(1954). We must aim to give what protection we can to those who are especially susceptible.

The practitioner is in a strong position as regards early diagnosis. Case finding is highest in those people referred for *x*-ray examination by practitioners. There is no effective substitute for a practitioner who is quick to detect and act upon early suggestive symptoms or signs. As a corollary it should everywhere be an easy matter for a doctor to have his patient *x*-rayed. Where facilities are still lacking, they should be pressed for insistently until made available; miniature films are inexpensive, are quite efficient, and are useful in this connexion.

Hospital and sanatorium treatment is now much more available in most parts of the country, but some areas lag behind. Long waits for surgery—up to two to six months—are still existent; these, apart from anything else, result in wasteful blockage of beds.

Regional hospital boards and hospital management committees are sensitive to criticism on this matter. If there is delay in effective treatment, pressure by a practitioner will do much to obviate it.

The policy of vaccinating school-leavers with B.C.G. remains in a far too nebulous state. No clear lead has been given. The evidence available should be sifted as soon as possible with a view to establishing a national policy. The full possibilities regarding hostels for continued segregation and sheltered workshops require further study, but this should be undertaken with a view to promoting a suitable scheme of action and not lead to further delay. Evidence is still awaited regarding the most appropriate regime of chemotherapy for the long-term sputum-positive patient, and at what intervals it should be applied.

Summary

It can be asserted that chest disease presents us with a challenge. Much of it is preventable—it is not being prevented. Our community and our profession are dying needlessly. Clean and uninfected air in town and workplace is essential—it can be obtained. Cigarette-smoking has been shown to be more dangerous to health than any other national habit. Unless the irritant and carcinogenic effects can be eliminated, further manufacture and sale should be seriously questioned. No consideration of tax collection should blind us to the need for action.

Last century saw great progress in eradicating intestinal disease. More spectacular progress can now be made in ridding us of diseases of the chest. This challenge is a personal and a national one. Economically, action is essential—humanely, it is imperative.

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Health education was considered mainly from the nursing point of view by a group of doctors and senior nursing personnel at the 1954 Summer School arranged by the Central Council for Health Education at Reichel Hall, Bangor, North Wales. The group rejected the suggestion that specially trained health educators were necessary in hospitals. After the medical staff, the ward sister was the key person in instructing patients and their relatives. But if she were to have time to do this properly it might be necessary to lighten some of her other duties.

INCREASED PLASMA BILIRUBIN IN NEWBORN INFANTS IN RELATION TO BIRTH WEIGHT

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Some degree of jaundice is often shown by newborn babies in whom there is no evidence of haemolytic disease. The extent and duration of jaundice are rather variable (Davidson *et al.*, 1941), but are thought to be more marked among premature infants (Hsia *et al.*, 1953). The condition is generally regarded as an innocuous one, as is implied by the customary description—"physiological jaundice." However, a more serious view is suggested by recent reports (Aidin *et al.*, 1950; Claireaux *et al.*, 1953), which show that prematurity and jaundice may be followed by pigmentation of the brain and death of the infant. This association had led us to re-examine the relation between birth weight and the incidence, degree, and duration of the increased bile-pigment content of the plasma of newborn babies. The nature of the plasma pigment has also been determined, since there is evidence that bilirubin is damaging to the brain.

Methods

The basis of the survey was a series of plasma bile pigment estimations, at approximately daily intervals, on a group of "normal" newborn babies which were selected to provide a wide range of birth weights. In order to determine the highest plasma pigment concentration reached in each baby the study was continued until the amount of bile pigment in the plasma had dropped markedly from the previous day's figure, or had dropped appreciably on two consecutive days.

Birth Weight.—This was drawn from the hospital case records.

Selection of Patients.—The one criterion for including a baby in the survey was its birth weight. During the period of this investigation all babies in certain wards, up to a maximum of nine babies in each weight group, were studied, excepting those babies that were known to have haemolytic disease or some other pathological feature. The plasma pigments of some very small babies were not determined during the first day or two because of their clinical condition. Additional babies, to whom attention was drawn because they were jaundiced or deeply jaundiced, were studied with respect to the type of serum pigment, but are not included in the series.

Bile Pigment Estimations.—Heel-prick blood was collected with heparin or oxalate, and 0.05 to 0.2 ml. of plasma was used for quantitative estimation by van den Bergh's diazo technique (King, 1951). For the most part estimations were made daily, though there were occasional intervals of 48 hours.

*Working on a grant from the Medical Research Council.

Identification of Pigments.—Extracts of plasma pigments were prepared and examined chromatographically (Cole and Lathe, 1953) to distinguish bilirubin, which is indirect-reacting, from the other bile pigments which react directly in the van den Bergh test.

Results

Amounts of Bile Pigment.—The study included 49 babies ranging from 2.75 to 10.24 lb. (1.2 to 4.6 kg.) birth weight. Of these, 19 were "premature" infants—that is, they weighed 5.5 lb. (2.5 kg.) or less at birth. For analysis the premature and normal-weight infants were divided at pound intervals into three and five groups, respectively. The changes in plasma bile pigment were plotted for each baby and the maximum height and the day on which this occurred were noted. The maximum height of plasma bile pigment of the babies in each group is plotted as an average, and standard deviation, in Fig. 1. The day on which this peak occurred is presented in a similar way in Fig. 2. It would have been desirable to plot average curves of daily bile pigment concentrations for the babies of each weight group, but as the same number of samples were not taken from each baby this method was not satisfactory. As an alternative, individual graphs of five "typical" babies, varying in weight from 3.8 to 9 lb. (1.7 to 4.1 kg.) are given as examples in Fig. 3.

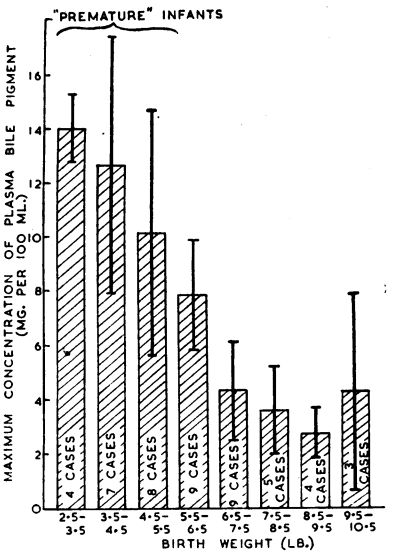

FIG. 1.—Relation between the birth weight of infants and the maximum concentration of plasma bile pigment which occurs during the neonatal period. The average for each weight group is shown as a column, and the limits of one standard deviation are shown as a vertical line.

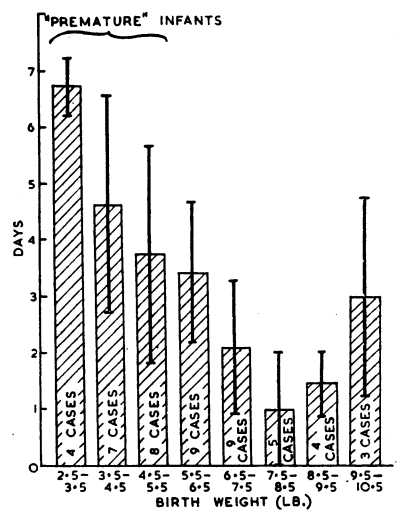

FIG. 2.—Relation between the birth weight of infants and the day on which the maximum plasma bile pigment concentration occurs. The average for each group is shown as a column, and the limits of one standard deviation are shown as a vertical line.

Type of Pigment.—The type of bile pigment found in the plasma of newborn babies was determined chromatographically in more than 40 plasma samples from 10 babies in whom the plasma pigment concentrations were over 7 mg. per 100 ml. The predominant pigment in every instance behaved on the chromatogram like bilirubin. The minor amounts of direct-reacting bile pigments have not been estimated quantitatively, but they appear to be about 5–10% of the total, or less. In some instances of high bile pigment concentration rather large quantities, probably 10–20%, of direct-reacting bile pigments were observed during the phase of decline of the total plasma bile pigment.

Discussion

This study serves to emphasize three aspects of bile pigment metabolism in the newborn infant. Firstly, although clinical reports have often suggested that jaundice is more common among premature infants, an examination of Fig. 1 shows that the presence of a great excess of bile pigment is characteristic of small newborn infants. Among these infants high concentrations of bile pigment occur in the plasma with a consistency which has not been reported previously. Thus of 11 babies weighing less than 4.5 lb. (2 kg.) at birth 9 had plasma pigment concentrations of over 12 mg. per 100 ml. at some time during the neonatal period, and five reached levels of 15 mg. or higher. The tendency for low birth weight to predispose to high plasma pigment concentration holds true throughout the range of birth weights of 3 to 9 lb. (1.4 to 4 kg.) even though there is considerable variation within some of the individual groups. Nevertheless, instances of high bile pigment among babies of normal weight are much less frequent than among the small babies, in whom it predominates. Thus, excluding haemolytic disease, hyperbilirubinaemia in the newborn is essentially a condition of infants of subnormal weight. The same tendency is expressed, in a minor way, in infants of normal weight.

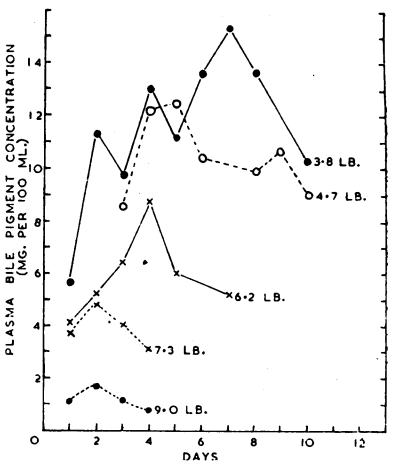

FIG. 3.—The course of plasma bile pigment concentration during the neonatal period of five "typical" babies of varying birth weights.

The series of infants have also been examined with regard to the length of the gestation period. The results are very similar to the analysis by birth weights, but in a small series no distinction can be drawn between the effects of age and those of growth of the foetus.

These elevated pigment levels in small babies were reached partly as a result of a more rapid rise of pigment, but also by a prolongation of the phase of rising pigment, as shown by the peak day in Fig. 2. The time required for return to a lower level of pigment after the peak had been reached was also more prolonged among the smaller babies, as exemplified in Fig. 3. Thus the tissues of small infants are exposed to higher concentrations of bile pigment for a longer period than are those of larger babies.

Secondly, when the type of pigment is taken into consideration it is clear that the neonatal period of the small newborn infant forms a second category, additional to haemolytic disease of the newborn, in which the tissues are exposed to large amounts of bilirubin. Claireaux *et al.* (1953) have commented on the significance of the fact that in neonatal haemolytic disease there occur much greater concentrations of plasma bilirubin than are found in the adult. High plasma bilirubin is very exceptional in the adult, since the predominant pigment of obstructive jaundice differs from bilirubin. Billing (1954) has shown that in these cases the amount of indirect-reacting pigment—that is, bilirubin—seldom exceeds 7 or 8 mg. per 100 ml. In adult cases of haemolytic jaundice this level is very rarely reached. The

greatly increased concentration of plasma bilirubin in neonatal haemolytic disease is undoubtedly of importance in the development of brain jaundice, and this may also be true of the substantial amounts of pigment which have now been shown to occur in premature infants unaffected with haemolytic disease. Claireaux *et al.* (1953) suggested that the time taken for the accumulation of the bilirubin in the non-haemolytic form of neonatal jaundice might account for the fact that these babies tend to die about the seventh day rather than on the second, as do those affected with brain jaundice due to haemolytic disease. It remains to be seen, of course, what factors other than plasma bilirubin concentration may affect the degree to which bilirubin penetrates the "premature" and "normal" newborn brain.

Thirdly, the degree of bilirubinaemia occurring in most of the small infants indicates that there usually exists a much greater defect of bilirubin metabolism than has previously been suggested. In recent years the conception that neonatal jaundice is not haemolytic in origin has gained much ground since the demonstration by Mollison (1948) that in the newborn infant there is no greatly elevated rate of erythrocyte disappearance to which the jaundice could be ascribed. More recent studies of normal infants (Fashena *et al.*, 1950) and of premature infants (Arthurton *et al.*, 1954) have confirmed this. The accumulation of bilirubin in the plasma is now usually attributed to a reduced excretory capacity of the newborn liver, though the degree of reduction is seldom sufficiently emphasized.

It is possible to compare the excretory ability of the small newborn infant with that of the normal liver, as estimated indirectly by Weech *et al.* (1941) in the human, and directly by Billing and Weinbren (1954) in experimental animals. From these studies one may calculate the normal rate of excretion of bilirubin when the plasma pigment concentration is 10 mg. per 100 ml., an amount which occurs frequently in small newborn infants. In the course of ten hours the normal liver can excrete an amount of bilirubin equivalent to all the haemoglobin in the body. The daily production of bilirubin by a newborn infant would be disposed of in fifteen minutes. Thus, under these circumstances, the liver of a small newborn infant can excrete bilirubin at a rate of only 1 or 2% of the normal adult liver.

This very low level of excretory activity of the liver of small newborn babies cannot be explained by some general factor such as reduced circulation or involution of the left hepatic lobe (Emery, 1953), since if all the liver functions were affected to this extent life could not be supported. The fundamental hepatic defect of non-haemolytic jaundice of the newborn must therefore have a highly specific character, probably confined to the immediate metabolism of bilirubin.

A possible explanation of the character of this defect is suggested by the fact that the high concentrations of plasma bilirubin are associated with only minor amounts of the direct-reacting bile pigments. This contrasts with experiments in which comparable plasma concentrations of bilirubin were maintained by intravenous injection of rats and rabbits. In these a substantial proportion of direct-reacting bile pigments, chiefly pigment I, also appeared in the plasma (Cole *et al.*, 1954; Billing, 1954). This suggests that the transformation of bilirubin to the direct-reacting bile pigments is greatly limited in the newborn baby. Malloy and Lowenstein (1940), as a result of a study of a strain of congenitally jaundiced rats, have proposed that this alteration of the indirect-reacting bilirubin to direct-reacting bile pigment is a prerequisite for the excretion of bilirubin by the liver. Such a chemical change probably would have the degree of specificity which is required to explain the presence of a great deficit in bilirubin metabolism while other liver functions remain relatively unimpaired.

The general features and mode of development of the non-haemolytic form of neonatal jaundice appear to be the following. During the period of intrauterine life bilirubin is removed across the placenta (Findlay *et al.*, 1947). Under normal circumstances, as seen in the large infant, the impending loss of this route of disposal at birth is anticipated by the development of an adequate excretory function of the liver during the later weeks of foetal existence. It is this development which is uncompleted in the small newborn infant. Thus "physiological" jaundice is not to be interpreted as an indication of rapid adjustment after birth, as has been claimed, but arises from lack of development before birth. This is the reason why it is characteristic of the newborn infant whose foetal growth has been interrupted by early delivery or retarded by adverse conditions. It is essentially abnormal rather than "physiological."

Summary

It is characteristic of prematurity that there is a high concentration of bile pigment in the plasma during the neonatal period. The influence of birth weight on the amount of pigment extends throughout the range of birth weights of 3 to 9 lb. (1.4 to 4.1 kg.), and is most fully expressed among small infants. In these the plasma pigment concentration often rises to 12 mg. per 100 ml. or above. Under these circumstances the liver's capacity to excrete pigment is estimated to be 1–2% of normal.

The plasma bile pigment has been shown to be bilirubin. The specific defect of bile pigment metabolism in the newborn infant may be a reduced capacity of the liver to transform bilirubin to direct-reacting bile pigment.

Prematurity is thus a second condition in which the tissues are exposed to high concentrations of bilirubin.

We are grateful to the medical and nursing staff of Queen Charlotte's Hospital for their co-operation in this study. Our gratitude is due to Miss O. B. Sweet, who carried out the laborious task of securing specimens for analysis.

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A new employment centre for the elderly of Finsbury was opened by Lord HORDER on November 11 at a ceremony presided over by the Mayor. Lord Horder said that he was happy to know that the new centre was to be called "Brooke House" as a well-deserved compliment to his old friend Dr. BLYTH BROOKE, medical officer of health for the borough, to whose enthusiasm this project was largely due. It was common knowledge, Lord Horder went on, that we were an ageing population, but there were now hundreds of thousands of men and women who, at an age which even 10 years ago would have marked them down as too old for any activity, were able to make a contribution, not only to their own health and happiness, but to that of the community. The human machine was very like a factory—it needed to be kept going by work. By denying elderly people the opportunity to do the work for which they were fit the community lost some useful service, and the people themselves, owing to lack of employment, aged more quickly. The centre, managed by the Employment Fellowship in co-operation with the borough council, employs 86 old people, of average age 72.