EXAMINATION OF THE INCIDENCE OF MALFORMATIONS
 FOR EVIDENCE OF DRUG TERATOGENESIS*

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The discovery that thalidomide can cause human malformations has been followed in recent years by a large number of reports of malformations in the offspring of women who have taken other drugs in pregnancy. But it has remained uncertain whether any of these drugs are teratogenic, since those reporting on them have not been in a position to relate their findings to the distribution of malformations in the general population.

There are two reasons why population data are needed for the interpretation of associations between drugs and malformations. Firstly, the relative frequencies of the different types of defects in the general population need to be compared with those in affected children born after exposure to the drug in question; if teratogenic, it is likely to cause only a few specific types of defects, which will therefore be present in an abnormally high proportion of the exposed group. Secondly, comparisons between the population incidence of malformations at different times are needed to detect or exclude the changes that are likely to occur if any drug which is being used increasingly has teratogenic properties. These changes may be either prolonged trends or short-term fluctuations. If a drug is used to treat endemic conditions such as anxiety or morning sickness, its output is likely to rise gradually as it becomes more widely known, and consequently any related increase in the malformation rate is also likely to be prolonged. Short-term fluctuations in incidence may occur if a teratogen is being used in the treatment of epidemic diseases (of which the commonest in pregnancy is influenza).

In three previous reports (Leck and Millar, 1962, 1963; Leck, 1963) we examined the incidence of certain malformations in Birmingham for short-term fluctuations between 1957 and 1961, and found

some evidence of increases following influenza epidemics. In the present communication, the same data, extended to include births in 1962-63, are examined for prolonged trends, and also used as a standard with which to compare the relative frequencies of different types of malformations in affected children born after exposure to meclozine, a drug which several workers (*e.g.* Watson, 1962; Pettersson, 1964) have suspected of teratogenicity. As there was an outbreak of influenza at the beginning of 1962, the possibility of a repetition of the increases in incidence observed after earlier epidemics is also examined.

MATERIAL AND METHODS

At the close of each of the last three years (1961-63), data on malformed children born during the year and resident in Birmingham at the time of death or survey have been obtained from necropsy reports and other Local Authority records of stillbirths and dead children, and from health visitors and lists of hospital admissions. The 1961 survey (which also included births in 1957-60) was described by Leck and Millar (1963); during the period covered by this survey 102,042 children (including stillbirths) were born to parents resident in Birmingham at the time. The number resident at the time of death or survey (including immigrants) was rather smaller, and similar discrepancies are a feature of the population figures for 1962-63 (Table I).

TABLE I
 BIRMINGHAM RESIDENTS BORN IN 1962-63

Group		Year of birth	
		1962	1963
Number resident at birth		22,699	22,759
Number resident at time of death or survey	Stillborn	432	430
	Died	433	451
	Alive	20,914	20,983
Total		21,779	21,864

* This inquiry was assisted by a grant from the Association for the Aid of Crippled Children, New York.

The 1961 survey was restricted to types of malformations in respect of which the methods used were thought likely to give fairly complete ascertainment; but, when the records of deaths and hospital admissions in 1962-63 were searched, several hitherto unknown cases of these defects were ascertained in children born in 1957-61. Almost all these children had hydronephrosis, hypospadias, cleft lip, or cleft palate. Most of those with hydronephrosis or hypospadias were more than a year old at the time of the original survey and, as there seems to be no practicable way of ascertaining all cases of these defects in infancy, they will not be considered further. There were six new cases of cleft lip (one born in 1959, one in 1960, and four in 1961) and four of cleft palate without cleft lip (one born in 1957 and three in 1961); as most of these children were only a few months old at the time of the 1961 survey, it was probably because they were too young to have been admitted to hospital that they were not ascertained from in-patient records at that time. To minimize this source of error, hospital waiting lists as well as in-patient records were examined in the most recent survey, and cases listed in the first half of 1964 as well as in 1963 were included.

The only other 1957-61 cases ascertained since the first survey were two with spina bifida (born in 1959 and 1960) and single cases of anal atresia (1960), radial agenesis (1961), and diaphragmatic hernia (1961).

TOTAL INCIDENCE

147,500 children (including stillbirths) were born to Birmingham residents in 1957-63, and the frequency of malformations in this population is examined in Table II. Basic data for 1957-61 are not included since they were given by Leck and Millar (1963). As in the earlier paper, incidence was estimated on the assumption that the malformation

rates observed in children living in the city at the time of survey applied also to the rather larger number who were resident at birth and not known to have died. The estimates of incidence for 1957-61 differ slightly from those published earlier, since they include cases ascertained since 1961 and exclude two instances of spina bifida occulta (a survivor born in 1958 and a 1961 stillbirth).

From the estimates of incidence for 1957-63 given in the last column of Table II, the expected distribution of defects in a sample of thirteen malformed children was calculated, and compared (in Table III) with the distribution observed in the thirteen British children with defects of these types reported to have

TABLE III

NUMBER OF MALFORMATIONS OF EACH TYPE REPORTED IN THIRTEEN AFFECTED BRITISH CHILDREN BORN AFTER THE TAKING OF MECLOZINE IN PREGNANCY, COMPARED WITH THE NUMBERS EXPECTED IF THE DISTRIBUTION OF MALFORMATIONS IN SUCH CHILDREN WAS THE SAME AS IN ALL BIRMINGHAM BIRTHS.

Type of Malformation		Number of Cases	
		Reported	Expected
Neural	Anencephalus	2	3.5
	Spina bifida, etc. ..	5	4.1
Alimentary	Cleft lip	—	1.8
	Cleft palate	2	0.9
	Oesophageal atresia, etc. ..	—	0.5
	Anal atresia	1	0.5
Limb Deficiencies	Amelia, phocomelia ..	1	0.2
	Transverse terminal defects	—	0.3
	Defects limited to thumbs and/or radii ..	1	0.2
Other	Exomphalos	—	0.7
	Diaphragmatic hernia (not hiatal) ..	—	0.6
	Bilateral renal agenesis, etc. ..	1	0.5

TABLE II

INCIDENCE OF MALFORMATIONS (per 1,000 total births) IN BIRMINGHAM, 1957-63

Type of Malformation		1957-61 Incidence	1962			1963			Total Incidence
			Number		Incidence	Number		Incidence	
			Dead	Alive		Dead	Alive		
Neural	Anencephalus	2.58	32	—	1.41	39	—	1.71	2.26
	Spina bifida aperta, cephalocele (without anencephalus)	2.73	33	18	2.28	26	29	2.47	2.62
Alimentary	Cleft lip	1.28	6	19	1.14	1	14	0.69	1.17
	Cleft palate (without cleft lip)	0.60	2	13	0.69	2	10	0.55	0.61
	Oesophageal atresia, tracheo-oesophageal fistula	0.39	2	1	0.13	5	3	0.36	0.34
	Anal atresia	0.33	4	2	0.27	6	5	0.49	0.35
Limb Deficiencies	Amelia, phocomelia	0.11	1	2	0.14	—	—	—	0.10
	Transverse terminal defects*	0.17	—	4	0.18	—	5	0.23	0.18
	Defects limited to thumbs and/or radii	0.14	—	1	0.05	2	1	0.13	0.13
Other	Exomphalos	0.47	9	2	0.49	6	—	0.26	0.44
	Diaphragmatic hernia (not hiatal)	0.40	11	2	0.58	4	1	0.22	0.40
	Bilateral renal agenesis or hypoplasia	0.34	8	—	0.35	6	—	0.26	0.33
All Individuals with One or More of the Above		8.92	99	63	7.26	86	68	6.89	8.35

* Excluding defects limited to fingers or toes

been born after the administration of mectozine (Carter and Wilson, 1962; Fagg, 1962; Macleod, 1962; Watson, 1962; Salzmann, 1963; Smithells and Chinn, 1963, 1964). Comparison of the two sets of figures does not suggest that any particular type of malformation occurs especially often after the taking of mectozine. There is no other drug (apart from thalidomide) in respect of which enough British

cases of malformations have been reported to warrant such an analysis of the types of defects concerned.

PROLONGED TRENDS IN INCIDENCE

In order to demonstrate whether the incidence of any defect showed a prolonged trend, separate rates were computed for three periods: 1957-59, 1960-61, and 1962-63. The first period was made longer than the others because the birth rate was lower at that time. The rates for each period are shown in the Figure, together with the results of χ^2 tests applied to the rates for each malformation.* According to

* The numbers of malformations used in the χ^2 tests were those actually observed. They did not include cases in children removed from the city and were thus related in most instances to populations rather smaller than the total number of city births. These populations were estimated by dividing the observed numbers of malformations by the rates shown in the Figure (which like those in Table II are corrected for children leaving the city).

FIGURE.—Secular changes in incidence of malformations in Birmingham, 1957 to 1963.

these tests the decrease shown by anencephalus and the 1960-61 peak in the incidence of amelia and phocomelia were very highly significant. With these exceptions the most marked changes were those in respect of cleft lip and defects of the thumbs and radii, and each of these changes was practically confined to a single year: the incidence of radial and thumb defects was greatly increased in 1958 (Leck and Millar, 1963) and the rate for cleft lip was particularly low in 1963 (Table II).

The fluctuation shown by amelia and phocomelia is broadly similar in form to that exhibited by the output of thalidomide 9 months earlier (Leck and Millar, 1962; Smithells and Leck, 1963), and can reasonably be ascribed to the use of this drug in early pregnancy. The fact that none of the other malformations examined has become substantially commoner in recent years seems to be consistent with the view that, with the exception of thalidomide, none of the drugs which were used increasingly in the treatment of endemic conditions during this period is an important cause of human malformations.

INCIDENCE FOLLOWING INFLUENZA EPIDEMICS

Following an analysis of claims to sickness benefit received at the National Insurance offices in Birmingham, it was concluded in a previous communication that influenza might be regarded as epidemic in the city when the weekly number of new claims was more than 1,500 above the 1953-61 average for the time of year. Three such epidemics occurred during the period when the children born in 1957-61 were susceptible to teratogenic agents, and four defects—cleft lip, oesophageal atresia, anal atresia, and exomphalos—were shown to be significantly commoner among births 26-40 weeks after these epidemics than in the remainder of 1957-61 (Leck, 1963).

Influenza was again epidemic between December 20th, 1961, and January 23, 1962. 8,129 births occurred 26-40 weeks after this epidemic and 37,329 during the remainder of 1962-63. In Table IV these two groups of births are compared in respect of the incidence of the four defects which showed significant increases following earlier epidemics.* Although the individual defects did not all become more common after the 1961-62 epidemic, the incidence of all children with these defects again showed a considerable rise, whereas the rate for other malformed births did not increase materially.

* The rates given in Tables IV-VII, unlike those quoted earlier, are not corrected for children who left the city before they could be ascertained, since the two sets of uncorrected rates would be affected almost equally by emigration and can therefore be compared directly.

TABLE IV

1962-63 RATES FOR THOSE MALFORMATIONS WHICH WERE ESPECIALLY COMMON FOLLOWING INFLUENZA EPIDEMICS IN 1957-61, COMPARED WITH RATES FOR OTHER MALFORMED INDIVIDUALS

Type of Malformation	Incidence (per 1,000 total births)		Ratio ($\frac{a}{b}$)	Equiv- alent Ratio for 1957-61
	(a) 26 to 40 wks after epidemics	(b) At other times		
Cleft Lip ..	1.60	0.72	2.2	1.4
Oesophageal Atresia, etc. ..	0.12	0.27	0.4	2.4
Anal Atresia ..	0.37	0.38	1.0	2.0
Exomphalos ..	0.49	0.35	1.4	1.9
All Individuals with One or More of the Above ..	2.58	1.69	1.5	1.5
All other Malformed Individuals ..	5.29	5.06	1.0	0.9

Following the 1957-61 epidemics, especially marked increases were shown by the incidence of cases in which the four malformations were associated with each other (Leck, 1963) or with other defects. The increase which followed the 1961-62 epidemic was also rather more marked in cases with multiple defects (Table V), but on this occasion only one of the four characteristic malformations (associated with one or more other defects) was present in each case.

TABLE V

INDIVIDUALS WITH CLEFT LIP, OESOPHAGEAL ATRESIA, ANAL ATRESIA OR EXOMPHALOS, CLASSIFIED ACCORDING TO WHETHER THEY HAD ONE OR MORE OF THE MALFORMATIONS LISTED IN TABLE II

Period of Birth	Number of Malformations per Individual	Incidence (per 1,000 total births)		Ratio ($\frac{a}{b}$)
		(a) 26 to 40 wks after epidemics	(b) At other times	
1957-61	One	2.16	1.70	1.3
	Two or More	0.93	0.32	2.9
1962-63	One	2.09	1.39	1.5
	Two or More	0.49	0.29	1.7

The incidence of single and multiple defects during the whole period 1957-63 is examined in Table VI (overleaf).

The statistically significant increases following epidemics shown by cleft lip, oesophageal atresia, anal atresia, and exomphalos were all especially pronounced in respect of births with multiple defects. On the other hand, the incidence of individuals with multiple defects not including one of these four malformations was not increased following epidemics.

TABLE VI

INCIDENCE OF MALFORMED INDIVIDUALS IN 1957-63 CLASSIFIED ACCORDING TO WHETHER THEY HAD ONE OR MORE OF THE MALFORMATIONS LISTED IN TABLE II

Type of Malformation		Incidence (per 1,000 total births)		Ratio ($\frac{a}{b}$)
		(a) 26 to 40 wks after epi- demics	(b) at other times	
Cleft Lip (with or without cleft palate) ..	Alone	1.36	0.95	1.4
	With other defect(s)	0.19	0.03	6.3
Oesophageal Atresia, etc.	Alone	0.36	0.24	1.5
	With other defect(s)	0.19	0.04	4.8
Anal Atresia ..	Alone	0.16	0.21	0.8
	With other defect(s)	0.32	0.09	3.6
Exomphalos ..	Alone	0.26	0.20	1.3
	With other defect(s)	0.42	0.18	2.3
Individuals with None of the Above Defects	Single defect ..	5.81	5.97	1.0
	Multiple defects ..	0.10	0.11	0.9

At first sight these findings seem to suggest that influenza may be a cause of the four defects mentioned, and especially of cases in which these defects are associated with each other or with additional malformations. However, this suggestion is not supported by a comparison between the amount of sickness among insured workers caused by each epidemic and the changes in malformation rates which followed (Table VII). The incidence of the four defects occurring singly was highest after the smallest epidemic, and did not rise after the most extensive one. Cases with multiple defects were also

commonest after the smallest outbreak. This association between the smallest epidemic and the largest increases in malformation rates is the reverse of what might have been expected if the rates had been affected by influenza itself. It is however possible that the disease is related to a teratogenic influence—perhaps a therapeutic agent—which was especially widespread in the 1960-61 epidemic. In an attempt to identify this influence (if it exists) an inquiry into the antenatal history of the affected children born in Birmingham after epidemics is now being planned.

SUMMARY

Data relating to 147,500 Birmingham children (including stillbirths) born in 1957-63 were used to estimate the incidence of the more common, severe, and readily-diagnosed malformations. The use of the figures as a standard with which to compare the types of defects observed after the taking of drugs in pregnancy was illustrated by reference to meclozine, which was not found to be associated with any particular type of defect.

No type of malformation showed a formally significant increase extending over the whole period, although anencephalus became less common and the incidence of amelia and phocomelia rose and then fell. An influenza epidemic in 1961-62 was followed by an increase, comparable to those observed previously, in the combined incidence of cleft lip, oesophageal atresia, anal atresia, and exomphalos.

The findings seem to be consistent with the view that thalidomide may be the only teratogenic agent

TABLE VII

THE AMOUNT OF SICKNESS ASCRIBED TO EACH INFLUENZA EPIDEMIC, AND THE SUBSEQUENT INCIDENCE OF INDIVIDUALS WITH CLEFT LIP, OESOPHAGEAL ATRESIA, ANAL ATRESIA, OR EXOMPHALOS (CLASSIFIED ACCORDING TO WHETHER THEY HAD ONE OR MORE OF THE MALFORMATIONS LISTED IN TABLE II). RATES RELATING TO BIRTHS 26 TO 40 WEEKS AFTER EPIDEMICS ARE GIVEN IN ITALIC TYPE

Date of Birth	Total Births	Incidence (per 1,000 total births)		New Claims to Sickness Benefit ascribed to Influenza during Related Epidemic*
		Single Defects	Multiple Defects	
Jan. 1, 1957-March 11, 1958	22,978	1.74	0.22	No epidemic
March 12-Aug. 5, 1958	7,968	<i>1.63</i>	<i>0.88</i>	41,637
Aug. 6, 1958-July 28, 1959	19,834	1.71	0.40	No epidemic
July 29-Dec. 8, 1959	6,779	<i>1.92</i>	<i>0.44</i>	30,250
Dec. 9, 1959-June 20, 1961	32,935	1.64	0.33	No epidemic
June 21-Oct. 31, 1961	7,951	<i>2.89</i>	<i>1.38</i>	17,961
Nov. 1, 1961-June 19, 1962	14,430	1.59	0.21	No epidemic
June 20-Oct. 30, 1962	8,129	<i>2.09</i>	<i>0.49</i>	21,167
Oct. 31, 1962-Dec. 31, 1963	26,496	1.36	0.34	No epidemic

* Number in excess of seasonal average (calculated from figures for the last four years in which there was no epidemic between the relevant dates).

among the drugs which have been used increasingly in recent years to treat non-epidemic conditions in pregnancy; but the possibility that the incidence of malformations is affected by the treatment of epidemic infections needs further study.

For access to the above data I am greatly indebted to Dr E. L. M. Millar (Medical Officer of Health, Birmingham) and his staff, and to the medical staff and statistical and records officers of local hospitals. I am also grateful to Mrs Eileen Armstrong, Miss Ida Giles, and Mrs Betty Mann, for help in assembling the data.

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