mena, and haematological, renal, and liver function tests showed no abnormalities ascribable to chlormethiazole.

Discussion

Chlormethiazole proved a useful adjunct to the standard drug treatment in seven out of the nine episodes of status epilepticus in this study. The patients were highly selected in that they remained refractory to diazepam in adequate doses and three had failed to respond to intravenous thiopentone.

The value of intravenous diazepam in the immediate management of status epilepticus is well established.[5 6] Its failure in some patients is probably due to inadequately maintained blood levels[7] and is best overcome by the use of a continuous intravenous infusion. There remains, however, a small group of "refractory" patients.[5] In these cases it had previously been our practice to give intravenous thiopentone as the drug of second choice. In subanaesthetic doses it can produce profound respiratory depression[8] and in our experience the patient often needs assisted ventilation. Thus an effective alternative to diazepam is needed which is less apt than thiopentone to cause respiratory depression.

There are several reports of the efficacy of intravenous chlormethiazole in status epilepticus.[9-12] In all except one doses of between 1·2 g and 3 g were given as a bolus and repeated at intervals of up to four hours. The reports are uniformly enthusiastic about the results, but varying degrees of depression of the level of consciousness and respiration were encountered. Houdart and Laborit [11] used a similar regimen to ours (0·3 g/h as a constant infusion) and their patients did not have these side effects. More recently Manhire and Espir[13] described a case of status epilepticus in which chlormethiazole controlled the fits but only at a rate of infusion (1·5 g/h) which resulted in coma.[14] We obtained satisfactory results with a rate of infusion of 0·5-0·7 g/h without serious impairment of consciousness or depression of respiration.

We think that chlormethiazole deserves wider recognition as an effective therapeutic agent in the management of status epilepticus.

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Requests for reprints to Dr. Loh.

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For Debate . . .

Infant Leukaemias and Cot Deaths

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Summary

Infant leukaemias differ from childhood leukaemias in ways which suggest that when haemopoietic neoplasms combine fetal origins with rapid growth rates they prevent normal development of the reticuloendothelial system and thus cause the sudden death of apparently healthy babies (stillbirths or cot deaths). Cot deaths are commoner in boys and have a peak incidence during the first half of infancy—that is, during the period most affected by the switch from passive to active immunity. Babies born from July to December, who are intensively exposed to winter conditions from 1 to 5 months of age, are also at special risk. During this period more girls and more children born from January to June die of leukaemia; and within three months of birth an exceptionally high ratio of myeloid to lymphatic leukaemias has been replaced by a low ratio, which persists throughout childhood.

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Introduction

Illnesses which might have proved fatal if they had not been treated with antibiotics are more often precursors of leukaemias than solid tumours.[1] This observation was the starting point of an inquiry into causes of latent period deaths which eventually necessitated comparisons between infant leukaemias and cot deaths.[2] Several observations suggested that both the childhood peak of leukaemia mortality and the small proportion of myeloid cases among childhood leukaemias[3] might be artefacts caused by greater difficulty in recognizing infant than childhood leukaemias and the inclusion of more myeloid than lymphatic leukaemias among the infant cases. For example, most, if not all, childhood cancers have fetal origins.[4] Secondly, we had

reason to believe that (*a*) immunological competence is lost during the latent phase of leukaemia[1]; (*b*) preleukaemia is an unrecognized cause of stillbirths as well as deaths ascribed to pneumonia[5]; and (*c*) only since the discovery of drugs which compensate for loss of immunological competence have infants seemed to be less leukaemia prone than older children.[6] Finally, myelocytes have faster rates of cell division and maturation than lymphocytes,[7] and the rate of cell turnover is much the same for normal and malignant leucocytes.[8] Therefore myeloid leukaemias with fetal origins are more likely to cause in utero replacement of leucocyte stem cells with mutant cells (and thus prevent normal development of the reticuloendothelial system) than lymphatic leukaemias.

Thus infant deaths from leukaemia and cot deaths were compared; the results are presented here.

Leukaemia and Cot Deaths in 1 to 6-month-old Children

Though leukaemia mortality rates have always been higher for boys than girls and have never shown any signs of being influenced by seasonal factors[6] this was not true of leukaemia deaths in children aged 1-5 months (table I). In this age group, which accounts for less than 3% of childhood leukaemias, there were more girls than boys who died of leukaemia; more summer than winter deaths; and over twice as many deaths among January to June births than among July to December births. The last finding was of key importance because babies who are born in the second half of the year are intensively exposed to winter conditions between 1 and 6 months of age and so are more likely to die from respiratory infections in their first six months than January to June births (see table II).

TABLE I—*Seasons of Birth and Death for Infants with Leukaemia*[4]

Infant Leukaemias		Age at Death (Months)			
		0	1-5	6-11	All Cases
Season of death	Jan.-March	11	27	55	93
	April-June	6	45	43	94
	July-Sept.	2	43	31	76
	Oct.-Dec.	3	22	37	62
Season of birth	Jan.-March	11	44	38	93
	April-June	6	50	47	103
	July-Sept.	2	18	39	59
	Oct.-Dec.	3	25	42	70
Cell types*	Myeloid	6	37	32	75
	Lymphatic	1	38	63	102
	Undifferentiated	15	62	71	148
Sex	Boys	13	66	86	165
	Girls	9	71	80	160
Total no. (%)		22 (6·8)	137 (42·2)	166 (51·1)	325 (100)

*Within two months of birth 12 infants died of myeloid and three of lymphatic leukaemia, and between 2 and 4 months 12 and 17, respectively, died.

Since the risk of dying during delivery is the same all the year round the figures in table I effectively ruled out stillbirths as the only reason why there might be more difficulty in recognizing infant than childhood leukaemias. Cot deaths have not decreased in frequency since antibiotics were discovered, and they affect boys more than girls; are commoner in winter than summer; and have a peak incidence from 1 to 5 months of age (table III). Therefore babies born from July to December should be at greater risk from cot deaths than those born from January to June, and this might be the reason why the deaths ascribed to leukaemia from 1 to 5 months of age have less in common with childhood leukaemias than neonatal cases or leukaemia deaths in the second half of infancy (tables III and IV).

TABLE III—*Seasons of Birth and Death for Cot Deaths*

Cot Death Syndrome		Age at Death (Months)			
		0	1-5	6-11	All Cases
Season of death	Jan.-March	3	127	31	161
	April-June	3	83	21	107
	July-Sept.	4	59	17	80
	Oct.-Dec.	7	99	27	133
Season of birth	Jan.-March	3	83	23	109
	April-June	4	52	28	84
	July-Sept.	3	104	27	134
	Oct.-Dec.	7	129	18	154
Sources	Northern Ireland	3	123	32	158
	Oxfordshire	10	131	39	180
	Birmingham	4	114	25	143
Sex	Boys	12	220	49	281
	Girls	5	148	47	200
Total no. (%)		17 (3·5)	368 (76·5)	96 (20·0)	481 (100)

TABLE IV—*Leukaemia and Cot Deaths as Causes of Death from 1 to 5 Months of Age. Figures are Comparitive Mortality Indices.*

Months	Birth Months		Death Months	
	Leukaemias	Cot Deaths	Leukaemias	Cot Deaths
January	154	78	54	120
February	144	88	96	153
March	103	79	75	146
April	150	54	78	116
May	118	69	151	89
June	148	51	156	67
July	41	112	125	39
August	77	119	131	61
September	45	114	111	87
October	79	137	71	101
November	51	162	86	90
December	89	138	65	134
Jan.-March	134	82	75	140
April-June	139	58	128	91
July-Sept.	54	115	122	62
Oct.-Dec.	73	146	74	108

The cot deaths in these tables include 158 cases from Northern Ireland,[9] 180 from Oxfordshire,[10] and 143 from Birmingham.[11] In each series there were more July to December than January to June births and in the combined series of deaths between 1 and 6 months of age both the high-risk birth months and the high-risk death months corresponded to low risk months for leukaemia deaths and vice versa (table IV).

The small proportions of male cases of leukaemia and winter deaths from leukaemia in the exceptional age group (1-5 months) were preceded and followed by "normal" proportions (table I), and by 3 months of age an exceptionally high ratio of myeloid to lymphatic leukaemias had been replaced by the low ratio which is typical of childhood but not of adult leukaemias.

TABLE II—*Seasonal Cycles of Pneumonia Deaths expressed as Comparitive Mortality Indices**

First Month in Each Cycle		Subsequent Months in Each Cycle										Half-yearly Totals	
		2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	2nd-6th	8th-12th
January	222	116	111	109	81	75	67	68	74	81	88	106	99	83
February	116	111	109	81	75	67	68	74	81	88	106	222	67	114
March	111	109	81	75	67	68	74	81	88	106	222	116	81	123
April	109	81	75	67	68	74	81	88	106	222	116	111	74	129
May	81	75	67	68	74	81	88	106	222	116	111	109	73	128
June	75	67	68	74	81	88	106	222	116	111	109	81	75	32
July	67	68	74	81	88	106	222	116	111	109	81	75	83	99
August	68	74	81	88	106	222	116	111	109	81	75	67	114	67
September	74	81	88	106	222	116	111	109	81	75	67	68	123	81
October	81	88	106	222	116	111	109	81	75	67	68	74	129	74
November	88	106	222	116	111	109	81	75	67	68	74	81	132	73
December	106	222	116	111	109	81	75	67	68	74	81	88	128	75
Jan.-June	119	94	86	80	74	75	81	106	114	120	126	125	82	118
July.August-Dec.	81	106	114	120	126	125	119	94	86	80	74	75	118	82

*Standard (100) = the daily risk of dying from pneumonia at any age (in England and Wales i n 1970).

TABLE V—*Observed and Expected Numbers of Childhood Leukaemias and Actual Numbers of Unexplained Stillbirths and Cot Deaths. Results are Yearly Numbers of Deaths 1968-72*[6]

	Adults (≥15 Years)					Children (<15 Years)					Unexplained Stillbirths (I.C.D. P68)	Cot Deaths in 1972 (I.C.D. 795)
	Lymphatic	Myeloid	Monocytic	Unspecified	Total	Lymphatic	Myeloid	Monocytic	Unspecified	Total		
Observed ..	916	1366	145	292	2719	213	73	7	46	339	440	474
Expected ..						213	317	7	625	1162		

Discussion

During infancy two things happen which may explain why a childhood peak of lymphatic leukaemia mortality is not preceded by a peak incidence of non-specific and myeloid leukaemias. The level of immunological competence becomes less dependent on maternal factors (passive immunity) and more dependent on the child's own immune system (active immunity), and there is a wave of sudden deaths of apparently healthy babies which barely affects the neonatal period but has passed its peak by 4 months of age.

The risk of dying from leukaemia is the same during both halves of infancy, but in the age group most affected by the sudden death hazard (1-5 months) there are fewer male cases and winter deaths. Also an initially high ratio of myeloid to lymphatic leukaemias is suddenly replaced by a low ratio, which persists until the end of childhood and is then replaced by a moderately high ratio.

We do not know how often difficulty in replacing passive with active immunity is the underlying cause of deaths which have respiratory factors as terminal causes. Nor do we know how often (if at all) immune deficiencies are caused by in-utero replacement of leucocyte stem cells with mutant cells. On the other hand, loss of immunological competence is an early consequence of leukaemia,[1] childhood leukaemias have fetal origins,[4] and myeloid leukaemias have relatively short latent periods.[8] Therefore the youngest batch of lymphatic leukaemias (which was barely detectable before antibiotics were discovered) could be preceded by a larger group of non-specific and myeloid leukaemias in which the proportion of unrecognized cases is exceptionally high because recognition depends on the whole of the latent period being spent in an infection-free environment. In Britain this condition is unlikely to be met by babies who are born in the second half of the year because they are intensively exposed to winter conditions from 1 to 5 months of age. Since this is the age group most affected by deaths which are due to difficulty in replacing passive with active immunity a likely alternative to a leukaemia death is a death from infection which is not recognized as such because there were none of the usual reactions to foreign proteins.

Therefore in infants aged 1-5 months a small proportion of July to December births among those dying from leukaemia might indicate that only a small proportion of infant leukaemias are being recognized; and a large proportion of July to December births among cot deaths might indicate that terminal causes of death in cases of infant leukaemias are no easier to recognize than underlying causes.

The conclusion that infant leukaemias cause some sudden deaths of apparently healthy babies invites comparisons between actual numbers of stillbirths and cot deaths and estimated numbers of children with leukaemia affected by the sudden death hazard. The provisional estimates in table V are based on three assumptions.

(1) Myeloid and lymphatic leukaemias together have the same frequency among adults and children with leukaemia, but there is better recognition of adults with myeloid leukaemia than children. Therefore the observed myeloid:lymphatic ratio for adult cases is the expected ratio for childhood cases (1.49). (2) The hazard of sudden death affects the youngest batch of children with non-specific leukaemias as much, or more than, the youngest group of children with cell-specific leukaemias. Therefore the expected ratio of non-specific to myeloid cases among childhood leukaemias is the observed ratio for infant leukaemias (1.97, table I). (3) The only cell-specific cases affected by the sudden death hazard are myeloid leukaemias. Therefore the expected number of lymphatic and monocytic cases among childhood leukaemias is the observed number.

The observed numbers in table V[6] show that from 1968-72 in England and Wales the yearly number of childhood deaths ascribed to leukaemia (339) was smaller than the yearly number of unexplained stillbirths (440) or the number of cot deaths in 1972 (474). But the difference between the observed and expected numbers of childhood leukaemias (823) was slightly smaller than the total number of unexplained deaths of apparently healthy babies (914).

The data on cot deaths were obtained from Professor Peter Froggatt (Northern Ireland), Jean Fedrick (Oxfordshire), and Professor Hugh Cameron (Birmingham). The data on infant leukaemias were collected by a network of Medical Officers of Health, the Oxford University department of social medicine, and the Marie Curie Memorial Foundation. The costs of the investigation were defrayed by a grant from the United States Department of Health, Education. and Welfare (contract number 223-75-6001), negotiated by the Bureau of Radiological Health.

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