SPECIAL ARTICLE

Canadian Thalidomide Experience

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ABSTRACT

Data are presented on 115 children, including three sets of twins, born in Canada in 1961 and 1962 with congenital malformations associated with the use of thalidomide by their mothers in early pregnancy. The epidemiological method is described. Of the 115 children, 74 were alive at the time of reporting, 41 of these being severely handicapped; 8 had been stillborn; 33 had died. Limb involvement was usually bilateral, affecting the upper limbs alone in 42 cases, and the upper and lower limbs in 41. Of 112 mothers, only 60 had had the drug prescribed by the physician providing maternity care; 87 were estimated to have first taken the drug before their last menstrual period or within 56 days thereafter. A plea is made for the development of better methods of collecting information on the occurrence of congenital malformations, with the aid of practising physicians.

THE thalidomide episode probably represents the first recorded epidemic of iatrogenic disease affecting the human fetus. In the spring of 1962 it was apparent that Canada would share with other countries the impact of the use of this drug by pregnant women—manifested in the birth of children with an unusual pattern of congenital malformations involving the limbs. The limb malformations have been described in a variety of ways, but the term most used has been phocomelia, or "seal limbs", referring to the most severe involvement. Associated external malformations described have included deformities of the ears and hemangiomata of the forehead and upper lip. Among the serious internal malformations reported have been gastrointestinal, cardiac and renal lesions. With the accumulation of more case material during the past year a wider variety of malformations has been reported, but the above-noted syndrome, namely, limb malformations associated with gastrointestinal, cardiac or renal lesions, remains the most characteristic.

Historical Summary

The sequence of events whereby this unusual occurrence of severe limb malformations was first recognized and later associated with the introduction of a new drug is well documented. In 1961, Wiedemann and Aeissen[1] in West Germany reported the appearance of an unusual number of children with these malformations but did not suggest any specific cause. Reports of an association between the malformations and the availability of a new drug, thalidomide, appeared almost simultaneously from West Germany and Australia. Lenz,[3] at a meeting of German pediatricians in November 1961, voiced his suspicions. In the same month, McBride[2] in Australia noted from experience in his own practice the appearance of children with limb malformations and atresias of the gastrointestinal tract. He reported this observation to the manufacturer and at the same time wrote to the *Lancet* and the *Medical Journal of Australia*, drawing the problem to medical attention. These letters appeared in mid-December 1961. Further evidence of the association was reported in February 1962 by Speirs[5] from Stirlingshire, Scotland, who carried out a very thorough study of the prenatal drug intake of 10 mothers who had infants born with severe deformities of this pattern. He confirmed that eight and perhaps nine of the mothers had received the drug in early pregnancy. Other British studies appeared, including those reported by Smithells[6] in Liverpool and by Leck and Millar[7] in Birmingham, as well as further West German reports from Lenz and Knapp,[4] Pfeiffer and Kosenow,[8, 9] and Weicker *et al.*[10] Taussig[11, 12] reported the overseas experience in North American literature. The first published report of an affected Canadian child appeared in April 1962;[13] further cases were published in September,[14] October[15] and December[16] of the same year.

THE CANADIAN SITUATION

Chronology of Drug Availability

On April 1, 1961, the Merrell product, Kevadon, went on sale by prescription only.

On October 23, 1961, the Horner product, Talimol, went on sale by prescription only.

On December 5 and 7, 1961, a letter was sent to physicians by both companies reporting information from abroad on the occurrence of congenital malformations in the offspring of a few mothers who had taken thalidomide early in their pregnancies. These letters included the warning that the drug should not be administered to pregnant or pre-

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menopausal women who might become pregnant.

On February 21, 1962, a second letter to physicians was sent by the Merrell Company, indicating that observation of the previously mentioned contraindication was still necessary.

On March 2, 1962, both drugs were withdrawn from the Canadian market by the companies at the request of the Food and Drug Directorate, Department of National Health and Welfare, Canada. Physicians were so informed by the companies.

On April 10, 1962, a letter to physicians from Dr. C. A. Morrell, Director, Food and Drug Directorate, requested that samples on hand be returned to the supplier or destroyed, and that side effects of new drugs be reported to him.

On July 20, 1962, a letter to all physicians from Dr. C. A. Morrell requested that physicians review their files and advise their patients who might have a supply of the drug in the home to destroy it.

This episode was obviously an event of historic significance, one that should be documented as carefully as possible. It was felt that a national study of the occurrence of this syndrome associated with maternal drug intake was feasible in Canada for several reasons. The drug had been available for a shorter period than in the United Kingdom or West Germany, the population at risk was smaller than in these countries, and further, it had always been restricted in Canada to prescription sale. The Department of National Health and Welfare therefore made the decision about a year ago to undertake such a study.

Before the study was embarked upon, present statistical resources were explored to determine the rate of occurrence of malformations of this nature before the drug had been available. This endeavour to establish a baseline against which an increase might be measured met with little success. Information was sought from death and stillbirth registrations through the Dominion Bureau of Statistics. Published data from Physician's Notice of Birth forms from several provinces were examined. None of these sources proved of direct value, since the International Statistical Classification of Diseases and Causes of Death had been used to classify the malformations in all instances. In this classification, limb malformations of these types are grouped with a number of other conditions, so their numbers cannot be obtained readily. The registries for handicapped children or adults maintained in several provinces did not all publish reports which included classification of disabilities. Nowhere in Canada was there an institution where data on congenital malformations generally had been collected in sufficiently large volume to provide the kind of data needed on this occasion. In other words, it was virtually impossible to obtain any idea of the frequency of occurrence of this rare syndrome. It would probably be equally difficult to determine rates of occurrence of much more common malformations through present sources. Yet without basic information on so-called "normal" incidence of these problems attempts to measure fluctuations are meaningless.

From the outset, the study was planned as an epidemiological one, to include data on stillbirths and infants who had died after birth, as well as survivors. Information was sought regarding the date of birth of the child, the congenital malformations present, and the prenatal history of the mother, such as the date of her last menstrual period, the time of intake and the amount of thalidomide ingested, complications of pregnancy and other drugs prescribed.

The first approach was made directly to physicians through their professional associations. Letters were written in early June 1962 to The Canadian Medical Association, l'Association des médecins de langue française du Canada, the College of General Practice of Canada, the Society of Obstetricians and Gynaecologists of Canada, and the Canadian Paediatric Society. The request was made to physicians to report documented cases to the Food and Drug Directorate. The Canadian Medical Association referred the matter to its Provincial Divisions; the Canadian Paediatric Society and the Society of Obstetricians and Gynaecologists organized case-finding studies among their members. These studies were undertaken in mid-summer, 1962. It should be mentioned that some physicians had already reported cases directly to the Food and Drug Directorate. Provincial Health Departments were asked to assist in case-finding on August 3, 1962.

Federal-Provincial Conference

On August 1, 1962, the Minister of National Health and Welfare proposed a meeting with representatives of provincial governments to discuss a program of assistance to families affected, in which the national government would share. The Federal-Provincial Conference was held on August 17, 1962. There now was an obvious need to know the number of surviving children and the nature and severity of their disabilities in order to plan for their habilitation. It was recommended that case-finding efforts be continued and co-ordinated by the Department of National Health and Welfare.

Epidemiological Method

In order to achieve uniformity in data collection, a suggested plan of study was sent to all Provincial Health Departments. This included a description of the syndrome as reported up to that time in German and English language literature, and a case-study form.

Several additional suggestions were made: first, that the physicians who had provided care be contacted personally by one physician having responsibility for collection of data in a community or the province as a whole; secondly, that with the approval of the attending physician, the investiga-

tor should be enabled to confirm or supplement data by direct contact with the pharmacist, hospital, rehabilitation agency, or the family, where this was indicated. The following definition was provided as a guide to case selection:

"A Definition of the Syndrome Associated with Thalidomide

"Information is still inadequate on either the clinical manifestations of this syndrome or its relationship with maternal thalidomide intake to establish a precise definition in clinical terms. However, examination of the English language literature and two German articles has revealed the following data:

"The most unique characteristic of this syndrome is the presence of deformities of the long bones of the limbs resulting in shortening and other abnormalities. The arms are involved in the majority of cases, the legs less frequently. All degrees of severity are reported from complete absence of limbs to minor involvements of phalanges. Typically both sides are affected but not always equally. The terms used to describe these deformities include ectromelia, dysmelia, phocomelia, micromelia, amelia, peromelia and hemimelia. Other anomalies which are frequently associated are absence or malformation of the external ear and the external auditory meatus. These may be associated with paralysis of the side of the face. Much less serious findings frequently associated are hemangiomata of the forehead and upper lip.

"Frequently internal anomalies are present in addition to the limb anomalies. The most common of these appear to involve the gastrointestinal tract. The genitourinary system and the heart are also mentioned frequently. Apparently those infants which fail to survive, succumb to one or other of these anomalies."

The plan suggested was followed in general in most provinces. Two provinces altered the case study form but essential information was retained except that one substituted "week" for "day" in the question regarding the time when the drug was prescribed. Three provinces used hospital authorities as their main source of information. Hospitals made available data on infants born in 1961 and 1962 with malformations which met the provincial criteria. Three provinces utilized information on the "Physician's Notice of Birth" to identify possible cases. One province made a direct approach to physicians in addition to seeking information through hospital channels.

More detailed information was then sought on this case material from the physician providing maternity care. In two provinces the local Medical Officer of Health was given the responsibility of obtaining further data about the infant and the course of the mother's pregnancy. In other provinces this was done by one physician of the Provincial Health Department staff. Information was obtained by personal interview where possible, otherwise by correspondence. Regardless of the initial screening procedure adopted, other informational leads were followed up in a similar way. In no instance was it reported that the attending physician refused to co-operate. In only one province did the investigator make a direct contact with the family where indicated. Two provinces have indicated that there are a few cases with suggestive malformations on which maternal data have not yet been obtained.

Questions might well be raised as to the wisdom of delegating so widely the responsibility for the field aspects of this study or for the data-collection. There were a number of reasons for this. Health matters generally are matters of provincial jurisdiction, including the study or definition of health problems. When the investigation was undertaken, there were no accurate statistics on the incidence of this syndrome in the United Kingdom or West Germany, yet the estimates of 500-800 in the former and up to five or more thousand in the latter country were alarming, to say the least. It was impossible to predict what numbers might be found in Canada. (More recent reports of surveys by local health authorities in the United Kingdom reduce these estimates substantially, to 348 surviving children.[17, 18] No national statistics have yet been published for West Germany.) Speed was of great importance, since the difficulties involved in obtaining accurate information on drug intake particularly had been well illustrated by overseas investigators. This procedure for case-finding had the advantage of mobilizing personnel familiar with the local situation and in closer touch with physicians in the area. Perhaps most important of all, the emotional realities of the situation for families and physicians, as well as the possible legal implications, demanded that the investigation be carried out with the greatest tact and understanding. The use of a number of investigators to obtain information undoubtedly produced data of varying accuracy and completeness. However, this source of bias, manifest perhaps more often by omission than error, cannot be measured.

CLINICAL DATA

Case Selection

From the individual records provided by Provincial Health Departments, the Canadian Paediatric Society, and the Society of Obstetricians and Gynaecologists of Canada, and by physicians directly, cases were selected for analysis by the author if they met four criteria:

1. A clinical syndrome within the general description given above.
2. A confirmed intake of thalidomide.
3. Evidence that the drug had been ingested at about the estimated time of conception or within 12 weeks of the date of the last menstrual period.
4. Evidence that the drug had been obtained from a Canadian source.

Case Incidence

One hundred and fifteen cases met these criteria. Of this number eight were stillborn and 33 died

in the neonatal period or in the early months of life; the remaining 74 infants were alive at the time of reporting, which extended from August 1962 to May 1963.* In addition, three cases were reported in which the drug had been obtained overseas. It is possible that more cases of this sort occurred, particularly among Canadian service families posted overseas in countries where the drug had been available earlier and for a longer period than in Canada.

TABLE I.—CASE INCIDENCE BY MONTH OF BIRTH

Month	*Cases*
November 1961	3
December 1961	3
January 1962	12
February 1962	3
March 1962	9
April 1962	10
May 1962	14
June 1962	13
July 1962	19
August 1962	12
September 1962	5
October 1962	9
November 1962	2
December 1962	1
Total	115

Of the total number of cases, six were born late in 1961 and 109 in 1962 (Table I). Fig. 1 shows graphically the case incidence by month of birth.

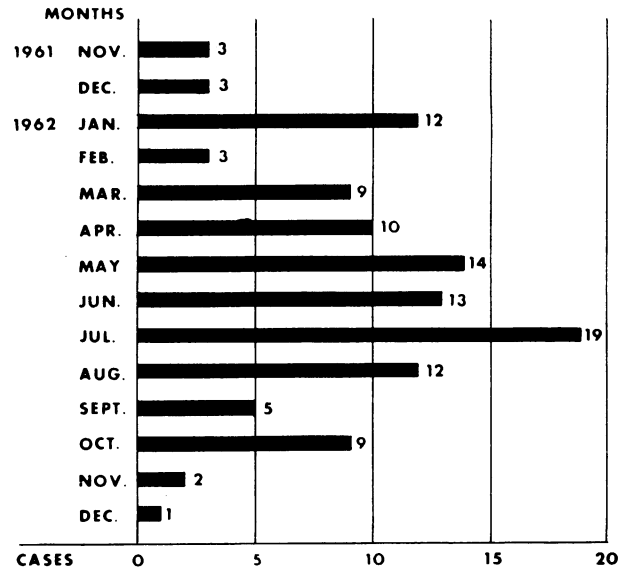

Fig. 1.—Cases of congenital malformations associated with maternal thalidomide intake by month of birth—Canada, 1961-1962.

Severity

An attempt was made to classify cases according to the severity of the malformations reported. It is admitted that this cannot be very precise since the information received varied in its quality. Some descriptions were brief while others contained detailed autopsy findings. In some instances a pediatric report amplified a less detailed clinical description from another source. Nevertheless, it is assumed that the information on malformations apparent on external examination was reasonably accurate though perhaps not inclusive. Three grades of severity were recognized:

I. *Least severe*—simple defects or combinations of the following: Minor defects of one or two limbs such as absence or malformation of phalanges. Defect of one or two limbs but not complete absence of a part—for example, absence or deformity of radius. Abnormal or hypoplastic external ear or ears but not absence. Facial palsy. Correctible atresia or stenosis of gastrointestinal tract, such as anal stenosis.

II. *Intermediate* – varying combinations and degrees of malformations not classifiable in grades I or III.

III. *Most severe.*—Malformations of two or more limbs—for example, shortening, major defect or absence. Any single limb or ear malformation with associated internal malformation—cardiac, gastrointestinal, or renal. Any uncorrectible internal malformation or malformations regardless of degree of limb malformations—such as severe cardiac malformation or multiple defects incompatible with life.

TABLE II.—SEVERITY OF MALFORMATION OF STILLBORN, DEAD AND SURVIVING CHILDREN

Vital status	*Least severe numbers*	*Intermediate numbers*	*Most severe numbers*	*Total*
Stillbirths	0	0	8	8
Deaths	0	4	29	33
Survivors	15	18	41	74
Total	15	22	78	115

It is noted that over half of the surviving children are severely handicapped and will require extensive and prolonged habilitation services.

TABLE III.—MALFORMATION OF LIMBS BY UNILATERAL OR BILATERAL INVOLVEMENT

Limbs	*Unilateral*	*Bilateral*	*Total*
Upper limbs only	8	42	50
Lower limbs only	0	4	4
Upper and lower limbs	0	41	41
Total	8	87	95

In 19 of the cases reported there was no mention of limb involvement. The degree of limb involvement is indicated in Table III, which confirms reports from elsewhere that upper limbs tend to be involved more often than lower limbs, and that the involvement is usually bilateral.

*Two additional cases with survival have been reported. One child born in January 1962 has very minor deformities of both hands. Another born in May 1962 has abnormalities of intermediate degree of the special senses, and a minor abnormality of one foot.

Characteristics of Mothers

Among the 115 cases were three sets of twins, so that 112 mothers were involved. The age of the mothers, their parity and previous pregnancy history were analyzed for the majority of mothers but the findings were not considered significant. In three families there was a history of congenital malformation but not in the parents or siblings of the affected child.

TABLE IV.—DRUG INTAKE

Source	*Mothers*
Physician providing maternity care	60
Physician providing other care	13
Professional access	18
Miscellaneous	10
Not indicated	11
	112

The source of the drug as indicated in Table IV was somewhat of a surprise. Almost half of the mothers had not received the drug from the physician providing maternity care. In some cases there was evidence that this physician was not aware of medical care being given by another physician. The "professional access" group includes a number of physicians' families.

TABLE V.—PURPOSE OF DRUG ADMINISTRATION

Purpose	*Mothers*
Sedative	72
Antinauseant	8
Sedative and antinauseant	5
Not stated	27
	112

The fact that the drug did not appear to have been used widely in Canada as an antinauseant may have limited its damaging effects by limiting its use in early pregnancy.

Dosage

The data concerning the total amount of drug consumed were not sufficiently accurate to be meaningful. One reason for this appeared to be the fact that a significant proportion of the drug available at the time was in physicians' samples. Apparently physicians do not record the nature and quantity of drug samples given to patients as accurately as they record prescriptions.

Time of Intake

As indicated in the criteria for case selection, all mothers of affected children were considered to have ingested thalidomide at the time of conception or within 12 weeks of the last menstrual period. However, the precision with which this information was recorded varied to some extent, from days to months. As with total dosage, it was impossible in most cases to know the period of time during which the drug was ingested, so that use will be made only of data on the time of first intake. Twelve records did not provide usable information, while 100 records had more definitive information which could be used to calculate or estimate the time of intake.

TABLE VI.—TIME OF FIRST MATERNAL DRUG INTAKE IN RELATION TO LAST MENSTRUAL PERIOD

Time	*Mothers*
Before last menstrual period	11
After last menstrual period	
1 to 28 days	23
29 to 56 days	53
57 to 84 days	13
Inadequate information	12
	112

DISCUSSION

The assumptions on which this national study was undertaken appear to have been sound. The case material described is thought to include a high proportion of the Canadian children affected by the ingestion of thalidomide by their mothers during the period of its availability in Canada. However, there may be a group of affected children in which the intake of the drug could not be confirmed, and by the same token there may be cases attributed to thalidomide which would have occurred regardless of the intake of the drug. The teratological and pharmaceutical implications of the thalidomide episode in general have been dealt with elsewhere, yet there are features which are of importance here for other reasons. One problem is highlighted, namely, the serious inadequacy of information on the rate of incidence of congenital malformations generally. When one considers other environmental agents about which there is world concern, it is apparent that better methods of obtaining such incidence data on a systematic basis must be developed, and fairly urgently. In the final analysis such information, its completeness and accuracy are dependent on the reporting of physicians in practice even though it may add to the paper burden they already carry. Data from such devices as Physician's Notice of Birth, Registries for the Handicapped, or even completion of hospital discharge summaries relative to malformations present, all add to the pool of knowledge.

The method whereby the information for this study was obtained might be considered rather cumbersome, but in the atmosphere which prevailed at the time the study was undertaken, it was the only practical one. Credit for providing these data therefore must go to a number of hospital and public health personnel as well as to the attending physicians. It is gratifying that such complete information was made available to the Department in a sensitive area of this sort.

While the clinical information provided by this study lacks the uniformity of other studies carried

out by one or two individuals, in general it confirmed their findings. One example is the pattern of limb malformation, i.e. predominance of upper limb and bilateral involvement. Data concerning maternal intake of the drug illustrate the variety of sources other than the most obvious, the physician providing maternity care. This message should be apparent. The time of drug intake emphasizes the vulnerable period of fetal development, the early weeks of pregnancy.

Finally, an episode of this sort may occur again, probably not as a result of the use of a drug or any other known teratogen but following the introduction of a new factor into the maternal and fetal environment of unsuspected teratogenic potential. The world was perhaps fortunate that thalidomide was associated with an unusual pattern of congenital malformation. Had it affected predominantly the cardiac or central nervous systems, those having the highest incidence of malformations, it might yet have escaped notice. Practising physicians must act as the eyes and hands of a nation-wide surveillance system sensitive to increases in malformations and assiduous in reporting these to appropriate agencies collecting such information.

SUMMARY

Data are presented concerning 115 children born in Canada in 1961 and 1962 with congenital malformations of the type associated with the use of thalidomide by women in early pregnancy.

The case-finding and epidemiological method of ascertaining the impact of the use of thalidomide by mothers of these children is described.

Some of the difficulties involved in obtaining accurate data promptly on the occurrence of congenital malformations are illustrated.

Of the 115 children, 74 were alive at the time of reporting, eight had been stillborn, and 33 had died in the neonatal period or in early infancy.

Of the 74 surviving, 41 were classified as severely handicapped and would require extensive and prolonged habilitation services.

The pattern of limb involvement revealed that upper limbs were affected more frequently than lower, and both upper and lower limbs as frequently as upper limbs alone. Both limbs were usually affected.

The various sources from which the mothers received the drug suggest that new drugs should be handled with greater care by professional people having access to them. Further, the public must be made more aware of the potential danger of taking drugs prescribed for others.

The vulnerability of the fetus in the early weeks of pregnancy has been illustrated.

It is suggested that this kind of episode may occur again following the introduction of a new environmental factor of unsuspected teratogenic potential. Practising physicians must be sensitive to note apparent increases in malformations and assiduous in reporting these to appropriate agencies collecting such information.

The author wishes to express appreciation to the Society of Obstetricians and Gynaecologists of Canada, the Canadian Paediatric Society, and Provincial Health Departments through whose auspices the data were collected, and to the Research and Statistics Division, Department of National Health and Welfare, for assistance in data analysis.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The first number of a new quarterly, *The British Journal of Surgery*, has recently been issued. It is under the direction of an editorial committee, of which Sir Berkeley Moynihan is chairman and Mr. Hey Groves, of Bristol, editorial secretary, and which comprises the names of twenty-eight distinguished surgeons of Britain and Ireland. In a brief introduction Sir Rickman Godlee explains the objects which its founders have in view, pointing out that "if justification is needed, it may be found in the fact that, while in all other countries in both hemispheres where the study of surgery is most active, there are special journals devoted to the subject. In Great Britain alone the progress of surgical thought and enterprise is for the most part only recorded in publications which embrace the whole subject of medicine." And, indeed, one can only wonder why *The British Journal of Surgery* has not been in existence these many years, for, to judge from this initial number, it is destined to occupy a foremost position among scientific journals, a position commensurate with the importance of British surgery.

The first issue comprises about one hundred and fifty pages. The frontispiece is, appropriately, a portrait of Lister; and the contributions are as follows: "Symptomless renal haematuria," by David Newman; "Gall-stones," by D'Arcy Power; "Perineoscrotal dermoid cysts," by Albert Carless; "Marginal resection of the tongue," by Sampson Handley; "Autoplastic graft of fibula into humerus," by H. M. Davies; "Fractures of the spine of the tibia," by Robert Jones and S. Alwyn Smith, of Winnipeg; "Intratracheal anaesthesia," by R. E. Kelly; "Recent methods of anaesthesia," by F. E. Shipway; "The nature of surgical shock," by A. R. Short. Interesting features are a series of case reports under the heading, "Instructive Mistakes," and short notes of rare cases.—*Canad. Med. Ass. J.*, 3: 801, 1913.