children were: respiratory syncytial virus (six children), influenza A (two), parainfluenza virus type 3 (one), H-strain rhinovirus (one), and adenovirus type 1 or 5 (three). We would emphasize, however, that in all 13 cases only small amounts of virus could be found in the lungs. The brunt of the infection involved the ciliated epithelial cells of the smaller bronchi and bronchioles, and figs. 6 and 7 show cells infected with respiratory syncytial virus and parainfluenza virus type 3 respectively. Very occasionally, infected cells were seen in a plug of cell debris situated within the bronchiole (fig. 8). The distal epithelial cells were rarely involved but fig. 9 shows the involvement of such cells by respiratory syncytial virus infection.

Discussion

In cases of sudden and unexpected death in infancy where no obvious cause can be found at necropsy, histological examination of the lungs allows the grouping of the pathological features in a meaningful way. The vascular congestion, alveolar and subpleural haemorrhage, and lobular collapse seen in group 1 are features commonly present in deaths thought to be due to an acute allergic reaction. If this were the case for those 33 children, then we have no evidence of the nature of the sensitizing agent. Such a reaction could account for the hypoxic changes found in the conducting tissue of the heart in the "sudden death in infancy syndrome" described by Ferris (1973).

Group 2 has most meaning for us at this early stage of our studies. Diligent scrutiny showed the histological features of lymphocytic bronchiolitis, and in 13 of the 16 children respiratory viruses were present in the lungs. This means that nearly one-third of all the sudden and unexpected deaths in this series had histological evidence of virus infection. Nine of the viruses associated with these deaths are of the type which appear from our studies and those of others to be the cause of acute respiratory illness of childhood and seldom, if ever, carried by children without illness (Chanock *et al.*, 1961; Gardner, 1968). The assumption may be made, therefore, that these viruses played a part in the process leading to the death of these children. This view is strengthened by the demonstration by immunofluorescence of virus in the distal epithelial cells of the alveolar ducts and the ciliated cells of the smaller air passages in those deaths where the histological features vary from minimal lesions shown in fig. 2 to a fully developed bronchiolitis, as depicted in fig. 3.

Speculations on the pathogenesis of respiratory virus infection in young children suggest that bronchiolitis may be a type 1 allergic reaction (Gardner *et al.*, 1970). In this study about one-third of sudden and unexpected deaths in the series were associated histologically with features characteristic of virus infection and this was confirmed in four out of five cases by the physical presence of virus. This correlation of histological response and isolation of virus must surely be significant. This conviction is not lessened by the scanty distribution of virus in group 2, which resembles certain deaths from bronchiolitis we have previously described (Gardner *et al.*, 1967; Gardner *et al.*, 1970). The finding of minimal invasion of distal epithelial cells, the involvement of ciliated epithelial cells in the lower respiratory tract, and the occurrence of infected cells in occasional plugs of debris in the bronchioles further substantiates this similarity. That viruses are involved in a proportion of sudden and unexpected deaths seems to us to be established, but the precise mechanisms leading to death are still a matter of speculation.

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Epilepsy and Pregnancy: A Report from the Oxford Record Linkage Study

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Summary

The files of the Oxford Record Linkage Study were used to identify 223 infants delivered to 168 epileptic women as the result of 218 pregnancies. There were six stillbirths, two of which were grossly malformed. It was shown that the population of epileptic mothers differed significantly from the total reproducing population in respect of social class. Each pregnancy resulting in a livebirth was therefore matched exactly for social class, civil status, maternal age, parity, hospital, and year of delivery with three control deliveries resulting in livebirths. The defects noted at birth were abstracted from the Record Linkage files, and any subsequent hospital admissions or deaths of the children were also abstracted.

There were highly significant excesses of congenital abnormalities among the infants born to epileptic mothers (13·8% of livebirths had some degree of defect of congenital origin compared with 5·6% of controls, P <0·0005). It was shown that neither the frequency with which the mother had fits nor the length of time she had had the epilepsy seemed to bear any relation to the frequency of defects in the offspring—with the exception of the two mothers who developed epilepsy in the first

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trimester of pregnancy—both of whose infants had major abnormalities.

There was a suggestion that of the anticonvulsant drugs ingested phenytoin was far more likely than phenobarbitone to produce defects, but that if the two drugs were taken together the effect was even more pronounced. There appeared to be a dosage effect with phenobarbitone but not with phenytoin. It was concluded that the results were impossible to interpret without some estimate of the genetic link between epilepsy and other abnormalities but that the present evidence strongly suggests that anticonvulsant drugs have a substantial teratogenic effect.

Introduction

Meadow (1968) drew attention to a possible association between anticonvulsant drugs ingested by pregnant women and congenital malformations in the child when he reported on six infants with cleft lip born to epileptic mothers on anticonvulsants. Since then he has collected a series of 32 cases (Meadow, 1970). In the United States Pashayan *et al.* (1971) found that four of 100 mothers of infants with clefts of lip or palate or both were epileptic, and in Holland Elshove (1969) collected a series of seven infants with congenital malformations delivered to six epileptic mothers.

In order to ascertain the increased risk (if any) to the infant of the epileptic mother it is necessary to follow the outcome of a large series of pregnancies. Six series have been published to date with varied methodology and results: Janz and Fuchs (1964) in Germany described 225 births to women on anticonvulsants, 5 (2·2%) of which were malformed, 3 (1·3%) being clefts; Elshove and Eck (1971) in Gröningen included a series of 65 infants delivered to women on epileptic drugs, 10 (15·4%) of which had congenital malformations, 5 (7·7%) being clefts of the lip with and without cleft palate; German *et al.* (1970a) gathered data from the records of the New York hospital on 243 livebirths delivered to epileptic women, 13* (5·3%) of which were malformed, only 1 (0·4%) having a cleft palate; Speidel and Meadow (1972) in Leeds identified 329 infants delivered to epileptic women, 17 (5·2%) of which had severe congenital defects, 3 (0·9%) being cases of cleft lip; South (1972) in London described 22 infants delivered to epileptic women on anticonvulsants in early pregnancy, 2 of which (9%) had cleft lip; and Lowe (1973), in the first population-based study, showed that 6·7% of 134 infants born in Cardiff to women on anticonvulsants had congenital defects compared with 2·7% of all newborns.

The present study was undertaken to provide further information on the extent of the risk to the infants of epileptic mothers, and to attempt to clarify the factors involved.

Material and Methods

The Oxford Record Linkage Study (Acheson, 1969; Baldwin, 1972) started in 1962 and has collected data concerning all births (whether hospital or domiciliary), all other hospital admissions, and all deaths of residents in Oxfordshire and, since 1966, in most of Berkshire—a population of some 800,000 persons with about 14,000 births a year.

For hospital births, detailed descriptions of pregnancy and delivery and of any abnormality or illness of the baby are abstracted by trained clerks from the hospital notes. In the case of domiciliary deliveries the midwife who delivered the infant sends her notes to the Study and clerks then abstract and code the relevant information including details of any abnormality of pregnancy as well as of any illness or defect in the child.

*Actually they state that 14 had defects, but appear to have included hyaline membrane disease as a malformation.

For the purposes of the present study all women coded as having epilepsy and delivered of a child in the period 1 January 1966-31 December 1970 were identified. The files were then searched to ascertain whether these mothers had been delivered of any other infants over this period but failed to be included in our initial sweep either because the delivery occurred before the onset of the epilepsy or because the epilepsy had not been included among the details of pregnancy (in the event the latter occurred only once).

In ascertaining whether the infant had any defects, not only was note taken of the description of such on our delivery files but the general files were also searched for any subsequent hospital admissions or deaths up to 31 December 1970. In this way it was possible to follow up the children delivered in 1966 to the age of 4 but those delivered in 1970 were unable to be followed further than the end of that year.

The control series was chosen as follows. For each pregnancy resulting in a livebirth to an epileptic mother three control pregnancies resulting in livebirths were chosen, matched for maternal age, parity, social class of the father, civil status of the mother, year of delivery, hospital of delivery and, as closely as possible, for area of residence. In those instances where more than three controls could equally well be chosen, the three deliveries nearest in time to that of the epileptic mother were selected. The names of all the children were obtained from the birth certificates (which are also on our files) and the hospital admissions and subsequent deaths of the children so identified were traced in the same way as those of the children delivered of epileptic mothers.

In order to ascertain the drugs taken during the relevant pregnancies, the general practitioner of each epileptic mother was asked for details of all anticonvulsant drugs taken since January 1965 as well as for the age of the onset of the epilepsy and the approximate number of fits each year.

Results

MATERNAL AGE

In all 168 epileptic mothers were identified, having 218 pregnancies resulting in 223 live and stillborn children in the period under study. The ages of the epileptic women at each delivery were compared with the ages of all women delivered in the area over the five-year period. There was a tendency for the epileptic women to be younger—53% were under the age of 25 at delivery compared with 44% of all women at delivery. The difference was barely significant ($X^2=4·2$; D.F.$=1$; $P<0·05$).

PARITY

There were no differences in the parity of the epileptic mothers at delivery compared with that of all mothers delivered in the area (41% of the index pregnancies were to primipara compared with 37% of all deliveries, and 13% of pregnancies in both series were to women of parity three or more).

SOCIAL CLASS

The contrast between the epileptic series and all births is most striking when social class is considered (table I), there being a high proportion of lower social classes among the epileptic series.

CONTROLS

Since the incidence of congenital abnormality in the total population of births varies with the social class distribution, it was felt important that the births to the epileptic mothers should be

TABLE I—*Social Class (Registrar General, 1966) of Husbands of Epileptic Mothers at Birth of each Child compared with that of all Mothers in Oxford Record Linkage Study delivered 1966-70*

Social Class	Epileptic Series		All Births 1966-70	
	No. of Pregnancies	%	No. of Pregnancies	%
I and II	34	15·6	16,357	23·3
III	93	42·7	32,823	46·8
IV	39	17·9	9,831	14·0
V	28	12·8	4,203	6·0
Armed Forces	15	6·9	3,429	4·9
Other	9	4·1	3,502	5·0
Total	218	100·0	70,145	100·0

$\chi = 28{\cdot}7$; D.F. = 5; $P < 0{\cdot}001$.

compared with closely matched controls. Unfortunately, for technical reasons it was possible to match only for livebirths. Consequently the six stillbirths delivered to the epileptic mothers will be considered separately.

STILLBIRTHS

Among the 71,000 total deliveries to women resident in the area over the five-year period there were 754 stillbirths—that is, an incidence of 10·6 per 1,000 total births. Among the 223 infants delivered to the epileptic women there were six stillbirths (an incidence of 26·9 per 1,000). Three of these were macerated with no external evidence of malformation, one was a fresh stillbirth delivered by caesarean section, the mother suffering from status epilepticus and aspiration pneumonia, and the remaining two were grossly deformed; both with hydrocephalus, one with coexisting spina bifida.

LIVEBIRTHS

Of the 217 infants liveborn to the epileptic mothers, three died in the neonatal period (14 per 1,000), whereas of the 649 control livebirths 10 died neonatally (15 per 1,000). Most (seven) of the latter, including a set of triplets, were delivered on, or before, the 30th week and two of the remainder had severe malformations.

Indeed it was a feature of the control series as a whole that there were more deliveries at low gestation compared with the epileptic series (table II). In order to ascertain whether the birth weights of the babies delivered to epileptic mothers were low for their gestation—that is, whether the infants were growth retarded—only the infants delivered at term (here defined as 39 to 41 weeks) were compared. No evidence of growth retardation is shown in table III.

Similarly, in an attempt to see whether the infants of epileptic mothers are more likely to be asphyxiated at birth, only term deliveries were considered. There is some difficulty in comparing Apgar scores over the period 1966 to 1970 as some hospitals changed their method of recording, and indeed some have only recently started to do so. Data are therefore presented from only one large maternity hospital in the area where they have consistently reported their measurements in terms of a scale A to E, E being very severely asphyxiated.

TABLE II—*Gestation of Deliveries of Epileptic Mothers compared with Controls (Livebirths Only)*

Gestation (Weeks)	Epileptic Series		Control Series	
	No. of Pregnancies	%	No. of Pregnancies	%
<30	1	0·5	6	1·0
31-34	1	0·5	12	1·9
35-36	6	2·8	23	3·6
37-38	30	14·1	98	15·4
39-41	137	64·6	364	57·2
42+	12	5·7	62	9·7
Not known	25	11·8	71	11·2
Total	212	100·0	636	100·0

TABLE III—*Comparison of Birth Weight Distribution of Infants Delivered between 39 and 41 Weeks*

Birth Weight (g)	Males			Females		
	Controls	Epileptic		Controls	Epileptic	
		Obs.	Exp.		Obs.	Exp.
Under 2,500	7	2	2·8	3	3	1·1
2,500-2,999	27	7	10·8	32	13	11·3
3,000-3,499	58	29	23·2	81	16	28·7
3,500-3,999	68	31	27·2	47	23	16·7
4,000+	30	7	12·0	12	7	4·2
Total	190	76	76·0	175	62	62·0

Where expected No. of infants of epileptic of sex S and weight W is $\frac{Cws}{Cs} \times Es$, where Cws is the No. of controls of weight W and sex S, Cs is the total No. of controls of sex S, and Es is the total No. of infants of sex S in the epileptic series.

Among the 106 control infants delivered at term in this hospital 89 (84·0%) were given classification A and only five (4·7%) C and under. Among the 40 infants of epileptic mothers delivered at term in the same hospital 32 (80·0%) were considered to be in Apgar category A and 3 (7·5%) C and under.

A further criterion useful in assessing asphyxiation was a consideration of whether oxygen was administered. This therapy was applied in 25 of 137 (18·2%) infants of epileptic mothers delivered at term compared with 53 of 364 (14·6%) infants of control mothers delivered at term.

Thus both measurements indicate a slight but insignificant increase in the proportion of infants of epileptic mothers suffering from asphyxia at birth.

MORBIDITY IN THE NEONATAL PERIOD

There have been consistent reports of a decreased incidence of neonatal jaundice among infants of mothers taking phenobarbitone in late pregnancy (Trolle, 1968) as well as the well-documented increase in the incidence of haemorrhagic disease (Mountain *et al.*, 1970). Of the infants delivered at term in the present series, 12 (3·3%) of the 364 control infants developed jaundice neonatally compared with only 1 (0·7%) of the 137 infants in the index series. There was only one instance of haemorrhage recorded among the infants delivered at term—a control infant with conjunctival haemorrhage. Among preterm deliveries, however, there were three neonatal deaths with intracranial haemorrhage—two being infants of epileptic mothers.

Other symptoms noted in the neonatal period among the index cases delivered at term were: one infant with meconium plug syndrome, one with cerebral irritation, four with cyanotic attacks, and two with convulsions due to barbiturate withdrawal; the corresponding numbers in the control series were none, one, three, and none.

CONGENITAL ABNORMALITIES

The malformations noted at birth in the two series are listed in Appendices A and B. The various types of birthmark, skin tags, heart murmurs, abnormalities of hair distribution, and other minor defects have been omitted. Of the 217 livebirths delivered to the epileptic women there were 17 (7·8%) infants with malformations compared with only 21 (3·2%) of the 649 controls ($\chi^2 = 7{\cdot}1$; D.F. = 1; $P < 0{\cdot}01$). Note that there was only one case of hare lip and cleft palate.

On tracing hospital admissions of the children in both series, further abnormalities which could have been considered to be congenital in origin were discovered: these are listed in Appendices C and D. Of the 638 control infants surviving the neonatal period only 15 (2·4%) could be described as having

some sort of defect, nine of these being cases of hernia and four congenital heart disease. Of the 214 infants of epileptic mothers surviving the neonatal period, however, as many as 14 (6·5%) were admitted to hospital with some type of defect ($\chi^2=7·3$; D.F.$=1$; $P<0·01$).

When comparing all defects—that is, those recognized at birth and those discovered later—the incidence of defect among livebirths to epileptic mothers is 13·8% (30/217) compared with 5·6% (36/649) among their controls—that is, the incidence appears to be more than doubled ($\chi^2=14·7$; D.F.$=1$; $P<0·0005$).

DRUGS

On writing to the doctors who had been the general practitioners of the index mothers at the time of delivery for details of anticonvulsant therapy we had an impressive, immediate, and very helpful response. Unfortunately it was up to six years since the deliveries of some of the women and they had moved out of the area completely. Many others also had moved but we were able to trace them through the local executive councils, whereupon their current general practitioners were contacted. In this way details of the anticonvulsants taken in 183 (84%) of the pregnancies were ascertained. A further two of the mothers had died (one of drowning and the other of inhalation of vomit during an epileptic fit), and the general practitioners no longer had their notes.

The number of infants (including the stillbirths) whose maternal drug regimen in the first trimester had been ascertained, and the proportion of defects in each drug category are shown in tables IV and V. Ignoring the categories in which the numbers were small, one can conclude from table V that there is a prima facie suggestion that maternal phenobarbitone ingestion alone does not present an increased incidence of defect over infants of mothers not taking drugs, but that in combination with phenytoin the proportion of infants with defects is more than doubled. The incidence of defects among infants of mothers taking phenytoin alone, while being much higher than that among infants of mothers taking phenobarbitone alone, is lower than that among infants of mothers taking phenytoin in combination with phenobarbitone.

TABLE IV—*Proportion of Defects According to Anticonvulsants taken by Mother in First Trimester (All Births)*

Anticonvulsant*	No. of Infants	No. with Defects
None	19	2
Phenobarbitone	111	16
Phenytoin (Epanutin)	113	23
Primidone (Mysoline)	24	6
Diazepam (Valium)	10	1
Ethosuximide (Zarontin)	6	0
Sulthiame (Ospolot)	5	2
Phensuximide (Milontin)	2	2
Troxidone (Tridione)	2	1
Carbamazepine (Tegretol)	2	1
Methixene hydrochloride (Tremonil)	1	0
Pheneturide (Benuride)	1	0
Methoin (Mesontoin)	1	0
Sodium amytal	1	0
Chlordiazepoxide (Librium)	1	0

*Not mutually exclusive.

TABLE V—*Anticonvulsants Taken in First Trimester of each Pregnancy by Mothers for whom we have Relevant Data (All Births)*

Anticonvulsant Category*	No. of Infants	No. with Defects	Percentage with Defects
None	19	2	10·5
Phenobarbitone alone	41	2	4·9
Phenytoin alone	33	5	15·2
Phenobarbitone + phenytoin	50	11	22·0
Phenobarbitone + phenytoin + other	15	3	20·0
Phenobarbitone + other	5	0	—
Phenytoin + other	15	4	26·7
Other	5	1	20·0

*The categories are mutually exclusive.

In order to see whether any sort of dosage effect was detectable table VI has been computed. It can be seen that there appears to be a dosage effect with phenobarbitone. Overall the incidence of defects among the infants of women taking 60 mg or less a day (9%) is less than half that among infants of women taking 90 mg or more (20% defects). Conversely a high dosage of phenytoin appears to have, if anything, a negative effect on the incidence of defects.

TABLE VI—*Proportion of Defects among Infants of Mothers Taking Only Phenobarbitone or Phenytoin or a Combination of the Two (All Births). (Cases with Known Dosage Only)*

Dosage/Day in First Trimester	Phenobarbitone		Phenytoin	
	<60 mg	>90 mg	<200 mg	>220 mg
Phenobarbitone <60 mg	0/15 (0%)	X	3/17 (18%)	0/3 (—)
Phenobarbitone >90 mg	X	2/19 (11%)	3/12 (25%)	3/10 (30%)
Phenytoin <200 mg	3/17 (18%)	3/12 (25%)	4/19 (21%)	X
Phenytoin >220 mg	0/3 (—)	3/10 (30%)	X	1/11 (9%)
Total	3/35 (9%)	8/41 (20%)	10/48 (21%)	4/24 (17%)

ONSET OF EPILEPSY

The proportion of infants with defects is shown in table VII according to the age of onset of the mother's epilepsy. There is no clear pattern.

TABLE VII—*Frequency of Defects among Children of Epileptic Women According to Age at which Onset of Epilepsy Occurred (All Births)*

Age at Onset of Epilepsy	No. of Infants	No. of Defects	Percentage with Defects
Under 10	35	8	23
10-16	56	5	9
17-19	23	4	17
20+	45	8	18
Not known	64	7	11

The time between the onset of the epilepsy and the relevant pregnancy is shown in table VIII. Only one defect was ascertained among the nine cases for which the mother's epilepsy had not begun until after the first trimester (in four of these the onset was in the puerperium and in two the first fit occurred one year after delivery). The most notable point, however, is the fact that the only two mothers in whom the onset was during the first trimester were delivered of infants with major defects (one duodenal atresia, one congenital heart disease).

TABLE VIII—*Frequency of Defects among Infants of Epileptic Women According to Length of Time Since Onset of Epilepsy (All Births)*

Time of Onset of Epilepsy as Related to Pregnancy	No. of Infants	No. of Defects	Percentage with Defects
Onset after delivery	6	0	11
2nd and 3rd trimesters	3	1	
1st trimester	2	2	100
Up to 2 years before	16	3	19
3-4 years before	21	4	19
5-9 years before	42	4	10
10+ years before	69	11	16
Not known	64	7	11

TABLE IX—*Frequency of Defects among Infants of Epileptic Women According to Frequency of Fits (All Births)*

No. of Fits a Year	No. of Infants	No. with Defects	Percentage with Defects
None	44	6	14
1-2	23	2	9
3-12	50	7	14
13+	26	4	15
Not known	80	13	16

NUMBER OF FITS

As with the age of onset, we rely on the general practitioners' reports for an assessment of the number of fits a year. There certainly does not appear to be any relation between the number of fits and the likelihood of the infants having a defect (table IX).

Discussion

It has been shown that the mothers ascertained as epileptic in the Oxford area differ in their age and social class distributions from the total maternity population. As both factors have some influence on the incidence of congenital defects it is imperative for comparison that the controls have the same distribution. Even when the controls were matched for social class, maternal age, and parity there were more than twice as many defects among the livebirths delivered to epileptic mothers—both considering those identified at birth and those presenting later in childhood. In all some 14% of the children delivered to epileptic women were identified with some type of defect (5·6% controls) and it must be recognized that this is necessarily a minimum estimate for several reasons: (1) not all developmental defects identified after the neonatal period will have necessitated a hospital admission—for example, mental retardation; (2) some 20% of the mothers are no longer living in the region and hence their children, even if admitted to hospital, would not have done so in the Record Linkage area; and (3) because the period of follow-up was variable—up to five years for the infants born in 1966 but less than one year for those delivered in 1970—it is likely that a further few years of follow-up would identify yet more cases of defect.

One of the more interesting points is that the risk of an epileptic woman in this area having an infant with hare lip is, from the present figures anyway, small compared to that apparent from the Dutch study (Elshove and Eck, 1971). This could be an effect either of differing degrees of epilepsy, of different anticonvulsant regimens, or of chance.

The present data seem to indicate that it is not the fits themselves which have a teratogenic effect, for then one would expect a higher rate of defect among the women who had frequent fits. In fact table IX indicates that the woman whose epilepsy is so well controlled that she has no fits has as great a risk of having a child with a defect as the woman having relatively frequent fits. On the other hand there is the suggestion that there is an increased risk of defect with increased daily intake of phenobarbitone, but no dosage effect with phenytoin. A combination of the two drugs, however, appears even more likely to produce an infant with defects than either taken separately (a result also apparent from Lowe's (1973) study).

Unfortunately, there were not enough women taking other drugs to provide meaningful results. There has recently been a strong suggestion that troxidone is teratogenic (German *et al.*, 1970a, 1970b). In only one pregnancy in the present series was this drug prescribed, and of the twins subsequently delivered one had a single palmar crease (case 16) and both were retained with feeding difficulties in the premature baby unit.

It is, however, the two drugs phenobarbitone and phenytoin that are of primary interest at present, especially as nearly 9% of National Health Service prescriptions are said to be for barbiturates or barbiturate-containing drugs (Tattersall, 1965). Nelson and Forfar (1971), in a retrospective study of drugs prescribed to 458 women delivered of malformed infants compared with 911 controls, found that the group of drugs most significantly associated with both major and minor abnormalities was the barbiturates. A similar finding was reported in a study instigated by the Royal College of General Practitioners (Crombie *et al.*, 1970).

Phenobarbitone, which has traditionally been used for its neurological effect, is now known to have a profound effect on the metabolism of the body as a whole. It has been reported not only to affect the steroid-hormone metabolism (Wilson, 1969); to increase the uptake of serum bilirubin by the liver (Matsuda and Takase, 1969), presumably as a consequence of increased bile flow (Thompson and Williams, 1970); to affect the metabolism of methyldopa (Kaldor *et al.*, 1971) and the raising of plasma gamma-glutamyl transpeptidase levels (Ideo *et al.*, 1971; Rosalki *et al.*, 1971); but also, as a result of altered vitamin D metabolism in the liver, to reduce the serum calcium and increase the serum alkaline phosphatase level (Hunter et al., 1971). Consequently it is not surprising that epilep-

APPENDIX A.—*Listing of all Infants with Congenital Defect Noted at Birth Delivered to Epileptic Woman*

Case No.	Sex	Defect	Drugs Taken Each Day in First Trimester	Maternal Age	Age at Onset of Epilepsy	Notes
1	F.	Spina bifida, hydrocephalus, talipes	300 mg phenytoin	33	Childhood	Stillbirth
2	F.	Hydrocephalus and other gross defects	250 mg primidone	32	16	Stillbirth
3	F.	Duodenal atresia	100 mg phenytoin from 6th week	31	31	Died 16 hr with massive intraventricular haemorrhage
4	F.	Abnormalities of both knees	None (first grand mal attack 2 weeks before delivery)	28	28	Died 15 days. Pneumonia and cerebral haemorrhage
5	M.	Mild spina bifida	150 mg phenytoin, 180 mg phenobarbitone	24	19	Twin
6	M.	Hirschprung's disease	300 mg phenytoin, 750 mg primidone	29	7	
7	M.	Very large anterior fontanelle—almost cranium bifidum; huge thick fingers	200 mg phenytoin, 90 mg phenobarbitone	36	29	
8	M.	Large pilonidal dimple; prominent ears with flattened tops, mild blepharitis	Not known	31	x	
9	M.	Bilateral undescended testes in mature infant; double tranverse palmar creases	Phenytoin, phenobarbitone	28	15	
10	M.	Bilateral undescended testes in mature infant	None	23	Childhood	
11	M.	Hypospadias; thumbs like fingers, nail hypoplasia incurvation of great toes	200 mg phenytoin, 750 mg primidone, 800 mg carbamazepine	22	9	
12	M.	Bilateral talipes	270 mg phenytoin, 90 mg phenobarbitone	21	16	
13	F.	Varus deformity	200 mg phenytoin, 60 mg phenobarbitone, folic acid	18	6	
14	M.	No toes L. foot; talipes	90 mg phenobarbitone	25	22	
15	M.	Hare lip and cleft palate	200 mg phenytoin, 60 mg phenobarbitone, 6 mg diazepam	19	17	
16	F.	Single palmar crease	300 mg phenytoin, 900 mg troxidone, 90 mg phenobarbitone	35	Childhood	Twin
17	F.	Clicking hip	90 mg phenobarbitone, 300 mg phenytoin	21	17	
18	M.	Clicking L. hip	60 mg phenobarbitone, 150 mg phenytoin	18	14	
19	F.	Slight click L. hip	90 mg phenobarbitone, 300 mg phenytoin	35	14	

tic patients on anticonvulsants for some years have been found to have significantly low bone density (Linde *et al.*, 1971). In addition, anticonvulsants are known often to cause folic acid deficiency (Baugh and Krumdieck, 1969; Parsonage, 1969).

Elshove (1969) reported that phenytoin injected into pregnant mice resulted in a cleft palate in a significantly high proportion of their progeny, and Roman and Caratzali (1971) reported that phenytoin and primidone administered to rats resulted in significantly more chromosome breaks than in control rats. From humans there is the evidence of de Toni *et al.* (1966) of an increased number of tetraploid and heteroploid mitoses in the lymphocytes of three children born to mothers on anticonvulsant therapy, and a case report of chromosome breaks in the son of a mother who had received anticonvulsants during pregnancy (Ayraud *et al.*, 1968). There also appears to be increasing evidence that phenytoin may be carcinogenic (*Lancet*, 1971) and that it results in a depression of cellular and humoral immunity (Sorrell *et al.*, 1971).

In view of the variable effects of these drugs it is possible that different defects could be caused by different mechanisms—for example, an abnormal steroid-hormone metabolism in the mother on anticonvulsants could be reflected in the increased incidence of malformations of the genitalia among the males in our series (three index cases, two controls). On the other hand one cannot rule out a genetic component in the finding of an increased incidence of defect among children of epileptic women, especially in view of the report from Dronamraju (1970) of a high proportion (17-20%) of patients with clefts having first or third degree relatives with epilepsy. As he did not ascertain the expected proportion it is not possible to know how much weight to place on the finding.

APPENDIX B.—*Listing of Control Liveborn Infants with Some Degree of Congenital Defect Noted at Birth*

Case No.	Sex	Defect	Notes
C.1	F.	Large teratoma of neck	Triplet; N.N.D.
C.2	F.	? Chromosomal abnormality	N.N.D.
C.3	M.	Down's syndrome; duodenal atresia	N.N.D.
C.4	M.	Spina bifida; hydrocephalus	N.N.D.
C.5	F.	Spina bifida, hydrocephalus, talipes	
C.6	M.	Meningomyelocele	Twin
C.7	M.	Down's syndrome	
C.8	M.	Ileal atresia	
C.9	F.	Fallot's tetralogy	Died 5 months
C.10	M.	Hypospadias	
C.11	M.	Mild hypospadias	
C.12	F.	Bilateral talipes	
C.13	F.	Slight bilateral talipes	
C.14	F.	Small pixy face, rather pointed L. ear, very short neck, long fingers	
C.15	F.	Short neck, puggy face	
C.16	F.	? Mongol	
C.17	F.	R. hip click	
C.18	F.	Bilateral clicking hips	
C.19	M.	Slight click R. hip	
C.20	F.	Bilateral clicking hips	
C.21	F.	Bilateral dislocated hips	

N.N.D. = Neonatal death.

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APPENDIX D.—*Listing of Control Infants with Abnormalities Not Noted at Birth but Diagnosed at Later Hospital Admission or Death*

Case No.	Sex	Defect	Notes
C.22	M.	Pyloric stenosis	Operated 2 months
C.23	M.	Congenital heart disease (subendocardial fibroelastosis)	Died 2 months
C.24	F.	Congenital heart disease, multiple skeletal abnormalities	Twin of C.29
C.25	M.	Congenital heart disease (ventricular septal defect)	Died 16 months
C.26	F.	Congenital heart disease (Fallot's tetralogy)	Catheterized 18 months
C.27	M.	R. inguinal hernia	Operated 2 months
C.28	M.	R. inguinal hernia	Operated 3 months
C.29	F.	R. inguinal hernia	Operated 4 months
C.30	M.	R. inguinal hernia	Operated 2 months
C.31	F.	Bilateral inguinal hernia	Operated 2 months
C.32	M.	R. inguinal hernia	Operated 1 month
C.33	M.	R. inguinal hernia	Operated 2 months
C.34	M.	R. inguinal hernia	Operated 4 months
C.35	F.	Umbilical hernia	Operated 3 weeks
C.36	M.	Extensive cerebral atrophy	Diagnosed 3 months

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APPENDIX C.—*Listing of Infants of Epileptic Mothers with Defects Not Noted at Birth but Diagnosed at Later Hospital Admission or Death*

Case No.	Sex	Defect	Drugs Taken Each Day in First Trimester	Maternal Age	Age at Onset	Notes
12	M.	L. inguinal hernia	90 mg phenobarbitone, 270 mg phenytoin	21	16	Operated 18 months
20	M.	Squint	100 mg phenytoin	24	22	Operated 1 year
21	F.	Mental retardation	90 mg phenobarbitone	28	22	Hospital admission for feeding problem (sib of case 19)
22	M.	Tyrosinosis	150 mg phenytoin	29	26	Diagnosed 1 month
23	M.	Congenital heart defect (ventricular septal defect)	150 mg phenytoin from 2nd month	23	23	Diagnosed 8 months
24	F.	Congenital heart defect	Not known	22	Not known	
25	F.	Rectal prolapse	Not known	17	Not known	At 2 years
26	F.	Umbilical hernia	Phenobarbitone, phenytoin	22	Not known	Operated 3 years
27	M.	Bilateral inguinal hernia	150 mg phenytoin, 180 mg phenobarbitone	23	Infancy	Operated 5 months
28	M.	R. inguinal hernia	Not known	28	Not known	Operated 4 months
29	M.	Pyloric stenosis	Phensuximide, primidone, phenytoin, sulthiame	24	Not known	Twins. Operated 1 month
30	M.	Pyloric stenosis				
31	F.	Dermoid tumour of occipital bone	100 mg phenytoin, 60 mg phenobarbitone	19	18	Excised 6 months
32	M.	Benign calcifying epithelioma R. shoulder	Primidone, phenytoin, phenobarbitone	30	Childhood	Excised 2 years

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Pattern of Gastric Emptying after Vagotomy and Pyloroplasty

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Summary

The pattern and rate of gastric emptying have been studied in 16 patients before and after vagotomy and pyloroplasty. The rate of emptying, expressed as half life in minutes, was not greatly changed by operation. After operation, however, there was a rapid initial phase of emptying, particularly marked in patients who had post-vagotomy diarrhoea.

Introduction

The operation of vagotomy and pyloroplasty is widely used in the treatment of duodenal ulcer but its long-term effects on gastric motility and emptying are not clear. The results of the few studies which have been undertaken have been conflicting. Buckler (1967) observed that the total emptying time of the stomach was prolonged after operation. Madsen and Pederson (1968), George *et al.* (1968), and McKelvey (1970) noted that after operation the stomach emptied more rapidly, particularly in patients with postoperative diarrhoea. The methods used in these studies, however, had some defects; in none was the emptying of ordinary food measured, and in three nasogastric intubation was necessary. In only one study (George *et al.*, 1968) were the same patients studied both before and after operation. Cowley *et al.* (1972) observed little difference in gastric emptying of solid food between patients after truncal vagotomy and pyloroplasty and a group of control patients except in the early postoperative period.

This paper is a preliminary report of a study of gastric emptying in patients before and after vagotomy and pyloroplasty.

Patients

Sixteen patients were studied before and after vagotomy and pyloroplasty. Details of the gastroduodenal disease and the type of operation performed are given in table I. In all cases the main indication for operation was intractable pain. The mean age (± 1 S.D.) was 51 ± 13 years.

TABLE I—*Details of Gastroduodenal Disease and Operations performed in 16 Patients*

	No. of Patients	T.V. and F.P.	S.V. and F.P.	T.V. and H.M.P.	S.V. and H.M.P.
Gastric ulcer	5	4		1	
Duodenal ulcer	8	4	2	1	1
Gastric and duodenal ulcer	2		1	1	
Hiatus hernia	1			1	

T.V. = Truncal vagotomy. S.V. = Selective vagotomy. F.P. = Finney pyloroplasty. H.M.P. = Heineke-Mikulicz pyloroplasty.
Note: (1) In selective vagotomy all the gastric branches of the anterior and posterior vagi were cut, leaving the hepatic and coeliac branches intact.
(2) The pyloroplasty was made using an incision of about 3 in. (7·5 cm) and closed with two layers of sutures.

Preoperative studies of gastric emptying were performed from two days to one year before operation. At least nine weeks were allowed to elapse after operation before gastric emptying was again measured to avoid the period of transient postoperative gastric stasis (Cowley *et al.*, 1972; Davies *et al.*, 1973). Usually patients were studied during the first year after vagotomy and pyloroplasty; four were studied less than three months and five were studied more than one year after operation.

Seven of the 16 patients experienced postoperative diarrhoea (defined as the passage of liquid stools three or more times daily) —four had continuous diarrhoea, two had episodic attacks lasting one day and occurring at intervals of one to three weeks, and one had diarrhoea only during the first postoperative month.

Method

Details of the method have been described previously (Griffith *et al.*, 1966; Griffith *et al.*, 1968). The upper abdomen was scanned, by an automatic scintiscanner with two detectors, at timed intervals after ingestion of a standard breakfast labelled with radioactive chromium (^{51}Cr). From each scan the amount of meal remaining in the stomach was calculated and expressed in terms of scanner counts. The first scan was performed as soon as possible after the end of the meal, usually at about 10 minutes, but in no case was there a delay of more than 16 minutes. For practical reasons it was not possible to standardize this interval.

For each patient the radioactivity remaining in the stomach at each scan (C_1, C_2, C_3, etc.) was calculated and plotted against time on a semilogarithmic scale (see fig.). The slope of the line through the points was straight in all but one of the patients. Thus, from the time of the first scan (10 minutes after the end of the meal) until the emptying process was almost complete, food left the stomach in an exponential manner. The rate of emptying could therefore be expressed as the half life ($t_{\frac{1}{2}}$) of the

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