INCIDENCE OF RETROLENTAL FIBROPLASIA IN ENGLAND AND WALES IN 1951

BY

J. T. BOYD, M.B., D.P.H.

Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine

AND

K. M. HIRST, M.B., D.P.H.

Ministry of Health

In 1952, on behalf of the Ministry of Health, we initiated an inquiry into the incidence and distribution of retrolental fibroplasia in England and Wales. At that time, all that was known with certainty about the disease was that it affected the smaller premature infants and that its geographical distribution was erratic.

Medical officers of health in England and Wales are aware of all live births in their areas that are premature, as defined by the internationally accepted birth-weight standard, since, from 1946 onwards, doctors and midwives have been asked to enter the birth weight of a live-born infant on the birth notification whenever the weight is 5½ lb. (2,500 g.) or less. (More recently the entry of the birth weight of babies of all weights, live-born and stillborn, has been requested.) On the basis of this information the medical officer of health of every local health authority was asked to make special inquiry about the condition of eyes of all the premature infants born in 1951 whose birth weight was not more than 4 lb. 6 oz. (2,000 g.) and who had survived at least two months—that is, those premature infants who were at risk by reason of low birth weight and who had survived long enough to demonstrate retrolental fibroplasia.

The inquiry was carried out by health visitors in the first place, and through them information was sought on birth weight, sex, place of birth (home or hospital), whether transferred to hospital after birth at home, whether single or multiple birth, and, in broad terms, on the condition of the eyes. Since all the infants were at least 10 months old when the inquiry started, seriously defective vision would have been apparent to the parents and the health visitors. In many cases of defective vision it was already known that the child was, or had been, under the care of an ophthalmologist, and an accurate diagnosis was thus readily obtained. In cases of doubt the co-operation of the family doctor and the ophthalmologist was sought and retrolental fibroplasia excluded or confirmed on expert opinion, sometimes after a period of observation and repeated examinations. By these means the details of the babies born, and information on the cases of retrolental fibroplasia occurring among them, were received from every local health authority.

Incidence in Relation to Birth Weight

In total the survey provided data on 6,926 infants, all of whom had weighed 4 lb. 6 oz. or less at birth, and who had survived for a period of at least two months. The distribution of these infants by place of birth, sex, and birth weight (Table I) showed that the great majority of them, 6,042 (87%), had either been born in hospital (or nursing-home) or were transferred there within two months; 797 infants (12%) were born at home and were not transferred; while the information regarding place of birth was incomplete for the remaining 87 (1%). There was a considerable excess of females among the total infants, and this excess became relatively larger with each successive decrease in birth weight.

The condition of the eyes was ascertained in all but 295 babies (4.3%), who either could not be traced or had left the country. These have been presumed normal. Among the total population of 6,926 infants 127 cases of retrolental fibroplasia were discovered, an incidence rate of 1.83% for infants of 4 lb. 6 oz. (2,000 g.) or lower birth weight. (For infants with a birth weight of 4 lb. (1,800 g.) or less the rate was 2.8%.) Detailed analysis of the incidence by birth weight (Table II) reveals a marked fall with increasing birth weight; a rate of 15.3% in infants whose birth weight had been under 2 lb. 4 oz. (1,000 g.) declines steadily to a rate of only 0.2% in infants with a birth weight between 3 lb. 14 oz. and 4 lb. 6 oz. (1,750 and 2,000 g.).

TABLE II.—*Incidence of Retrolental Fibroplasia Among* 6,926 *Premature Infants Born in England and Wales During* 1951

Birth Weight	No. of Infants	Cases of Retrolental Fibroplasia	
		No.	Incidence Rate %
Under 2 lb. 4 oz. (1,000 g.)	85	13	*15·3*
2 lb. 4 oz. (1,000 g.)– ..	302	40	*13·3*
2 „ 13 „ (1,250 „)– ..	867	36	*4·2*
3 „ 5 „ (1,500 „)– ..	1,790	30	*1·7*
3 „ 14 „–4 lb. 6 oz. (1,750–2,000 g.) ..	3,882	8	*0·2*
Total	6,926	127	*1·8*

Incidence in Relation to Place of Birth

All the 127 cases of retrolental fibroplasia occurred among the 6,042 infants who were born in hospital or were transferred there within two months, and none of the 797 who were born at home and remained there for the first two months of life developed the disease. This absence of cases among the "home" infants supports the view that the risk

TABLE I.—*Numbers of Premature Infants* Born in England and Wales During* 1951, *by Place of Birth and Birth Weight*

Birth Weight	Born in Hospital (or Nursing-home) or Transferred there within 2 Months			Born at Home and not Transferred to Hospital (or Nursing-home)			Place of Birth, or Subsequent Transfer Not Known			Total			
	M	F	Sexes Combined	M	F	Sexes Combined	M	F	Sexes Combined	M	F	Sexes Combined	M : F Ratio
Under 2 lb. 4 oz. (1,000 g.) ..	23	58	81	2	2	4	0	0	0	25	60	85	42 : 100
2 lb. 4 oz. (1,000 g.)– ..	106	186	292	4	6	10	0	0	0	110	192	302	57 : 100
2 „ 13 „ (1,250 „)– ..	356	448	804	17	37	54	5	4	9	378	489	867	77 : 100
3 „ 5 „ (1,500 „)– ..	731	904	1,635	70	68	138	4	13	17	805	985	1,790	82 : 100
3 „ 14 „–4 lb. 6 oz. (1,750–2,000 g.)	1,511	1,719	3,230	247	344	591	26	35	61	1,784	2,098	3,882	85 : 100
Total	2,727	3,315	6,042	340	457	797	35	52	87	3,102	3,824	6,926	81 : 100

* Infants whose birth weight was 4 lb. 6 oz. (2,000 g.) or less, and who survived two months or more.

of developing retrolental fibroplasia is closely associated with some factor connected with hospitalization. Applying the specific incidence rates by sex and birth weight observed in the total population of infants to the number of infants in each of the corresponding subgroups of the "home" population, it is found that as many as seven or eight cases would have occurred among the infants born at home and not transferred to hospital, if they had been subject to the same risks as the whole population. Making due allowance in this way for the differing sex and birth-weight compositions of the two groups, the incidence of retrolental fibroplasia in "hospital" infants can be directly compared with that in "home" infants. The difference between them is significant ($\chi^2 = 8.14$, n = 1, $P < 0.01$).

TABLE III.—*Incidence of Retrolental Fibroplasia Among Infants Born in or Transferred to Hospital (or Nursing-home)*

Birth Weight	Males			Females			Sexes Combined		
	No. of Infants	Cases of R.F.		No. of Infants	Cases of R.F.		No. of Infants	Cases of R.F.	
		No.	Rate %		No.	Rate %		No.	Rate %
Under 2 lb. 4 oz. (1,000 g.) ..	23	3	13·0	58	10	17·2	81	13	16·1
2 lb. 4 oz. (1,000 g.)– ..	106	20	18·9	186	20	10·8	292	40	13·7
2 lb. 13 oz. (1,250 g.)– ..	356	23	6·5	448	13	2·9	804	36	4·5
3 lb. 5 oz. (1,500 g.)– ..	731	21	2·9	904	9	1·0	1,635	30	1·8
3 lb. 14 oz.–4 lb. 6 oz. (1,750–2,000 g.) ..	1,511	7	0·5	1,719	1	0·06	3,230	8	0·3
Total ..	2,727	74	2·7	3,315	53	1·6	6,042	127	2·1

The overall incidence rate of the disease among infants born in or transferred to hospital, and with a birth weight not exceeding 4 lb. 6 oz. (2,000 g.), was 2.1 per 100 infants (Table III). It is of some interest to consider the incidence amongst the "hospital" infants with a birth weight not exceeding 4 lb. (1,800 g.). In these babies the incidence was 3.2%, a figure which may be compared with the 4.1% of "blind" babies observed in the Medical Research Council's inquiry (1955).

Incidence in Relation to Sex

Examination of the incidence in different birth-weight groups and for males and females separately (Table III) reveals two definite features. For each sex there is a pronounced decline in the incidence rates from the lower to the higher birth-weight groups (as has already been demonstrated for all infants in Table II). Secondly, the total incidence rate for males (2.7%) is considerably higher than that for females (1.6%), and with one exception there is a consistently higher male incidence in the separate birth-weight groups. The one exception occurred amongst the infants with the lowest birth weights (less than 2 lb. 4 oz.) (1,000 g.), where the female incidence rate was somewhat higher than that for males. The number of male infants in this birth-weight group was, however, small (only 23).

Comparison of the incidence in males and females, after due allowance for their differing birth-weight distributions, gives a highly significant difference ($\chi^2 = 17.20$, n = 1, $P < 0.001$). This difference does not necessarily establish sex, *per se*, as a factor affecting the incidence rate of the disease. It may well be a reflection of differing levels of maturity among the male and female infants. Female infants have lower birth weights than male infants of the same maturity, and male infants suffer a higher neonatal mortality in each of the birth-weight groups adopted here (Shapiro, 1954). Thus the fixing of an arbitrary upper limit of birth weight for the survey may have been responsible in part for the high female : male ratio of infants observed, and, as a corollary, may have caused the proportion of more immature infants to be greater among the males.

The effect of maturity on the comparison between the sexes can be at least partially eliminated by comparing the incidence among equal numbers of males and females at the lower end of the birth-weight scale. If, for example, the first 500 infants in each sex are chosen consecutively in ascending order of birth weight, the two groups so constituted should be reasonably similar in their levels of maturity. It can be estimated from Table III that the first 500 males have birth weights up to 3 lb. 5 oz. (1,500 g.) and the first 500 females birth weights up to 3 lb. 2 oz. (1,420 g.). The numbers of cases of retrolental fibroplasia with birth weights up to these levels were 47 males and 38 females. The difference is not statistically significant. It may well be, therefore, that the higher incidence among the male infants is largely a reflection of their lower level of maturity as compared with the female infants.

Incidence in Relation to Multiple Births

Of the infants included in this survey, 2,191 (36%) came from multiple births, and were made up of 2,077 twin babies, 105 members of triplets, and 9 members of quadruplets. From the triplets four infants and from the quadruplets three infants developed retrolental fibroplasia. Details of the incidence of the disease in twins are given in Table IV,

TABLE IV.—*Incidence of Retrolental Fibroplasia Among* 2,077 *Twins Born in England and Wales During* 1951

Birth Weight	All Twins			Twins Born in Hospital or Transferred to Hospital (or Nursing-home) within 2 Months		
	No. of Infants	Cases of R.F.		No. of Infants	Cases of R.F.	
		No.	Rate %		No.	Rate %
Under 2 lb. 4 oz. (1,000 g.) ..	17	3	17·7	16	3	18·8
2 lb. 4 oz. (1,000 g.)–	64	7	10·9	60	7	11·7
2 lb. 13 oz. (1,250 g.)–	260	16	6·2	233	16	6·9
3 lb. 5 oz. (1,500 g.)–	578	13	2·3	521	13	2·5
3 lb. 14 oz.–4 lb. 6 oz. (1,750–2,000 g.)..	1,158	0	0	940	0	0
Total	2,077	39	1·9	1,770	39	2·2

which shows that there were 39 cases, giving an overall rate of 1.9% and a hospital rate of 2.2%. Both these figures are in close agreement with the corresponding rates for all infants (1.8% and 2.1%). The same pattern of a marked decline in incidence of the disease with increasing birth weight was present among twins, and the incidence rates in the different birth-weight groups are similar to the corresponding rates for all infants.

Incidence in Relation to Region

The local health authorities were grouped into 11 regional areas and the incidence rates of retrolental fibroplasia in each of these areas obtained. Two measures of incidence were calculated for each region—a crude incidence rate based on all infants whose birth weight was not more than 4 lb. 6 oz. (2,000 g.), and an incidence rate based on infants

TABLE V.—*Incidence of Retrolental Fibroplasia in Different Regions of England and Wales* (1951)

Region	Incidence Rates (%)	
	All Infants	Infants Born in or Transferred to Hospital (or Nursing-home)
Northern	1·33	1·84
East and West Ridings..	1·05	1·15
North Midlands ..	2·03	2·39
Eastern	1·62	1·84
London	1·70	1·81
Southern	1·46	1·73
South-western ..	2·14	2·50
Wales	2·49	2·86
Midlands	0·89	1·04
North-western	2·74	3·07
South-eastern	2·45	2·75
England and Wales ..	1·83	2·10

of the same birth weights born in hospital or transferred there within two months of birth. Both measures show a considerable variation between different parts of the country (Table V). The experience of the Midlands region was the most favourable (all infants 0.89%, "hospital" infants 1.04%), and the highest incidence occurred in the North-western region (all infants 2.74%, "hospital" infants 3.07%).

Neither of these crude measures of incidence makes any allowance for possible differences in the sex and birth-weight distribution of infant populations in the different regions. The pattern of variation displayed by the crude rates can, however, be confirmed by a measure of incidence which makes adjustment for such differences. Thus the sex and birth-weight specific incidence rates for the whole country ("hospital" infants) were applied to the "hospital" infants of each region to give the number of infants "expected" to have developed the disease had there been no regional variation. Expressing the number of cases observed as a proportion of the "expected" number provides an index making appropriate allowance for differing sex and birth-weight distributions of the populations (Table VI). The wide

TABLE VI.—*Incidence in Each Region Compared with Incidence in England and Wales as a Whole (Based on Infants Born in or Transferred to Hospital or Nursing-home Within Two Months)*

Region	Relation Between Incidence and that of All E. and W.
Midlands	52% lower
East and West Ridings	43% ,,
London	25% ,,
Eastern	16% ,,
Southern	14% ,,
Northern	6% ,,
North Midlands	2% ,,
South-eastern	16% higher
South-western	27% ,,
Wales	60% ,,
North-western	65% ,,

variation between different regions was again apparent, with an incidence ranging from about 50% lower to more than 50% higher than that experienced over the whole of England and Wales. All three measures of incidence showed the rates to be highest in the North-western and Welsh regions and lowest in the Midlands and East and West Riding regions.

Summary

Particulars have been obtained from all local authorities in England and Wales of infants born in 1951 having a birth weight of 4 lb. 6 oz. (2,000 g.) or less and surviving at least two months. Of 6,926 such infants, 1.83% had retrolental fibroplasia. No case was found amongst the 797 infants born at home and never transferred to hospital. The incidence was closely related to birth weight, declining steeply with increasing birth weight. The incidence was higher in males than in females, but this difference may be due to male babies being less mature than female babies of the same weight. Twin babies showed the same incidence as single babies. Considerable regional variability was observed, with relatively high rates in Wales and the North-western counties and low rates in the Midlands and East and West Ridings of Yorkshire.

We are grateful to Professor A. Bradford Hill for helpful advice and criticism in the planning of the survey and in the preparation of this report. We are also deeply indebted to the medical officers of health, whose assistance enabled the survey to comprise the whole of England and Wales, to the many health visitors who compiled the detailed returns, and to the ophthalmologists who so readily co-operated.

REFERENCES

Medical Research Council Report (1955). *British Medical Journal*, 2, 78.
Shapiro, S. (1954). *Amer. J. publ. Hlth*, 44, 1142.

HEREDITARY COPROPORPHYRIA

BY

H. BERGER, M.D.

Universitätskinderklinik, Jennerspital, Berne, Switzerland

AND

A. GOLDBERG, M.B., Ch.B., F.R.F.P.S., M.R.C.P.

Department of Chemical Pathology, University College Hospital Medical School, London

In 1936 Dobriner reported a case in which a woman excreted large amounts of coproporphyrin (probably series III) and traces of uroporphyrin in the urine, and also large amounts of coproporphyrin (series I and III) and protoporphyrin in the stool. Although this woman was then a patient in a psychiatric ward, there were no apparent symptoms associated with the abnormal porphyrin excretion. Watson *et al.* (1949) described the cases of two men who excreted large amounts of coproporphyrin III in the urine and stools, unaccompanied by symptoms. They stated that this condition, which they called "idiopathic coproporphyrinuria," represented an "inborn error of metabolism," although they could not find evidence for any hereditary association of the abnormality.

The present paper describes the occurrence of a similar pigment disturbance in a Swiss boy, in his mother and father (who are first cousins), and also in his paternal aunt. The boy excretes much higher quantities of coproporphyrin in his urine and faeces than the others and also passes traces of uroporphyrin I in his urine. He has suffered from rickets, noted for the first time at 3½ years, as well as from riboflavine deficiency. An unusual amino-acid excretion pattern was obtained by paper chromatography in three of these four subjects. The term "hereditary coproporphyria" has been used for this condition, because of the genetic significance of these findings and because the porphyrins are excreted in the faeces as well as in the urine, principally in the faeces.

Methods

Porphyrins.—Quantitative determinations of porphyrins and porphobilinogen in the urine and stools were carried out as in a previous study (Goldberg, 1954). Since initial investigation had shown that the excess porphyrins were entirely ether-soluble, the isolation and identification were done as under "ether-soluble porphyrins."

Urinary amino-acids were identified by paper chromatography (Dent, 1951).

Riboflavine determinations were carried out by means of microbiological assay, using *Lactobacillus casei*, or fluorimetrically.

Case Report

This patient was born in 1944 after a normal labour. His mother had hyperemesis during pregnancy. Birth weight, 3 kg. He was breast-fed until the age of 7 months, then was given breast milk and vegetables until 1 year, when he was put on a mixed diet. His first tooth erupted at 1 year and he completed his primary dentition by the end of his second year. He started walking at 1½ years and spoke his first word at 2. About the age of 1½ years he had a generalized skin rash, which disappeared when milk was discontinued. About this time he also had diarrhoea, which was treated in the out-patient department of the Jenner-Kinderspital, Berne, Switzerland. At 3½ years he had a severe middle-ear infection, which later was complicated by a throat and lung infection. He recovered from