may not always be desirable to instil fluid into the bladder. If chlorhexidine solution is instilled its concentration should not exceed 1/5,000, since there is some evidence that stronger solutions—for example, 1/1,000—may irritate the bladder mucosa (Paterson *et al.*, 1960). Both procedures should therefore be of practical value and preferable to the prophylactic administration of systemic antibiotics, which is likely to breed drug-resistant pathogens.

Summary

Two methods of preventing urinary infection after catheterization of female patients have been investigated. Disinfection of the urethra prior to catheterization, by means of a lubricant containing chlorhexidine, was moderately effective against Gram-negative bacilli but not against *Streptococcus faecalis*. The instillation of chlorhexidine solution into the bladder after catheterization was very effective against all species of organisms encountered.

We are grateful to the Medical Research Council and to the Research Committee of the United Bristol Hospitals for grants which enabled us to do this work. We also thank Mrs. B. B. Lennon and Mr. G. H. Darling for help and advice; Dr. J. M. Simister, of Ward, Blenkinsop & Co., for generous supplies of penotrane jelly and urethral syringes; the clinicians who allowed us to study their patients; and the nursing staffs for their willing assistance.

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INCIDENCE OF MALFORMATIONS SINCE THE INTRODUCTION OF THALIDOMIDE

BY

IAN M. LECK, Ph.D., M.B., Ch.B.
 Lecturer in Social Medicine

E. L. M. MILLAR, M.D., M.Sc., D.P.H.
 Medical Officer of Health, Birmingham; Lecturer in Public Health

Department of Social Medicine, University of Birmingham

Material

Several recent reports indicate that administration of thalidomide ("distaval") in early pregnancy may be followed by the birth of a malformed child. Most of the affected children have had reduction deformities of the limbs, sometimes associated with malformations of the ears, eyes, or viscera (McBride, 1961; Burley, 1962; Ferguson, 1962; Lenz, 1962a, 1962b; Morgan, 1962; Pfeiffer and Kosenow, 1962a, 1962b; Rogerson, 1962; Russell and McKichan, 1962; Stabler, 1962; Willman and Dumoulin, 1962). These defects have become much commoner since the introduction of thalidomide (Lenz, 1961; Wiedemann, 1961; Pfeiffer and Kosenow, 1962a, 1962b; Watson, Slater, and McDonald, 1962), and the combined results of five inquiries in the United Kingdom and Germany show that the drug was taken during pregnancy by mothers of at least 55 of 71 affected children (Lenz, 1961; Devitt and Kenny, 1962; Dunn, Fisher, and Kohler, 1962; Jones and Williamson, 1962; Speirs, 1962). Experimental evidence is also available: if pregnant rabbits are given a large dose of thalidomide similar malformations occur in a high proportion of the offspring (Somers, 1962).

The observations so far reported have been obtained by *ad hoc* inquiry, and it has not been possible to assess in a defined population of births either (a) the extent of the increase in frequency of reduction deformities of the limbs, or (b) whether the incidence of other malformations has also increased. In the present communication we attempt to provide this information using data for all Birmingham births in the five years 1957–61. This period was chosen because thalidomide was first marketed in the United Kingdom in April, 1958, and used increasingly during the next three years. As a result the risks of exposure to thalidomide in early intrauterine life were practically non-existent for children born in 1957–8, but increased steadily thereafter.

Data were recorded for two groups of children born in 1957–61: those who were stillborn or who died before the end of 1961 while resident in Birmingham, and those living in Birmingham at the end of 1961. Our sources of information about stillbirths and dead children were: (1) the records kept by the Public Health Department, including information obtained from birth histories, death certificates, and necropsy reports; and (2) the original necropsy reports of a few children whose other records were insufficiently precise. Details of survivors were obtained by requesting all health visitors in the city to furnish particulars of living malformed children on their lists.

A comparison with earlier results (McKeown and Record, 1960) suggests that there was reasonably complete ascertainment of all serious external malformations except cleft lip and palate. This deficiency was corrected by scrutinizing lists of patients treated for cleft lip and palate in local hospitals.

Reduction Deformities of Limbs

Table I shows the number of reduction deformities of the limbs that occurred in each year. There were four instances of sirenomelia (fusion of the lower limbs). This defect is quite different from the others in appearance, and has not become commoner. Eleven children had reduction deformities of the thumbs or radii. These defects often occur together (Potter, 1952), and as they are sometimes associated with thrombocytopenia and Fanconi's anaemia (Nilsson and Lundholm, 1960) they are regarded as aetiologically distinct from the other reduction deformities listed, which do not exhibit these associations. Seven of the 11 instances of radial and thumb defects occurred in 1958. A fuller account of them will appear elsewhere (Leck and Millar, 1962).

TABLE I.—Numbers of Reduction Deformities of the Limbs Among Total Births to Birmingham Residents, 1957–61

Type of Malformation	Year of Birth				
	1957	1958	1959	1960	1961
Sirenomelia	—	2	1	1	—
Reduction deformities limited to thumbs and/or radii:					
Bilateral	1	2	1	—	—
Unilateral	—	5	1	—	1
Other reduction deformities:					
Affecting all limbs	—	1	—	1	2
Limited to both upper limbs	—	—	—	2	4
Limited to both lower limbs	—	—	—	1	1
Limited to one upper and one lower limb	1	—	1	—	—
Limited to one upper limb	2	3	3	4	2
Limited to one lower limb	—	1	1	2	2
Total affected	4	14	8	11	12
Total births	19,322	19,714	19,770	21,198	22,038

Other reduction deformities of the limbs were present in 34 children. In two of them one arm and one leg were affected, and 20 had defects limited to a single limb. There is no evidence of an increase in incidence of either of these types of defect. Both arms or both legs were affected in eight children, and all four limbs in four. One of these 12 children with bilateral defects was born in 1958, four in 1960, and seven in 1961. These figures suggest that the rise in the incidence of reduction deformities in recent years is exhibited only by those that are bilateral. This conclusion is supported by the fact that in the nation-wide survey conducted by the College of General Practitioners the notification rate for ectromelia affecting more than one limb has risen since 1958, whereas the rate for other cases of ectromelia has not (Watson *et al.*, 1962).

As our concern in this paper is with those reduction deformities that have become more common, we shall now restrict attention to the 12 bilateral cases. Particulars of these are given in Table II. In 10 of them (Cases 2–10 and 12) the reduction deformities were severe and affected some segments of the limbs more than others, like those described in association with thalidomide. In Case 1 the limbs were all short, but the shortening was less extreme and there was no disparity between limbs or segments of limbs. In Case 11, the only reduction deformities were those exhibited by four fingers.

TABLE II.—Children with Bilateral Reduction Deformities of the Limbs (Excluding Sirenomelia; Radial and Thumb Defects)

Case No.	Date of Birth	Sex	Limb Malformations	Other Malformations	Survival
1	9/5/58	F	All limbs short but complete. 6 digits on each limb	Hydrocephalus. Hypoplasia of kidneys. Absence of ureters. Bladder solid. Urethral, vaginal, and anal atresia	Stillborn
2	12/3/60	F	Legs terminating immediately below knees	Ventricular septal defect. Absence of urinary tract, uterus, external genitalia, rectum, and anus. Duodenal stenosis. Meckel's diverticulum. Unfixed mesentery. Anomaly of lumbosacral spine. Absence of left half of pelvis. Ears low-set	"
3	24/8/60	F	Absence of arms. Small hands attached to shoulders	—	Alive
4	8/9/60	M	Arms immobile at shoulders and very short. No hands. One digit on each arm	Telangiectasis and microgyria of temporal lobes	Died aged 7 months
5	6/11/60	F	Absence of left arm. Right arm vestigial. Lower limbs grossly defective	Bilateral anophthalmos. Left megalo-ureter. Bicornuate uterus. Absence of vagina. Duodenal atresia. Absence of appendix	Stillborn
6*	25/4/61	M	Absence of arms. Primitive hands attached to shoulders, with 3 digits on left, 2 on right	—	Alive
7*	25/4/61	M	Shoulders maldeveloped. Absence of arms. Primitive hands attached to trunk, with 3 digits on left, 4 on right	—	"
8	11/5/61	F	Absence of arms. 3 digits on each shoulder	—	"
9	16/6/61	M	Legs terminating at knees. 3 digits on each leg	—	"
10	15/9/61	M	Absence of scapulae, arms, and legs. Primitive hands and feet attached to trunk. 2 digits on left hand, 3 on right hand, 6 on left foot	Coloboma of right eye. Absence of left kidney. Atonia of large intestine	Died aged 6 months
11	25/9/61	M	3rd, 4th, and 5th digits of left hand and 2nd digit of right hand replaced by skin tags. Ring constriction above right ankle	—	Alive
12	30/10/61	F	Absence of both upper limbs, excepting one digit on right shoulder. Absence of left thigh and right shin. 6 digits on right foot	Hypoplasia of left kidney. Hydronephrosis of right kidney. Duodenal stenosis and diverticulum	Died aged 2 days

* Cases 6 and 7 are dizygotic twins (Dunn *et al.*, 1962).

Three of the 12 children were stillborn, three died later, and six were alive at the time of writing (April, 1962). Internal malformations were found in all those who died, but have not so far been reported in any of the survivors.

In Fig. 1 the number of affected births in each four-month period is related to the amount of thalidomide sold to Birmingham wholesalers in the corresponding period of the previous year. The amounts sold have been expressed as percentages instead of as absolute figures, at the request of the manufacturers. In assuming that a year would elapse between the sale of a consignment of thalidomide and the birth of children affected by it, we have taken account of the time taken for the drug to pass from the wholesaler to the patient, as well as the interval (probably about eight months) between its administration and the birth of an affected child. Fig. 1 indicates that with the exception of Case 1 (which was shown above to differ morphologically from the others) the affected births all occurred after the

FIG. 1.—Frequency of affected births (histogram) compared with the supply of thalidomide to the Birmingham area one year earlier (continuous line).

introduction of thalidomide, and their frequency tended to increase with the amount of thalidomide supplied to the area.

We did not attempt to establish whether thalidomide had been taken in individual cases, since it was felt that information obtained so long after the event would be unreliable. However, a history of its administration during early pregnancy was obtained in respect of two mothers (Cases 10 and 12) included in another inquiry (Dunn *et al.*, 1962).

There are two discrepancies between our findings and some earlier reports. First, the introduction of thalidomide was not followed by an increase in frequency of reduction deformities limited to the thumbs and radii, which have apparently become commoner in West Germany (Lenz, 1961, 1962a; Wiedemann, 1961). Speirs's (1962) report suggests that radial and thumb defects associated with other reduction deformities may follow the administration of thalidomide.

The second discrepancy is between Speirs's series and our own. In 1961 he observed nine infants with bilateral deformities in about 3,000 births in Stirlingshire, as compared with seven in approximately 22,000 births in Birmingham. The lower figure does not seem to be due to incomplete ascertainment, since our survey did not miss any of six cases subsequently mentioned to us by colleagues. Probably the difference is due to greater use of thalidomide in Stirlingshire than in Birmingham. In April–September 1961, thalidomide consumption per head was twice as high in Scotland as in the West Midlands (D. M. Burley, 1962, personal communication), and Speirs inferred that it was higher in Stirlingshire than in most of Scotland.

Data collected by the manufacturers suggest that thalidomide sales to Birmingham before the end of 1960 accounted for about 1.2% of the total supplied to the United Kingdom. If the frequency of births affected by thalidomide is proportional to the amount consumed, the 10 Birmingham children with characteristic deformities (Cases 2–10 and 12) may therefore constitute about 1.2% of the number affected in the United Kingdom. The total number to be expected on this assumption would be about 800, about half of whom might survive and require expert attention and training. As the drug was not withdrawn from sale until December, 1961, some of those affected will not be born until the second half of 1962.

In West Germany, where thalidomide could be bought without a prescription and was used more than in Britain, Weicker and Hungerland (1962) estimated that at least 4,000 affected children had been born before the end of 1961.

Other Malformations

A number of other malformations have been described in association with reduction deformities of the limbs during the recent epidemic. A list of those reported in more than one patient is given in Table III, with estimates of the numbers described (a) in Cases 2–12 of the present series, and (b) in the reports quoted earlier. The figures from the earlier reports are minimal estimates, since some authors did not give the numbers affected, and others referred to unspecified alimentary, cardiac, and genito-urinary malformations. Haemangiomas, which have been reported several times, are not listed because they are not always congenital.

In an attempt to determine whether thalidomide can cause the malformations listed in Table III without stunting the limbs, we have examined (Table IV) the incidence of these defects in children whose limbs did not show reduction deformities of the type ascribed to thalidomide. As talipes and hydrocephalus are much

TABLE III.—*Other Malformations Reported in Association with Reduction Deformities of the Limbs During Recent Epidemic*

Malformation	No. Affected	
	In Present Series (Cases 2–12)	In Other Series (Minimal Estimates)
<i>External malformations</i>		
Musculo-skeletal :		
Polydactyly	2	2
Talipes	—	3
Special sensory :		
Anophthalmos, microphthalmos	1	2
Coloboma	1	1
Anotia, microtia	—	2
Accessory auricles	—	2
<i>Internal malformations</i>		
Alimentary :		
Oesophageal atresia	1	2
Duodenal atresia	1	3
Duodenal stenosis	2	9
Agenesis of appendix	1	3
Abnormally lax mesentery	1	1
Distonia of large intestine	1	2
Anal atresia	1	4
Cardiac : Ventricular septal defect	1	1
Genito-urinary :		
Renal agenesis, hypoplasia	3	2
Hydronephrosis, hydroureter	2	2
Vaginal atresia	2	1
Neural : Hydrocephalus	—	2
Respiratory : Choanal atresia	—	2

TABLE IV.—*Annual Incidence in Birmingham of Individuals with Malformations Listed in Table III. Cases 2–12 (Table II) are Excluded*

Group	Incidence of Affected Individuals (per 1,000 Total Births)				
	1957	1958	1959	1960	1961
External malformations in all births :					
Talipes	1.8	1.5	2.7	1.5	1.7
Other	0.4	0.5	0.2	0.2	0.5
Internal malformations in stillbirths and neonatal deaths :					
Hydrocephalus	1.7	1.9	1.4	1.3	1.0
Other	0.9	2.2	1.8	1.4	1.2

commoner in the general population than the other types of defects specified in Table III, they are listed separately.

Many instances of the external malformations specified in Table III are relatively trivial and require no treatment after the neonatal period. Most cases of this kind were probably forgotten and not notified to us, especially if birth took place early in the five-year period. Nevertheless neither talipes nor the other external malformations were reported more frequently in births at the end of the period than at the beginning. It is concluded that there has been no real increase in the incidence of these conditions.

Internal malformations are also sometimes overlooked, especially in the very young. Agenesis of the appendix, for example, causes no symptoms and is not discovered until the abdomen is opened for other reasons, and ventricular septal defect may be diagnosed after infancy. It follows that as children born in different years were not of the same age at the time of the present survey they are not comparable in respect of the incidence of all ascertained internal defects. For this reason the figures for internal malformations given

in Table IV relate only to instances in which stillbirth or neonatal death occurred. Both the figures for hydrocephalus and those for the other internal malformations show steady declines since 1958. Improvements in survival due to advances in treatment may have contributed, but are unlikely to have been great enough to mask an increase in total incidence.

Anencephalus, spina bifida, exomphalos, and clefts of the lip and palate—which are the commonest severe malformations readily recognized at birth—have not been reported to follow the administration of thalidomide. We have, however, examined their incidence (Table V), since ascertainment was reasonably complete. This table indicates that they have not become appreciably commoner since the introduction of thalidomide. The most striking variation in incidence during the period was in respect of cleft palate not associated with cleft lip. This was more than twice as common in 1958 as in any other year. This variation cannot be related to the administration of thalidomide.

Our data therefore suggest that in children with fully formed limbs the incidence of malformations has not increased since the introduction of thalidomide. It may be concluded that thalidomide can produce reduction deformities of the limbs alone or in association with other malformations, but that it is not usually a cause of other malformations occurring alone. Presumably the limb buds of the embryo are more susceptible than the viscera to the effects of the drug.

Comparable variations in susceptibility have been observed in rodent embryos with respect to deficiencies of riboflavin (vitamin B₂). When female rats are reared on a riboflavin-deficient diet, they generally produce offspring with skeletal malformations, including abnormally short limbs, syndactyly, and cleft palate; soft-tissue malformations are rare (Warkany, 1947). If pregnant rats are given galactoflavin (a riboflavin antagonist) a more severe deficiency occurs, and many of the offspring exhibit hydrocephalus, microphthalmos, ventricular septal defects, hydronephrosis, and a few other visceral anomalies, as well as skeletal defects (Nelson, Baird, Wright, and Evans, 1956). In mice, galactoflavin produces similar skeletal defects in association with hydrocephalus and oesophageal atresia (Kalter and Warkany, 1957). The response of the rodent embryo to riboflavin deficiency therefore appears to resemble that of the human to thalidomide in respect of the types of malformations produced and the fact that the skeleton is more susceptible than the viscera. A deficiency of nicotinamide (which participates in the same metabolic processes as riboflavin) produces similar skeletal defects in rodents (Murphy, Dagg, and Karnofsky, 1957; Pinsky and Fraser, 1960); its effects on rats also include hydrocephalus and malformations of the eyes, heart, and genito-urinary system (Chamberlain and Nelson, 1962).

TABLE V.—Annual Incidence in Birmingham of Individuals with Common Severe Malformations Readily Ascertained at Birth

Malformation	Incidence (per 1,000 Total Births)				
	1957	1958	1959	1960	1961
Craniorachischisis, anencephalus ..	3.1	2.6	2.8	2.1	2.3
Spina bifida, cephalocele ..	2.5	2.7	2.3	3.0	1.8
Exomphalos ..	0.3	0.6	0.4	0.3	0.7
Cleft lip (with or without cleft palate) ..	1.2	1.3	1.0	1.1	1.5
Cleft palate (without cleft lip) ..	0.4	1.2	0.5	0.5	0.3

One difference between malformations due to thalidomide and those caused by deficiencies of riboflavin and nicotinamide is that thalidomide does not appear to cause cleft palate.

In view of the similarities between the teratogenic effects of vitamin-B deficiencies and thalidomide, it is of interest that some patients receiving thalidomide in large doses develop glossitis and other oral lesions, which respond to treatment with vitamin-B complex. The lesions closely resemble those found in vitamin-B deficiencies, and the same may be true of the neuropathies which thalidomide sometimes causes (Robertson, 1962). These findings suggest that thalidomide may interfere with the metabolism of riboflavin or another vitamin of the B group.

A comparison of the formulae of riboflavin and thalidomide (Fig. 2) indicates that both have the sequence $-\text{CO.NH.CO}-$. The NH group is one point at which the coenzymes which contain riboflavin combine with their apo-enzymes (Horwitt, 1954). It therefore seems conceivable that thalidomide produces

FIG. 2.—Formulae of riboflavin and thalidomide. The $-\text{CO.NH.CO}-$ sequence is shown at the top of each formula.

its toxic effects, both in the embryo and in the adult, by competing with riboflavin-containing coenzymes for attachment to their apo-enzymes. There is, however, little overall similarity between the two formulae, so it is perhaps more likely that thalidomide inactivates one of the B vitamins by combining with it. In either case the effects would be those of vitamin-B deficiency.

Summary

The incidence of various malformations in Birmingham children born in 1957–61 was examined for secular changes.

Bilateral reduction deformities of the limbs have become commoner since the introduction of thalidomide in 1958, but unilateral deformities show no increase. Ten children, all born in 1960 or 1961, had bilateral defects of the type previously described in association with thalidomide, and five of them survived. It is estimated that in the United Kingdom similar defects may have occurred in about 800 children.

In children without reduction deformities of the limbs the incidence of other malformations does not seem to have risen.

There are several similarities between the toxic effects of thalidomide and those of vitamin-B deficiencies.

Most of the data used in this inquiry were collected or abstracted from existing records by Mrs. Eileen Armstrong, Miss Ann Cooper, Miss Ida Giles, Mrs. Betty Mann, and the health visitors of the City of Birmingham, with the help of Miss Milner, Miss Greening, and Miss Cook. Hospital and necropsy records were made available to us by Mr. O. T. Mansfield, Dr. K. W. Cross, the pathologists and records officers of local hospitals, and the City of Birmingham Coroner. Particulars of distaval sales were supplied by Dr. D. M. Burley, of the Distillers Co. (Biochemicals) Ltd. We are grateful to all these people for their ready co-operation.

ADDENDUM.—Since this paper was submitted data have been published by W. Lenz and K. Knapp (*Dtsch. med. Wschr.*, 1962, 87, 1232), G. Pliess (*Lancet*, 1962, 1, 1128), and R. W. Smithells (*Lancet*, 1962, 1, 1270) which indicate that syndactyly, dislocation of the hip, intestinal malrotation, biliary atresia, absence of the gall-bladder, horseshoe kidney, bicornuate uterus, and abnormal lobulation of the lungs and liver should be added to our list (Table III) of malformations which may occur in association with stunted limbs after the administration of thalidomide. Our data suggest that the incidence of these additional malformations in children with limbs of normal size has not risen recently. The reports of Lenz and Knapp and of Smithells also show that microtia is an exception to our generalization that thalidomide does not usually cause malformations in children with normal limbs. In their series most of those affected had stunted limbs, but between a sixth and a twelfth had limbs of normal size and microtia. Our data are consistent with this finding: absence of the auricle or external auditory meatus was notified in three Birmingham births in 1961 and none in 1957–60.

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STUDIES ON EFFECT OF
D-THYROXINE ON NORMAL SUBJECTS

BY

R. BARNES, M.B., B.S.

J. A. P. TRAFFORD, M.B., M.R.C.P.

AND

P. M. F. BISHOP, D.M., F.R.C.P.

Guy's Hospital, London

Clinical trials of various preparations of D-thyroxine have been undertaken in patients with myxoedema, coronary artery disease, and hypercholesterolaemia (Greene and Farran, 1958; Starr *et al.*, 1960; Greene *et al.*, 1961; Oliver and Boyd, 1961) which have shown that it is possible to produce a sustained depression of serum cholesterol level with no change of the basal metabolic rate or E.C.G. Few reports of the response of normal individuals to sodium D-thyroxine have appeared in this country. The present communication is a report on the effect of this compound on the blood cholesterol level and thyroid function of "normal" subjects—that is, individuals not suffering from myxoedema, coronary artery disease, or hypercholesterolaemia.

Material and Methods

Fifty-five euthyroid individuals volunteered to take part in the trial, which was conducted "double blind," in order to assess the significance of any possible side-effects which might have suggested that the compound has calorogenic properties. The subjects were given either a 4-mg. tablet of D-thyroxine twice a day or a placebo tablet of identical appearance. Fifty-one subjects completed the trial. Before and after one month's tablet administration the basal metabolic rate was determined in 38 according to our modification of the method of Robertson and Reid (1952) and the percentage of ¹³¹I uptake was measured in 32 by the method of Fields and Seed (1957). Only four subjects in each group ("treated" and "placebo") had their serum protein-bound iodine level estimated (method of Grossman and Grossman, 1955). It was not known to us, of course, which patients were given D-thyroxine and which the placebo until the end of the trial, when it transpired that 32 subjects received D-thyroxine and 19 the placebo. Blood cholesterol estimations were performed (method of Zlatkis *et al.*, 1953) immediately before and after the 28-day tablet administration in every case. (The normal range in the department of clinical pathology at Guy's Hospital, where these estimations were carried out, is 150–300 mg./100 ml.)

Most of the subjects were taken at random from the endocrine clinic and no weight-reducing diet was recommended during the period of the trial in those who were obese. The volunteers were not told the exact nature of the tablet nor of any possible side-effects, but were asked at the end of the trial whether they had noticed any untoward effects and were questioned in particular concerning the occurrence of increased sweating, palpitations, angina, or nervousness. No patient complained of any side-effect or complication.

Results

The results obtained with D-thyroxine (32 cases) and with the placebo (19 cases) are set out in the Table.