In chronic alcoholism, on the other hand, the incidence of carcinoma in this series was very high, namely 33·3%. In comparing alcoholic and non-alcoholic cirrhosis a figure of this magnitude was liable to occur by chance in only 1 of every 25 samplings. But after allowing for the fact that 24 of the 30 alcoholics, including all those with carcinoma, were males, the possibility of this difference having occurred by chance was raised to about 1 in every 7 samplings. It is quite possible therefore that the high incidence of malignant change among the alcoholics of this series merely reflected the sex incidence of alcoholic cirrhosis. The supposed high incidence of liver cancer in hæmochromatosis may have a similar explanation, for hæmochromatosis is very largely a disease of males. Warren and Drake (1951) deduced from the literature that this incidence was 18·9%, a figure which they considered to be more than four times that for cirrhosis in general; this figure is, however, appreciably less than that for males in the present series.

Finally an explanation must be sought for the differences between the figures set forth here and those in previous reports on the subject. It may well be that many of these differences are apparent rather than real, being due to use of the term cirrhosis for minor degrees of hepatic fibrosis without disruption of lobular pattern and without the clinical picture of the disease. It is claimed, however, that there are geographical variations in the liability of cirrhosis to undergo malignant change (Report of Conference on Liver Cancer, 1956, *Lancet*, ii, 782). In North America this liability is said to be lower than in Europe; but there is in the literature some evidence to the contrary. Thus Edmondson and Steiner (1954) found hepatic carcinoma in 4·5% of all cirrhotics, but in 19% of advanced atrophic cirrhosis. The corresponding figures of Wilbur *et al.* (1944) are 10·5 and 14·2%. Figures in excess of 10% are also given by Loesch (1939) and McNamara *et al.* (1950). Thus it may well be that uniform standards for the diagnosis of cirrhosis would result in similar figures for both America and Europe. Carcinoma as a complication of cirrhosis in tropical countries will not be discussed here.

SUMMARY

Primary carcinoma of the liver was present in 16·3% of 184 patients in whom cirrhosis had been diagnosed at necropsy. When only those patients actually dying of hepatic disease were considered, the incidence of malignant change was 18·6%. Corresponding figures for male cirrhotics alone were 23·7 and 29·7% respectively.

Post-hepatitic cirrhosis is seldom complicated by primary hepatic carcinoma. Its high incidence in alcoholic cirrhosis and in hæmochromatosis may depend on the fact that most patients with these diseases are males.

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Pseudocholinesterase in Early Infancy

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PSEUDOCHOLINESTERASE

PSEUDOCHOLINESTERASE is an enzyme present in the serum which destroys acetylcholine *in vitro*. It is not identical with the true cholinesterase of the red cells which hydrolyses acetylcholine at physiological concentrations. We determined the activity following Jones and Tod (1935) and McArdle (1940) by incubating serum with acetylcholine and a $NaHCO_3$ buffer in a micromanometer. On hydrolysis of acetylcholine to choline and free acetic acid one mol of CO_2 is liberated from $NaHCO_3$ for each mol of free acetic acid, and the CO_2 is measured manometrically. According to McArdle (1940) one unit of enzyme equals one μl. of CO_2 liberated by one ml. of serum in one minute at 37° C. Our normal range in adults is 55–125 units with a mean of 85 units.

Normal Pseudocholinesterase Levels in Adults, Children and Infants

It is well known that the normal pseudocholinesterase level shows great individual variation in adults, although it remains very stable from day to day in any one individual (Verebély, 1936; Hall and Lucas, 1937; Antopol *et al.*, 1937; McArdle, 1940; Sawitsky *et al.*, 1948; Callaway *et al.*, 1951; Kaufman, 1954). There is in adults no correlation between age and pseudocholinesterase level. The normal level in children is not as well defined as that of adults. Rather high values have been reported in children by McArdle (1940) who in 40 normal adults found a range between 51 and 121 units with a mean of 78, and in 20 children aged between 7 and 15 years observed a range between 71 and 166 units with a mean of 105 units. Although there is a considerable overlap between the values found in the two groups the overall difference is statistically significant. Hodges (1956) compared 52 healthy adults and 70 healthy children aged 3–10 years. The number of high values was greater among the children, but the differences were not significant statistically. Our own experiences are the same as those of Hodges. In contrast to children where the pseudocholinesterase level is if anything higher than in adults, low enzyme activity has been reported in newborn infants by Faber (1943) and McCance *et al.* (1949). Stead (1955) mentions that he has found the pseudocholinesterase level of the neonate at times to be as low as 40% of the adult mean.

Liver Function and Pseudocholinesterase Level in the Newborn

It is now accepted that a low pseudocholinesterase level can be an indication of lowered liver function. McArdle (1940), Wescoe *et al.* (1947), Kaufman (1954) and Hunt and Lehmann (1956), among others, have demonstrated the changes of pseudocholinesterase level with improvement or deterioration of liver function. It occurred to us that the low pseudocholinesterase level found at birth might be related to incomplete development of liver-cell activity—just as functional immaturity of the liver cell has been held responsible for the physiological hæmolytic jaundice of the newborn, the liver at birth being thought to be unable to metabolize an amount of bilirubin arising from red cell breakdown with which it would easily cope at a later age.

Mollison and Cutbush (1949) injected 5 mg. of bromsulphalein per kilogram of body weight into healthy adults and found that the liver removed 98% of the drug from the blood stream within one hour. In newborn infants receiving the same dose there was an average retention of 15% of the dye two hours after the injection. These results were interpreted as an indication of an immaturity of the excretory function of the newborn liver. They were in support of earlier work of Herlitz (1926) who also had described an abnormal bromsulphalein retention in the newborn, but they contradicted the observations of Salmon and Richman (1943) who had failed to do so. Yudkin *et al.* (1949) tested the bromsulphalein excretion in infants from 8 hours to 8 days old and found a higher proportion of normal values above the age of 4 days than below that age.

To obtain exact information on the pseudocholinesterase levels of infants seemed to us valuable not only for theoretical reasons but also from the practical point of view. In the diagnosis of neonatal hepatitis it is important to know what constitutes an abnormally low level in infants. Mollison and Cutbush (1949) and Yudkin *et al.* (1949) had not found a correlation between the degree of failure to excrete bromsulphalein at birth and the subsequent rise in bilirubin levels. We had hoped that the pseudocholinesterase level at birth might perhaps serve as a measure predicting the failure to metabolize bilirubin later on.

Results

We examined 87 cord bloods of which 43 were obtained at St. Bartholomew's Hospital and the remainder from Queen Charlotte's Maternity Hospital. It will be seen from Table I

Table I.—Pseudocholinesterase and Birth Weight

Weight lb.	Number	Mean (units)	Range (units)	Number	Mean (units)	σ
2–3	9	55	35–104	43	59	±15
3–4	10	55	37– 81			
4–5	24	62	34– 93			
5–6	16	62	36– 86	29	59	±13·3
6–7	13	55	38– 71			
7–8	9	66	38–110	15	70	±22·2
8–9	6	76	41–101			

Pseudocholinesterase levels in newborn infants.

that many values were below those considered normal in adults. The mean value was higher the greater the birth weight, but with all birth weights the lower range extended below the

normal adult range. In 61 of the 87 children definite information could be obtained on the duration of gestation, in addition to that of the birth weight. Table II shows that there was

TABLE II.—PSEUDOCHOLINESTERASE IN INFANTS

Age	Number	Mean (units)	Range (units)	σ
At Birth				
Premature ..	30	59	35–104	±16·6
Full term	31	66	38–110	±17·2
1–4 weeks	10	86	60–105	±15·9
4–8 weeks	14	94	68–150	±21·9

no difference when cord bloods of 30 premature and 31 full term babies were compared. Of the premature babies 6 had been born after a pregnancy lasting less than 30 weeks, and 24 after one lasting 30–35 weeks. There was also no difference in the results obtained in these two groups of premature infants. Table II also shows that in contrast to the newborn the pseudocholinesterase level in infants aged 1–8 weeks was within the range considered normal for adults and that in the group aged 4–8 weeks there was a number of children with a level higher than normal adult levels.

In view of the wide individual variation a much larger number of infants would have to be investigated to obtain statistically significant data supporting a rise of pseudocholinesterase level within the first few weeks of life. We decided therefore to examine the enzyme levels over the first weeks of life in 22 infants individually. These had been born at full term with a normal birth weight and were not jaundiced. Fig. 1 illustrates the results; the values

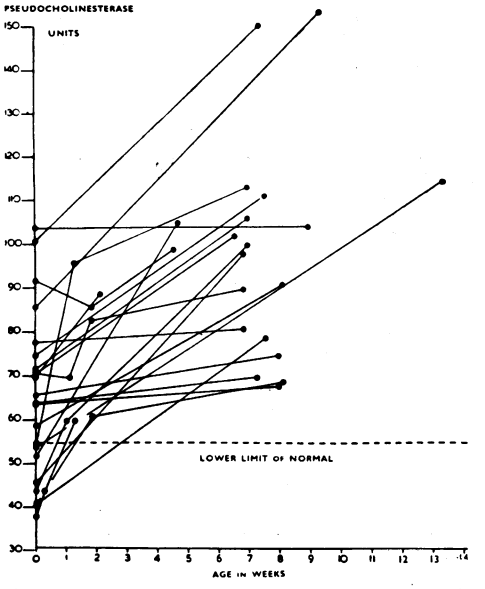

FIG. 1.—Serial observations on pseudocholinesterase level in 22 normal infants during the first weeks of life.

obtained at birth (but not those obtained later) are also included in Tables I and II. It will be seen in Fig. 1 that 8 of the 22 infants showed levels of 55 units and below at birth, and that the highest level was 104 units. With one exception, where at birth and just above nine weeks later the level was 104 units, all infants examined after one month showed a higher enzyme concentration than at birth. Within the second month of life all of 20 infants seen were found to have levels within the normal range. Furthermore whereas at birth only three values of 22 had been above 90 units, within the second month of life 13 of 20 were above this level.

The samples obtained at birth were cord blood, and those obtained later were capillary blood. Fig. 1 illustrates that the change from the enzyme concentration at birth to that seen later was gradual and could not be due to a difference between cord and capillary blood. It will be seen that in one instance the level rose from 38 units at birth to 44 units after two and to 60 units after nine days.

Unfortunately no correlation between pseudocholinesterase level at birth and subsequent rise of bilirubin level was found. On the other hand our observations allow the suggestion that except for the first few days of life a low pseudocholinesterase level can be taken to be pathological in infants as well as in adults. This conclusion has helped us on several occasions in the diagnosis of jaundice in infants, and has so far never failed us.

Conclusions

The pseudocholinesterase level was measured in the serum of 87 newborn infants. Whereas in adults the normal range is 55–125 units, the range in the newborn was 34–110 units. There was no difference between premature and mature newborn infants, and no correlation could be found between pseudocholinesterase level at birth and subsequent rise in bilirubin level.

In 24 normal infants aged 1–8 weeks the range was 60–150 units, and the low pseudocholinesterase level at birth is correlated with an immaturity of liver function as previously demonstrated by the measurement of bromsulphalein excretion.

Serial observations were made on 22 infants. 8 of them at birth had pseudocholinesterase levels lower than would be considered normal in adults. All values were normal when the infants were re-examined later on. Whereas only 3 of the infants had at birth a pseudocholinesterase level above 90 units, 13 such values were found in 20 infants re-examined within the second month.

It is suggested that after the first few days of life an abnormally low level of pseudocholinesterase can be considered pathological.

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