

# *Original Articles*

## **Malformations Caused by Drugs in Pregnancy**

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UP TO 1961, only a few cases of malformations in man have been attributed to drugs, notably aminopterin (Thiersch, 1952; <sup>1</sup> and 1960; <sup>2</sup> Meltzer, 1956; <sup>3</sup> and Warkany et al, 1959 <sup>4</sup>), busulfan (Diamond et al 1960 <sup>5</sup>), androgens and progestogens (Wilkins, 1960 <sup>6</sup>), cortisone (Bongiovanni and McPadden, 1960 <sup>7</sup>), quinine (Grebe, 1952; <sup>8</sup> Uhlig, 1957; <sup>9</sup> and Windorfer, 1953 <sup>10</sup>), insulin (Wickes, 1954 <sup>11</sup>), and tolbutamide (Larsson and Sterky, 1960 <sup>12</sup>).

A causal relationship has been well established only for aminopterin and for the androgenic and gestagenic hormones. A few cases of cleft palate following high doses of cortisone administered in early pregnancy are suggestive of a causative effect in view of similar results in animal experiments.

A connection between quinine intake for artificial abortion and malformations has been assumed in selected cases. However, no unbiased study is available. The malformations attributed to quinine have not shown any consistent morphological pattern (In-galls and Prindle, 1949; <sup>13</sup> Ferrier et al, 1964; <sup>14</sup> Fuhrmann, 1962; <sup>15</sup> Kučera and Benešova, 1962; <sup>16</sup> and Maier, 1964 <sup>17</sup>). One controlled study on drug intake in relation to the condition of the newborn did not give any indication that quinine in therapeutic doses may cause malformations (Mellin, 1964 <sup>18</sup>).

There is suggestive evidence, however, that quinine intake in pregnancy may cause deafness of the infant (Taylor, 1934, 1935; <sup>19,20</sup> Kinney, 1953; <sup>21</sup> Robinson et al, 1963; <sup>22</sup> and West, 1938 <sup>23</sup>).

On the basis of extensive animal experimentation, insulin might also be expected to be teratogenic in man. Yet all over the world pregnant diabetic women are treated with

insulin and kept under close supervision throughout pregnancy. Any striking teratogenic effect could not, under these circumstances, escape attention. Cardiac, skeletal, and multiple major malformations do occur with increased incidence in children of diabetic women. This association is, however, independent from insulin treatment (Pedersen et al, 1964 <sup>24</sup>). Even insulin shock treatment in pregnant psychotic patients does not usually produce malformations, although there is a suggestion that it might occasionally do so (Sobel, 1960 <sup>25</sup>). The case for the teratogenic action of tolbutamide in man is equally weak (Sterne and Lavieville, 1964 <sup>26</sup>).

Following McBride's <sup>27</sup> discovery that thalidomide causes certain types of skeletal and multiple malformations in man, many medical journals have been replete with letters and short communications reporting single instances of malformations in connection with drug intake in early pregnancy. A critical review of the abundant literature of that sort yields only an exceedingly meager harvest of established facts. This is a reassuring result. The human embryo seems to be remarkably well shielded from the effect of most drugs.

A low risk, however, is not excluded for any drug in common use. Several studies on meclizine have been interpreted as showing this drug to be completely safe. Yet, if the data from 15 studies are pooled, among 3,333 infants whose mothers were given meclizine in the first trimester, 12 showed cleft lip or cleft palate or both (Biering-Sørensen, 1963; <sup>28</sup> Carter and Wilson, 1962; <sup>29</sup> Diggory and Tomkinson, 1962; <sup>30</sup> Döring and Hossfeld, 1964; <sup>31</sup> Lask, 1962; <sup>32</sup> Macleod, 1962; <sup>33</sup> Meyberg, 1963; <sup>34</sup> Morandi and Marchesoni, 1963; <sup>35</sup> Pettersson, 1964; <sup>36</sup> Rosa, 1963; <sup>37</sup> Salzmann, 1963; <sup>38</sup> Sjövall and Ursing, 1963; <sup>39</sup> Smithells and Chinn, 1963 and 1964; <sup>40,41</sup> Villumsen and Zachau-Christiansen, 1963; <sup>42</sup>

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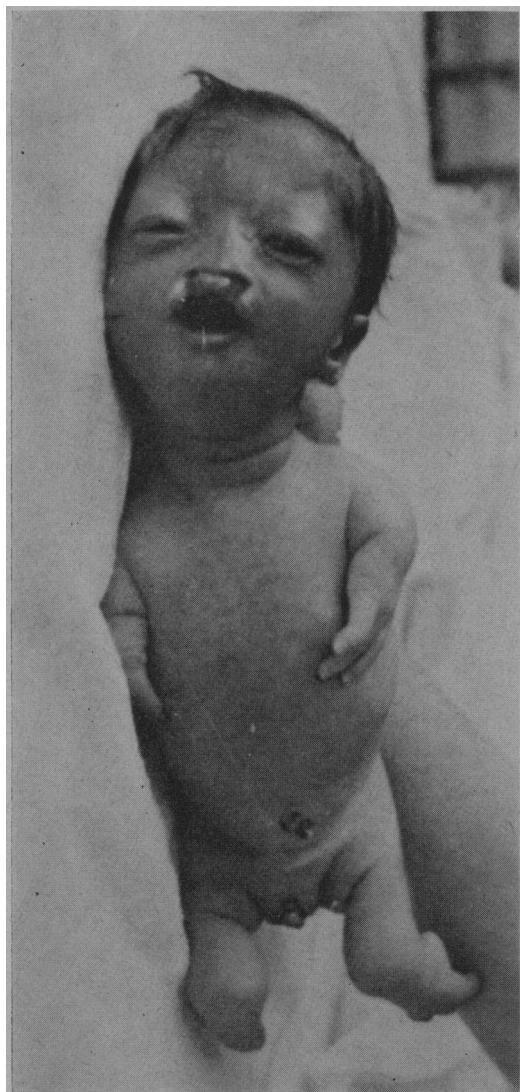


Fig 1.—Tetraphocomelia, cheilognathouranoschisis, and hypertrophy of the clitoris. No thalidomide was administered (photograph courtesy of Dr. Ap-pelt).

and Woodall, 1962<sup>43</sup>). This number is two to three times the expected number. Because cleft palate can also be experimentally produced by meclizine in rats (King, 1963<sup>44</sup>) and has been found in the human cases associated with meclizine, and because cleft palate alone is more common than in cases not associated with meclizine, the drug is still not completely cleared from the suspicion of an infrequent teratogenic activity. Winberg,<sup>45</sup> on the other hand, has found only one single case with information on meclizine consumption in the first trimester among 209 mothers of children with congenital heart disease, cleft lip or cleft palate, and club foot. In Mellin's<sup>18</sup> series of six

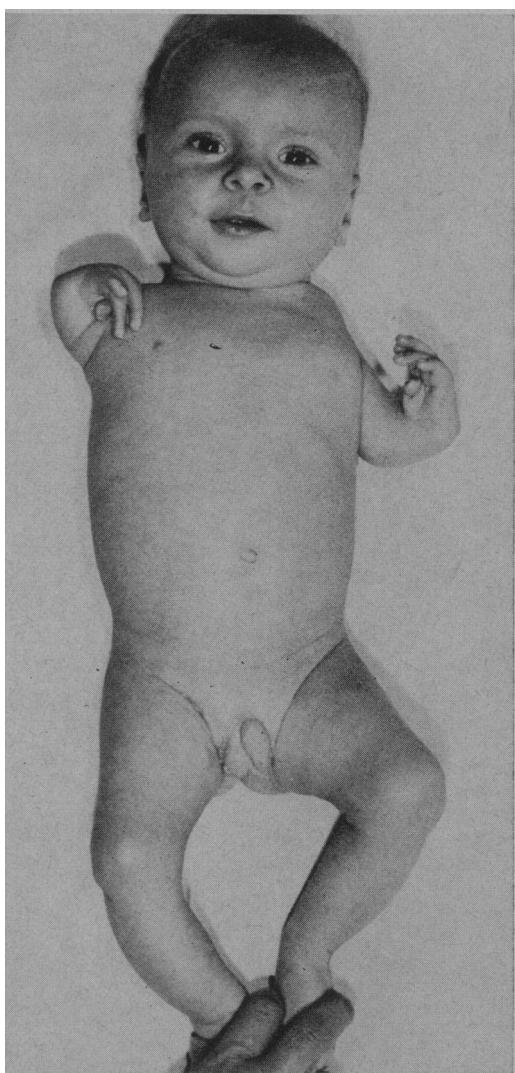


Fig 2.—Phocomelia-thrombocytopenia syndrome. There were five fingers on either hand, clinodactyly of the fifth finger, genu vara. A level of 16,000 thrombocytes per cubic millimeter was obtained on the 18th day (photograph courtesy of Professor Hepp).

cases of cleft lip, palate, or uvula, none were associated with meclizine. In fact, meclizine consumption was found in 1.9% of 266 pregnancies resulting in a malformed infant as compared to 2.4% in 532 pregnancies with normal babies. Even if a significant statistical association between meclizine and cleft palate could eventually be demonstrated, alternative hypotheses should be considered. Cleft palate might be related to the condition for which meclizine is given rather than to the drug. In two series of mothers of children with cleft palate, hyperemesis has been found to occur more frequently than in controls (Curtis and

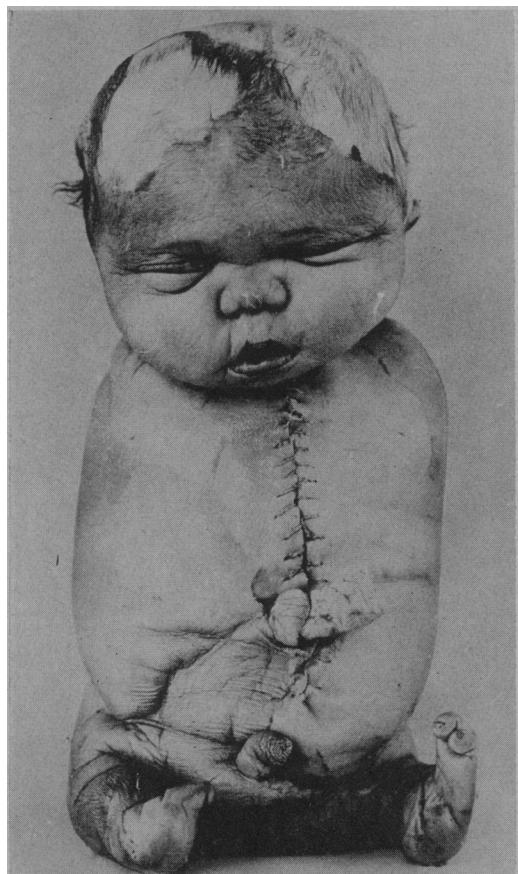


Fig 3.—Syndrome of aplasia of arms, aplasia of femora and fibulae, and defects of toes on fibular side. The child was born before the introduction of thalidomide (photograph courtesy of Dr. J. Kučera, Prague).

Fig 4.—Facial paralysis; anotia on the right side; microtia on the left side; complete deafness; and stenosis of the rectum. Three to four tablets of thalidomide were taken on the 77th day after last menstrual period, on the 22nd day after the rise of

TABLE 1.—Sales and Samples of Thalidomide in Western Germany

Year	Amount Distributed, Kg *
1957	33
1958	728
1959	3,800
1960	14,480
1961 (up to Aug)	11,060

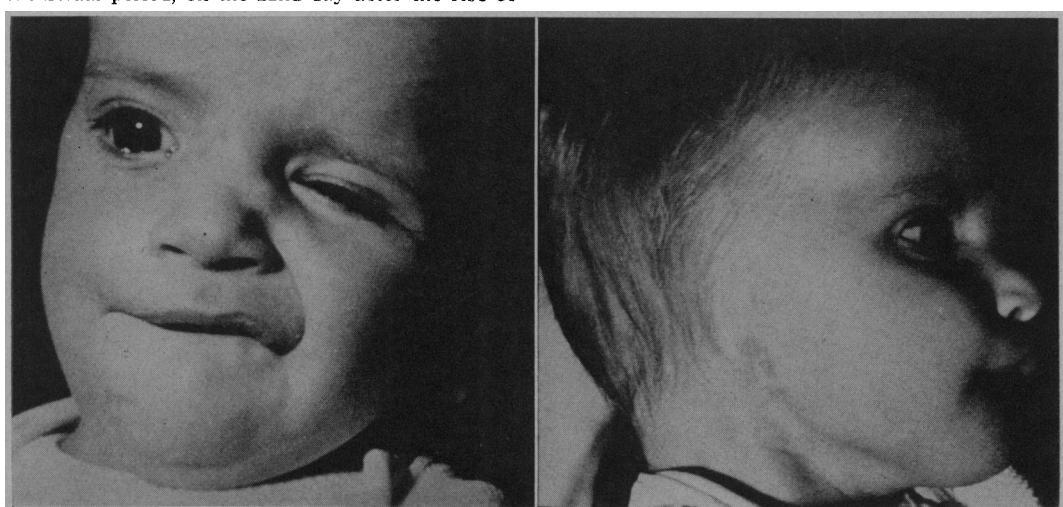
\* A total of 1,000 kg equals 1 trillion milligrams, which equals 20 million teratogenic doses.

Walker,<sup>46</sup> and Stark et al, 1962<sup>47</sup>). There is also rather good evidence that most anti-epileptic (Janz and Fuchs, 1964<sup>48</sup>) and antituberculotic drugs such as isoniazid, aminosalicylic acid, and streptomycin do not damage the human embryo (Jentgens, 1964;<sup>49</sup> Lowe, 1964;<sup>50</sup> and Varpela, 1964<sup>51</sup>).

The only drug after thalidomide found to be teratogenic in man is cyclophosphamide, an alkylating agent which caused aplasia of big toes, hernias, and minor facial and digital abnormalities in one infant (Greenberg et al, 1964<sup>52</sup>). Thus, thalidomide is still the only known teratogenic agent about which enough solid facts are known to permit valid conclusions of general interest.

Thalidomide was first introduced in 1956 under the proprietary name of Grippex, and was thought to be effective against influenza. The basis of this idea was that the febrile reaction to intravenous application of dead *Escherichia coli* germs in an unstated number of rabbits was depressed to a slight, un-

basal temperature. The menstrual cycles were irregular, 38, 41, 36, 44, 42, 80, 45, 45, and 42 days. This case shows how misleading "menstrual age" may be (photograph courtesy of Dr. Rüther).



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stated degree by an unstated dose of thalidomide. Later it was found that thalidomide had a sedative effect in man. In a paper by Kunz et al (1956),<sup>53</sup> the sedative action of thalidomide was also claimed to be demonstrated in mice. Strikingly enough, the report neither indicated the number of animals tested nor gave data of proper experimental controls. Moreover, some decisive experimental details were not explained in a meaningful way. The presentation of the toxicity data as well as the first clinical studies were on a similarly low level. In my opinion, the papers by Kunz et al<sup>53</sup> and by Jung (1956)<sup>54</sup> should not have been accepted for publication by the editor of a medical journal who should be aware of his responsibilities. Unfortunately, *Arzneimittelforschung* assisted in giving the green light to Grünenthal. Once the brakes were taken off, thalidomide, being a highly effective sleeping pill with amazing absence of acute toxicity even in high doses, triumphantly conquered the market (Table 1).

In the wake of its triumph, thousands of despaired and mourning parents were left with their dead or crippled children. The incidence of certain types of malformations of the limbs and ears followed the sales figures of the drug by a distance of about three quarters of a year, as is expected on biological grounds.

The hypothesis of a causative role of

Fig 5.—Phocomelia. The left hand has two fingers; the right hand, three fingers; and there was syndactyly of the third and fourth fingers. One tablet of thalidomide (100 mg) was taken on the 29th day after conception, or the 38th day after the last menstrual period. The unusually early date in relations to menstrual age is explained by the comparatively early conception (photograph courtesy of Dr. Rüther).

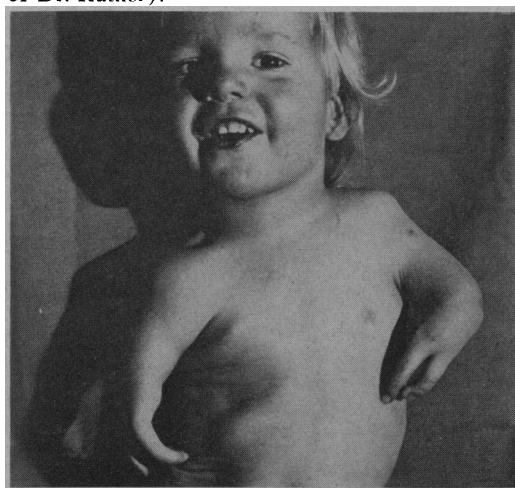


TABLE 2.—Sale of Thalidomide and Incidence of Thalidomide Cases

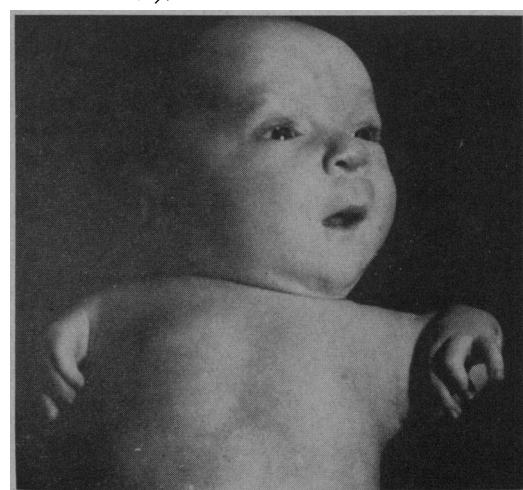
	Sale, in Kg	Thalidomide Cases
Austria	207	8
Belgium	258	26
Great Britain	5,769	349
Netherlands	140	25
Norway	60	11
Portugal	37	2
Switzerland	113	6
West Germany	30,099	5,000
United States	25?	10 + 7 *
	(2,500,000 tablets)	

\* Thalidomide obtained from foreign sources.

thalidomide has proved its predictive value when, by the end of July 1962, the wave of malformations abruptly declined all over the Federal Republic of Germany and somewhat later in those countries which had reacted less promptly to the warning.

The incidence of malformations of thalidomide type in various countries appears to be roughly proportional to their thalidomide sales (Table 2). Other variables may be involved, such as the relation between total thalidomide consumption and consumption in early pregnancy, more specifically between 35 and 50 days after the first day of the last menstrual period. In some countries, as Austria and Switzerland, pregnant women seem to be less inclined to swallow drugs than in others. There is complete lack of evidence that thalidomide would only be

Fig 6.—Phocomelia; the right hand has three fingers, the left hand has four fingers; the left femur is shorter than the right; and there is a hemangioma of the face on the nose and upper lip. A prescription of ten tablets of thalidomide (100-mg) was given on the 42nd day after the last menstrual period. In this instance, the drug is known, but the exact intake is not known (courtesy of Dr. Rüther).



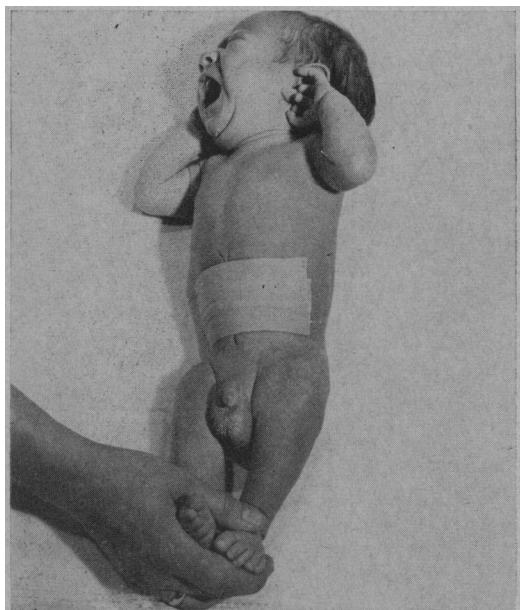


Fig 7.—Hypoplasia of the thenar eminences; triphalangeal thumbs; and shortened femurs with angulations. A prescription of thalidomide was given on the 44th day after the last menstrual period, but the intake of the drug is not exactly known.

teratogenic in certain populations or more teratogenic in some than in others. Typical thalidomide malformations have been observed in most European peoples, in Finnish Lapps, in Brazil, Argentina, Syria, Africa, Japan and Tai-Wan. Race, climate, or diet do not seem to be contributing factors.

It is difficult to express any definite opinion about the total number of thalidomide victims. Sufficiently complete and reliable figures are only available for Canada, the Netherlands, Sweden and the United States. Reasonably good estimates have also been made for Belgium, Denmark, Western Germany, Great Britain, Ireland, Norway, and Switzerland. A total figure of 7,000 cases seems to be a good, though conservative, approximation. I think it is unlikely that less than 6,000 or more than 8,000 children have been affected. The big unknowns are the numbers for Brazil, Italy, and Japan, ie, those countries which were particularly slow in withdrawing thalidomide from the market. In Japan, probably more than 1,000 children have been affected.

Some confusion has arisen by lack of attention to morphological detail. Phocomelia has, though rarely, been observed before thalidomide had been synthesized. Most previous cases of tetraphocomelia are clearly distinct from thalidomide phocomelia by

showing a cleft lip and palate, other facial malformations, and deformities of the legs different from those seen in thalidomide babies (Krüger, 1906;<sup>55</sup> and Wepler, 1937;<sup>56</sup> see also Fig 1). Another type of phocomelia, which superficially resembles thalidomide cases, has only been delineated since increased attention has been paid to limb deformities. In these cases, in contradistinction to thalidomide cases, five fingers are present, even if the radius and ulna are absent. Further diagnostic features are leukemoid changes, thrombocytopenia, and clinodactyly (Fig 2). Another condition which may be mimicked by thalidomide embryopathy is Fanconi's panmyelopathy, an autosomal recessive disorder in which absence of the thumbs and/or radii is the most characteristic malformation. Certain cases of the dominantly inherited Oram-Holt syndrome of phocomelia, aplasia or hypoplasia of thumbs, and cardiac malformation cannot be distinguished from some thalidomide cases. Many cases of a syndrome consisting of amelia of the arms, hypoplasia or aplasia of the femurs, and aplasia of the fibulae have been published since 1829 (Veiel,<sup>57</sup> Fig 3). Such cases have also been observed during and after the epidemic of thalidomide malformations, but not associated with thalidomide intake (Goerttler, 1963;<sup>58</sup> Jurczok and Schollmeyer, 1962;<sup>59</sup> and Hepp, 1962<sup>60</sup>). Recently, a syndrome of bone malformations in children of diabetic mothers has been described (Kučera et al, 1965).<sup>61</sup> In this syndrome, as in thalidomide cases, aplasia or hypoplasia of the femurs, malformations of the heart and of the kidneys, polydactylysm of the feet, and abnormalities of the coccyx may be seen. There are, however, some distinctive features. In malformed infants of diabetic mothers the arms are usually spared, whereas serious malformations of the lower spine are prominent. If one bone of the lower leg is absent in "diabetic embryopathy," it is the fibula; if one is absent in thalidomide babies, it is the tibia.

While it is not possible in each single case to infer from the type of malformations whether thalidomide is the cause, there are some patterns of malformations typical of thalidomide which had never been described before the introduction of the drug. Other types were excessively rare before, but were common during the thalidomide epidemic. In most cases, careful comparison with known thalidomide cases and with cases from

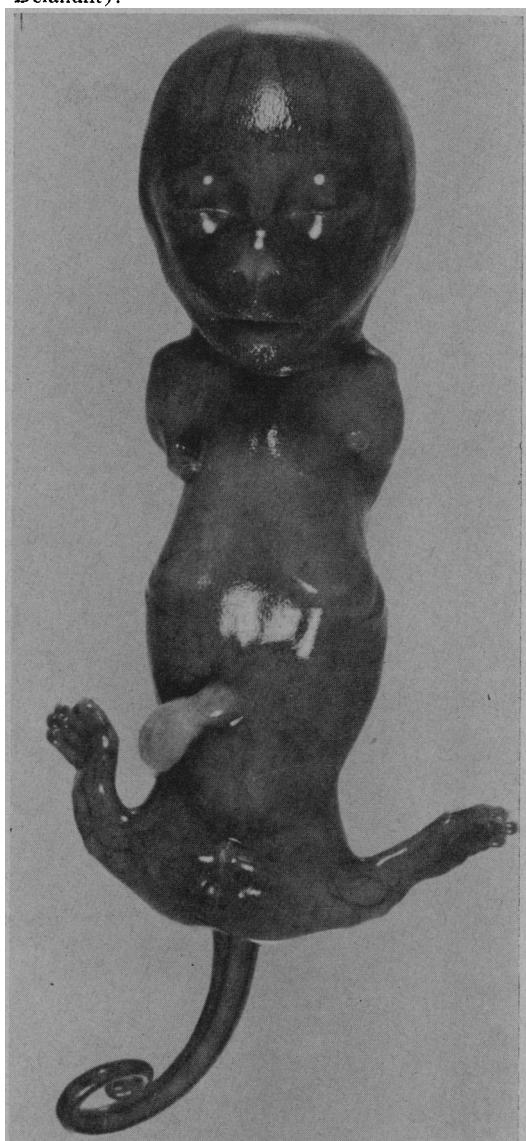
the older literature will permit a diagnostic decision.

The thalidomide embryopathy comprises a spectrum of apparently widely different types. In some children, the ears are absent, and the facial and ocular nerves are paralyzed. In others, deafness due to a gross defect of the inner ear, abducens paralysis, and preauricular appendages are the only signs. In still others, only the thumbs are absent. Phocomelia is shown only by a small percentage of thalidomide babies. Even among those cases, in which the upper extremities are affected, slight malformations of the thumbs represent the most common type. The morphological type of the malformation is essentially a function of the time of intake. No other factors have been shown to be involved by individual or by statistical studies. Some authors have assumed, though without supporting evidence, that thalidomide would cause malformations only in certain genotypes. This assumption is difficult to prove or to disprove. Binocular twins are, as a rule, likewise affected. If, as exceptionally occurs, only one twin is affected, his malformations are of a type attributable to thalidomide action at the very beginning or at the very end of the sensitive period. If organ development in the other twin were a few days retarded or accelerated in comparison to his affected twin, malformations would not be expected, because he would not have been exposed to thalidomide in the sensitive period of organ development, which is sharply limited.

Twin studies as well as the high risk revealed by infants born to mothers who before delivery said that they had taken thalidomide, show, that if there is any genetic predisposition, it is shared by most people. It has not been excluded, that every human embryo is genetically predisposed to the teratogenic action of thalidomide. Only a few family studies of thalidomide babies have been reported, and none of these showed any familial aggregation of related or similar malformations. I have collected data on 247 sibs of thalidomide babies. Among these, there were one case each of knock-knee, inguinal hernia, spina bifida, and cleft lip, and four cases of congenital abnormalities of the heart, but no cases of malformations of the extremities. Cardiac abnormalities are in excess of expectation; other malformations are not. The explanation is probably not to

be sought in a common hereditary tendency to cardiac and to thalidomide malformations. Heredity is of minor importance in cardiac abnormalities, and if heredity is involved, it is specific. Limb deformities are not more frequently found in sibs of children with congenital disease of the heart than in the general population. A more plausible explanation of the relatively high number of cardiac malformations among the sibs of thalidomide children is suggested by the even higher incidence of sudden deaths among the siblings, due to accidents, tumor, appendicitis, etc. The mental strain of mothers whose children are chronically sick or who have

Fig 8.—Thalidomide malformations in *Macaca irus philippensis* (photograph courtesy of Dr. Delahunt).



died often induced them to take thalidomide as a sedative.

As thalidomide is not metabolized enzymatically, but rather hydrolytically split in any aqueous solution, pharmacogenetic problems are probably not present, although motility of the intestine, pH of the intestinal content, or food ingredients binding thalidomide might be factors influencing the rate of absorption from the intestines of that highly insoluble compound.

By analyzing well-documented cases in which the time of intake is exactly known, it has been possible to construct a timetable of thalidomide embryopathy (Fig 4, 5, 6, and 7). This timetable is strikingly consistent. All cases with reliably documented intake follow the same pattern with surprisingly little scatter. Similar cases collected from the German, Dutch, Danish, Japanese, Finnish, Swiss, Swedish, and French literature show the same pattern (Nowack, 1965).<sup>62</sup>

There are several cases on record of mothers who said they have taken thalidomide during the sensitive period and yet produced perfectly normal babies. None of these cases has been documented reliably enough to exclude any doubts. Though no valid and extensive data are available, the risk of a malformation, if thalidomide has been taken between 35 and 50 days after menstruation, is probably higher than 50%. Even a 100% risk has not been strictly excluded. In experiments on monkeys, Delahunt<sup>63</sup> has so far found a 100% risk (Fig 8). Estimates lower than 50% are almost certainly due to inaccuracies in the time data or to erroneously equating early pregnancy and the sensitive period.

The thalidomide tragedy has broader implications than its scientific aspect as an experiment in human teratology. It has served to demonstrate dramatically what the consequences may be, if the release of a drug and the control of its action gets out of hand of responsible men in the medical profession. The doctor who treats his patients cannot be relieved from his moral responsibility in regard to drug effects neither by any state authority nor by the pharmaceutical industry. The doctor's fundamental and inalienable responsibility implies, however, not only his right, but his duty to ask questions; and he is entitled to expect honest answers from the pharmaceutical firms, even if his questions may not sound agreeable to those who are more accustomed to think in terms of profit

than of human suffering. Only the whole truth and nothing but the truth is an acceptable answer in face of the thalidomide tragedy. There is no other way than complete mutual honesty to restore between the medical profession and the pharmaceutical industry that confidence which is vital to the interests of both.

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#### Generic and Trade Names of Drugs

- Aminosalicylic acid—Pamisyl, Para-Pas, Parasal, Proposa, Resipas.
- Busulfan—Myleran.
- Cortisone—Cortogen, Cortone.
- Cyclophosphamide—Cytoxan, Endoxan.
- Isoniazid—INH, Niconyl, Nidrazid, Tyvid.
- Meclizine hydrochloride—Bonadettes, Bonine Hydrochloride, Bonamine.
- Thalidomide—Kevadon.
- Tolbutamide—Orinase.

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