structural organisation. Once teratology had spread beyond the narrow confines of the anatomical investigation of congenital malformations, it became, and has remained, extremely difficult to delimit its useful range. Nevertheless, if the subject matter of teratology today has only vague and ill-defined boundaries, its objectives are crystal clear. The main purposes of teratology are to find out why some babies enter the world suffering from physical, mental or metabolic handicaps from which the majority of their contemporaries are free, and, with the knowledge thus acquired, to remove or, at least, alleviate the effects of these conditions" (Woollam, '66).

The first challenge to me in the preparation of this lecture lay in what should have been a simple matter—the checking of a reference. I was familiar with the name Geoffroy de St. Hilaire, but in my ignorance had believed Geoffroy to be a first name. Learning to Josef Warkany's wonderful book ('71) for further guidance, I found to my consternation that there were two books by Geoffroy St. Hilaire, written by two different people. Geoffroy turns out to be part of the surname, and the authors have different christian names. So which, if either, was the first to use the term "teratology"? I was able to borrow both these venerable publications from the University of Glasgow.

Geoffroy St. Hilaire the Elder published the first volume of his "Philosophie Anatomique" in Paris in 1818, on the subject of the respiratory organs. The second volume appeared in 1822. It was orginally intended to be on the subject of osteology, but the author, who was a member of the Royal Academy of Sciences and a professor of Zoology and of Physiology, clearly became diverted by matters of greater fascination than dry bones, and wrote instead about Human Monstrosities (Fig. 1.) The book is essentially descriptive anatomy, but there is a hint of epidemiology, because he went to the trouble of finding out the numbers of annual births in Paris in order to get some idea of the prevalence of Parisian monsters. (Even in the early 19th Century, legitimate births were recorded separately from "natural" births, which reveals that one third of all births in

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This article is dedicated to Dr. Josef Warkany and will be cited in a special issue of Teratology.
Paris at that time were illegitimate.) But nowhere in the book do we find the word teratology.

Geoffroy St. Hilaire the Younger published his book in three volumes plus an atlas, of which volume one appeared in 1832, the next two volumes in 1836, and the atlas in 1837. The full title is lengthy (Fig. 2), but the alternative title is brief—"Traité de Tératologie." With only 10 years between the appearances of the two books (1822 and 1832), I had wondered if the two authors might be brothers, but the dedication page (Fig. 3) makes all clear. Isidore Geoffroy St. Hilaire, who coined the term teratology, is the son and pupil of the author of "Philosophie Anatomique."

We can be sure that he invented the term and did not simply borrow it from elsewhere. In his preface he explains the word, and in a footnote to the first page of his introduction he justifies its invention thusly: "I appreciate that I differ from the opinion of all anatomists in considering the corpus of knowledge about monstrosities as a distinct science, as a special branch of the great science of organisation: but I think I may say that this innovation, important for the future progress of the theory of anomalies, and the creation of a new word, which is an inevitable consequence, will be completely justified in the rest of this work."

The first serious challenge of teratology is its interdisciplinary nature. Introducing the word teratology in his preface, Isidore Geoffroy St. Hilaire wrote: "It should not be considered as a section of pathological anatomy; nor should it be seen as a simple branch of physiology, nor of philosophical anatomy, nor of embryology, nor of zoology; it should have equally close associations with all these sciences without being confused with any of them; ..." Today we would have to add a great many branches of science which were unborn in his time.

If teratology is difficult to define, the problem of defining a teratologist is even more daunting. Indeed, I wonder if such a person exists? The membership of this Society includes clinicians, epidemiologists, pharmacologists, cell biologists, anatomists, pathologists; but how many teratologists? We are all interested in normal and abnormal development, in the interactions between the developing organism and its environment, in the initial disturbances at molecular and cellular level, and in their consequences as macroscopic deformities and clinical disabilities. But we all approach these problems from a different angle determined by our education: we are programmed to think in different ways.

In the developing brain, not only is the number of cells important, but also the connections between them. The same principle applies to the developing science of teratology. The more disciplines involved, the greater the potential for progress. But the potential will only be realized if the communications are good. The more cells there are, the more synapses are needed. How can these communications be improved? I offer three suggestions.

The first is self-evident in our presence at this meeting. Societies and associations which bring together people working in different disciplines cannot but improve communications. At any scientific meeting attended by more than 20 people, and especially at any international scientific meeting, the greatest value lies in the opportunities for personal contact outside the lecture hall. The coffee breaks, the free evenings, the social occasions are the opportunities for establishing new synapses and for reinforcing old ones. These conversations are often the means to interdisciplinary understanding, sometimes to active scientific collaboration.

My second suggestion is that we must not be obsessed by the expertise of others, or overwhelmed by the extent of our own ignorance. However much we know of something, somebody else knows more. However well we understand something, somebody else understands it more fully. However profound the opinion we express, a better opinion can be found. But equally, however little we know, however poorly we understand, however superficial our opinion, there will be others in at best a similar state.

There are levels of knowledge, levels of experience, levels of understanding. It is not necessary to be a world authority on something to take an interest in it, know something about it, understand the basics of it, even express a point of view. To some extent we have to be specialists of some kind. But specialists are people who know more and more about less and less. We must try to strike a balance between the more and more and the less and less. We must be professional in our specialty, but we can be keen amateurs in related fields.

So we should try to know something about the disciplines related to teratology as well as knowing a lot about our own special area. I am a paediatrician, but through an interest in congenital malformation I have had the opportunity to dabble in epidemiology, in genetics, in drug teratogenesis, in nutrition. And in the process of dabbling I have picked up bits of knowledge and experience which have added
PHILOSOPHIE ANATOMIQUE.

DES

MONSTRUOSITÉS HUMAINES,

Ouvrage contenant une classification des monstres; la description et la comparaison des principaux genres; une histoire raisonnée des phénomènes de la monstruosité et des faits primitifs qui la produisent; des vues nouvelles touchant la nutrition du fœtus et d'autres circonstances de son développement; et la détermination des diverses parties de l'organe sexuel, pour en démontrer l'unité de composition, non-seulement chez les monstres, où l'altération des formes rend cet organe méconnaissable, mais dans les deux sexes, et, de plus, chez les oiseaux et chez les mammifères.

Avec Figures des Détails anatomiques.

Par M. le Ch. GEOFFROY-SAINT-HILAIRE,


PARIS,

Chez l'Auteur, rue de Seine-Saint-Victor, n° 33;
Et chez les principaux Libraires pour l'Anatomie.

1822.

Fig. 1
HISTOIRE
GÉNÉRALE ET PARTICULIÈRE

DES ANOMALIES
DE L'ORGANISATION
CHEZ L'HOMME ET LES ANIMAUX,
OUVRAGE COMPRENANT DES RECHERCHES SUR LES CARACTÈRES,
LA CLASSIFICATION, L'INFLUENCE PHYSILOGIQUE ET PATHOLOGIQUE,
LES RAPPORTS GÉNÉRAUX, LES LOIS ET LES CAUSES

DES MONSTRUOSITÉS,
DES VARIÉTÉS ET VICES DE CONFORMATION,
ou

TRAITÉ DE TÉRATOLOGIE,

Par M. Isidore Geoffroy Saint-Hilaire,
Docteur en médecine, professeur de zoologie et d'anatomie générale à l'Athénée royal de Paris, aide-naturaliste de zoologie au Muséum royal d'histoire naturelle, membre de la Société d'histoire naturelle de Paris, des Sociétés royales des sciences de Lille et d'Arras, du Muséum d'histoire naturelle de Douai, etc.

TOME PREMIER.
AVEC ATLAS.

PARIS,
J.-B. BAILLIÈRE,
LIBRAIRE DE L'ACADÉMIE ROYALE DE MÉDECINE,
RUE DE L'ÉCOLE DE MÉDECINE, N° 13 bii.
LONDRES, MÊME MAISON, 219, REGENT-STREET.
BRUXELLES, AU DÉPÔT DE LA LIBRAIRIE MÉDICALE FRANÇAISE.
1832.
A L'AUTEUR

DE LA

PHILOSOPHIE ANATOMIQUE,

SON FILS ET SON ÉLÈVE,

I. GEOFFROY SAINT-HILAIRE.
interest to my life and helped me to understand better the contributions of others. The second aid to communication, therefore, is for us to try to know a little about each other’s disciplines, and especially to encourage our younger colleagues in this attitude.

My third suggestion for improving interchange lies in our spoken and written scientific communications. Every science and profession, every trade and occupation develops a language of its own. Sometimes the invention of new words—like teratology—is necessary and justifiable. But all too often we develop a whole new jargon, a cocktail of neologisms, abbreviations, and in-phrases, which renders our contribution unintelligible to all but the fellow inmates of our own intellectual prison. Without doubt, three of the four oldest professions—the church, the law, and medicine—have been guilty of this for more centuries than anybody else. Doctors have done this deliberately, with the object of maintaining professional mystique, and have only recently begun to learn that medicine can be practiced more enjoyably as well as more effectively if the patient understands what is going on. The mark of a teacher is that he can explain anything he really understands to anybody capable of understanding. He should be able to explain silicon chips to a bench of bishops or lasers to a professor of moral philosophy. The language must be adapted to the audience.

So much for teratology and teratologists. The next challenge lies in the nature of teratogenesis. I am not concerned here with teratogenic mechanisms, but with the rather more philosophical (but nevertheless strictly practical) aspects of the cause-and-effect relationship. Having started to dabble in philosophy, I found that Aristotle described four kinds of cause, the Material, the Formal, the Efficient and the Final, but he was considering what we might now call attributes rather than a sequence of events.

In considering the causation of developmental defects, which may help us towards prevention, the historical departure point is the separation of causes into genetic and environmental. We can say of a mongol baby, "He is a mongol because he is trisomic for chromosome 21." We can say of a baby with congenital heart disease, cataracts and deafness, "He has these defects because his mother had rubella when she was 6 weeks pregnant." But when we look at babies with neural tube defects, isolated congenital heart disease, intestinal atresia, cleft lip and palate, or urinary tract malformations, we cannot as a rule identify a single cause, genetic or non-genetic. We may find evidence that genetic factors play a part and that non-genetic factors play a part and conclude that the causation of these common defects is multifactorial, a term which has come in for a good deal of abuse but is nevertheless valid. Multifactorial causation applies to any phenomenon which is not determined by a single cause.

May we consider for a moment the apparently simple statement, "Shalomycin is teratogenic." (I use a fictitious drug because I hope to convince you that this is a fictitious statement). Let us suppose that the teratogenic effect attributed to Shalomycin is congenital heart disease (CHD). What is the statement, "Shalomycin causes CHD," really stating? Does it mean that all CHD is attributable to this drug? Of course not. So we are not saying "Shalomycin is the cause of CHD." Does it mean that the administration of Shalomycin at the appropriate stage of pregnancy is invariably followed by CHD? This is very unlikely. So we are not saying "Shalomycin inevitably causes CHD," because sometimes it does not. The original statement is likely to have been based on the observation that CHD is found significantly more often in babies exposed to Shalomycin in utero than in babies not so exposed. From this observation we can make two deductions: first, that since intra-uterine exposure to Shalomycin is not invariably followed by CHD, the drug is not of itself a sufficient cause of CHD; second, that if we regard CHD as being, in most instances, of multifactorial causation, Shalomycin may be a factor in some cases. In other words, the role of Shalomycin is a lot less precise than might be assumed from the original statement, "Shalomycin is teratogenic."

The difficulties are much greater if we seek to justify the contrary statement, "Shalomycin is not teratogenic." The hypothesis that a drug, or any other agent, is never a contributory factor in any malformation is virtually untestable and therefore incapable of being confirmed or rebutted.

Before leaving the problem of drug teratogenesis, a word about the challenge of methodology. Most teratogenicity studies in humans have compared the frequency of one or more defects in babies exposed to one or more drugs in utero, with the frequency of the same defect(s) in a group of babies not so exposed referred to as the control group. Controls be-devil clinical research because humans are al-
progress in one field may well yield dividends in the biggest challenge to medical science, and the productive problems. This especially applies to ever difficult we find it to keep in touch with all for the other. The implication is this: that in children are, like cancer in adults, the inherent malformations represent only one consequence of teratogenesis provide a fascinating and instructive relation to drugs used in the management of reproductive problems. This especially applies to so-called fertility drugs, for which a control group is inconceivable.

The next challenge of teratology I shall refer to only briefly. We have considered how a multitude of disciplines come together in the science of teratology, and how the majority of birth defects arise not from a single cause but from a multitude of causes. In both these respects, many threads are woven into a single strand. But the converse is also true, for malformations represent only one consequence of disordered cell behavior. The very same factors which can lead to malformation may also lead to mutation or to cancer. The interfaces between teratogenesis, mutagenesis, and carcinogenesis provide a fascinating and instructive area for thought and for research. It has long been apparent that congenital malformations in children are, like cancer in adults, the biggest challenge to medical science, and the progress in one field may well yield dividends for the other. The implication is this: that however difficult we find it to keep in touch with all the components that make up the science of teratology, we must also be aware of developments in the areas of mutagenesis and carcinogenesis.

I would now like to leave the aspects of teratology which we study, to consider ourselves as members of a society, and consider our relationships with other members of society with different functions to perform. Teratology, especially human teratology, is a matter of concern not only to scientists, but also to the chemical and pharmaceutical industries, the legal profession, politicians, the media, and the general public. Industry exists to create wealth and provide employment: it exists to benefit society, not harm it. The legal profession exists to help individuals to redress wrongs. Governments exist to guide and safeguard the people who elected them. The media exist to inform the public. The discovery of a new environmental teratogen can be of enormous importance to any or all of them, as well as to the general public. How is the individual worker in the field, who probably feels extremely vulnerable, to relate to the giants of industry, law, government, and the media?

I raise these problems because I have encountered them all and have not found them easy. I am speaking as a clinician. The pharmaceutical industry is well represented amongst the membership of this Society, and I feel sure that it faces similar difficulties from time to time. Perhaps, therefore, I could start with the relationship between clinicians and the drug manufacturers. There are international differences in tradition, but my impression is that in most European countries, it is a love/hate relationship, at least as seen from the clinician’s side. He is grateful to the industry for developing and manufacturing the drugs which his patients need. He is grateful for the financial help it may give in funding research and sponsoring conferences, but at the same time, he is a little uneasy about accepting hospitality. He feels that he is in danger of selling his soul to the devil, and, indeed, the drug companies do not finance symposia or hand out ball-point pens from totally philanthropic motives.

The truth is that we—the clinicians and pharmaceutical companies—cannot get along without each other. There has to be symbiosis, a living together. Each must be responsive to the problems of the other. A company may develop a new drug and carry through chemical, pharmacological, and animal testing. If it looks sufficiently promising, clinical trials will be needed. The only clinical trials that are morally justifiable are good clinical trials, properly designed, properly controlled, properly supervised, and properly analysed. If competent doctors decline to carry out good trials, incompetent doctors will carry out bad trials.

Clinicians must therefore be responsive to the needs of industry to have adequate clinical
trials. Similarly, we must expect drug companies to be responsive to the anxieties of clinicians if they suspect that a drug is having undesirable side effects, whether teratogenic or otherwise. If there is a conflict between patients and profits, there must be a joint understanding that patients come first. The story of thalidomide in this respect was not altogether a happy one. That must not be allowed to happen again.

I therefore see the relationship between the pharmaceutical industry and individual scientists outside the industry as a partnership which involves mutual respect, responsiveness, and responsibility.

What about the law? The legal profession is potentially involved in teratogenesis every time a malformed baby is born to a woman who took a drug, or thinks she took a drug, or claims she took a drug, in early pregnancy. At the most conservative estimate, this means that at least 1 percent of all babies born provide potential grounds for litigation. The extent to which this potential is realised in practice varies very widely from one country to another, depending in part upon the litigiousness of the people, and in part upon the legal structure of the country, which may encourage or discourage such lawsuits (Brent, ’77).

The scientist may find himself being invited to help on either side. The lawyers representing the deformed child seek evidence or opinion to substantiate the view that the deformities were drug-induced. The lawyers representing the drug company seek evidence or opinion to substantiate the view that their product is not teratogenic. The natural inclination of the scientist is to have nothing to do with either side. Lawsuits occupy an inordinate amount of time. They demand your personal presence in inconvenient places at inconvenient times.

If these suits usually resulted in some relatively trivial settlement, we might be able to opt out with a clear conscience. But they do not, particularly in countries which accept the principle of punitive damages. These legal actions are highly significant to both parties. To severely deformed and handicapped children, a substantial sum of money in the bank can make a very big difference to their lifestyle. To a drug company, the payment of such substantial sums to a substantial number of children could spell bankruptcy.

A scientist who has neither evidence nor opinion to offer has no problem, but any who have evidence (which is often scanty) or opinion based on experience (of which there is little more, though not much) cannot really escape their responsibilities. There is too much at stake. Here again there has to be a symbiosis. Whose lawyers we work with will be determined by our scientific convictions. Our professional reputations are not up for auction. As citizens as well as scientists, we must, despite the inconvenience, be prepared to stand up for what we believe to be the truth.

I have left until last the relationship which is perhaps most difficult of all, namely, that between scientists and the media—newspapers, television, radio—and, through the media, the public at large. I said the media exist to inform the public, which is true, but the journalist exists to create a story that will help his paper to sell more copies or persuade more people to watch his TV channel. So he wants to personalize; we strive for anonymity. He wants uncomplicated statements that something either is so or is not so. We need to add conditions, provisos, circumstances, reservations.

Again there is a temptation not to get involved. The time scale for the media, and especially television, is the opposite of the legal time scale. They would like you in the studio in an hour; better still, 5 minutes; best of all, yesterday. But we spurn them at our peril. The media probably represent the biggest single influence on the lives of people exposed to them. They can do great good and great harm. There may be times when we need them, and, for this reason if for no other, we should try to be helpful to them. I can only speak from experience of the media in Britain, where misrepresentation and abuse of confidences are very exceptional.

There are, of course, predicaments which cannot be resolved by good relationships. Suppose a letter has been published in a medical journal suggesting, possibly on rather thin evidence, that a particular drug, widely used for many years, may have a teratogenic effect. How widely should this letter be publicised? If the suspicion about the drug proves to be ill-founded, publicity will have caused needless anxiety to many mothers who have taken it, will probably have resulted in some pregnancies being terminated, and may precipitate yet more lawsuits. Yet the journalist may see a saleable story with banner headlines, and will speak of "the public's right to know." As scientists, we cannot tell the media how to do their job. Perhaps our responsibility is to remember that journalists read journals as well as writ-
ing them, medical journalists read medical journals, and the letter we send off to the editor today may be on everybody's breakfast table the week after next.

In conclusion, I should like to return to my opening quotation from Woolam. "The main purposes of teratology are to find out why some babies enter the world suffering from physical, mental or metabolic handicaps from which the majority of their contemporaries are free, and, with the knowledge thus acquired, to remove or, at least, alleviate the effects of these conditions." The final challenge of teratology, but the greatest of them all, is the challenge of purpose, the challenge of relevance to the human situation. Research is designed to answer questions or to test hypotheses. I would like to add to every research protocol within the whole field of teratology, and to every application for a research grant, a compulsory question: "How do you see this work contributing to the understanding of human malformation?" For the central challenge lies in the hundreds of thousands of children born in the world every year with spina bifida, anencephaly, congenital heart disease, cleft lip and palate; with abnormal eyes, ears, kidneys, bowels; with deformed limbs. Whether we work with mouse or with man, with whole creatures, organs, tissues, cells, mitochondria, or molecules, we must never lose sight of the malformed multitudes. We must never forget that they are the challenge.

LITERATURE CITED