use of these instruments is more scientific than the direct pursuit of one's problems by simple appropriate methods; and the desire for the glamour and prestige of research rather than for the interest, pleasure, and satisfaction of searching.

Opportunities for the Practitioner

The practitioner can follow the natural course of disease and its modification by all manner of influences: a huge field of unending interest and challenge. He can study the efficacy and dangers of new remedies. Every effective measure opens new avenues for research into the fundamental nature of the disorder affected. Each great advance raises far more questions than it answers, and opens doors for useful investigation to practitioners who can see the opportunities. Any clinical field in which there is nearly universal acceptance of current ideas is ripe for critical questioning and productive research.

The exact observations of Trousseau in the middle of the last century led him to doubt the value of blood-letting and other current measures used in treatment of people with strokes, and he ceased to use these methods because, as he said, "experience has taught me that patients do better without them." William Pickles, during his years of general practice in Yorkshire, in addition to throwing much light on the epidemiology of common infections, was the first in England to report cases of Bornholm disease.⁶ Many similar examples of important contributions by practitioners of former and modern times could be cited did time permit.

But the great contribution of practitioners as a body cannot be cited in individual instances. They play a large if inconspicuous part in the advancement of medical knowledge. The accumulated good sense of a large number of thoughtful doctors has a wonderful influence: it dampens the excessive swings of medical fashion; buffers the over-enthusiastic claims for ill-founded methods of diagnosis and treatment; acts as the ultimate jury in clinical trials; and has a firm, strong educational influence.

The general principles of research methods and study are the same, no matter what the field. But techniques used vary greatly, and each must learn those appropriate to his problem. To produce much new knowledge requires virtually all the time of the investigator, allowing little opportunity for practice except in fields restricted to his special interests. But the critical research attitude of honest thinking and penetrating doubt on the part of the doctor in active practice is a catalyst which speeds up the learning process and gives new knowledge at a different but important level. It broadens his mind, increases his comprehension, and by its inherent discipline raises the standard of all aspects of his practice and of that of his closer associates.

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TREATMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN DUE TO RH-IMMUNIZATION*

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In all cases where there are grounds for suspecting maternal Rh-immunization the first problem facing those responsible for the newborn infant is the prevention of death *in utero* or the birth of a child already gravely affected. At the present time it can be reduced to a decision whether or not to induce labour before term.

Induction of Labour before Term

We have adopted this term in place of "premature induction of labour," as the aim is in fact not to bring about the birth of a premature infant in the generally accepted sense of an infant weighing less than 2,500 g. It is well known that premature infants develop more severe and more prolonged hyperbilirubinaemia than do those born at term, and for this very reason are more exposed to the danger of kernicterus.

Except in cases of necessity, where obvious signs of foetal distress demand immediate intervention (which

*The pathogenic bases for the individual aspects of the treatment have been given in detail elsewhere (Jouvencaux *et al.*, 1958), together with the results of 330 cases. These results, to which those for 1958 have been added, are summarized in the present paper, making a total of 399 cases.

then becomes a heroic measure) we do not induce labour until everything has been done to establish that the infant weighs over 2,500 g. With this aim, we have made it a rule not to induce before the end of the eighth month. The stage of pregnancy, calculated from the last period, is, however, often misleading, and is by itself a quite inadequate criterion. An obstetric examination, carried out by a skilled obstetrician experienced in such cases, is essential, including a radiological examination, which we consider indispensable.

Another condition necessary if the induction of labour before term is to be harmless is the avoidance of other than purely mechanical methods—bougie or rupture of the membranes. Obviously, in cases where the obstetric condition does not appear suitable for intervention of this kind there must be no question of taking any risk; one should refrain from or at least postpone intervention, unless the urgency of delivering an infant clearly showing signs of distress, together with dystocia, makes caesarean section imperative.

As the efficacy of the treatment of haemolytic disease of the newborn is essentially preventive, it is important

that the infants to whom it is applied should be as little affected as possible, even if such infants are, by virtue of their birth before term, theoretically more exposed to the risk of subsequently developing a greater degree of jaundice, and hence are in more danger of kernicterus. The more the treatment of haemolytic disease of the newborn at birth and in the first days of life is perfected and increases in efficacy, the more induction of labour before term is justified in order to obtain a living infant, since, properly treated, such infants will recover.

This shows, however, that it is impossible to separate the induction of labour before term from efficient treatment of the newborn infant, the former being justified only by an assurance of the latter. This is the third condition which we consider essential if labour is to be induced before term.

In view of the possibility of unexpectedly severe manifestations in first affected infants, or when the titre of the maternal antibodies is low, we are of the opinion that in all cases where on serological evidence the child may be assumed to be Rh-positive, and where the foregoing conditions prevail, induction of labour before term may and should be carried out. Only when it is possible to estimate the degree of affection of the child *in utero* much more precisely than at present will there be any alternative. Hitherto, radiological examination of the foetus and examination of the excretion of 17-ketosteroids and pregnanediol in the maternal urine have given results only at a stage much too late to be of real value. Bevis (1952) and Walker (1957) have obtained interesting results with the electrophoretic study of amniotic fluid, but only before the 35th week, and in practice puncture of the amnion remains very difficult to carry out routinely and repeatedly. Observation of the reticulocyte level in the mother has been proposed by Kondi and Jacobescu (1958); in women carrying badly affected children we have confirmed his finding of levels differing significantly from those found in 100 "normal" women at various stages of pregnancy, but the sensitivity of the method appears poor.

Although we have accepted the principle of routine induction of labour before term, and have practised it from the start, there are nevertheless many among our observed cases where the woman presented at the maternity hospital only at the onset of spontaneous labour, on whom induction of labour before term could not be performed. In these cases we have had a death rate *in utero* of about 10%, over half of which occurred in the last two months of pregnancy. One may assume that a certain number of these deaths could have been avoided. We have compared (Table I) the incidence of the type of delivery, spontaneous or induced, among live-born infants in relation to the results of treatment.

By taking all the necessary precautions, we have had practically no disappointing surprises as regards the weight of infants delivered by induction of labour before

term. Of 125 infants so delivered, 106 weighed over 2,500 g. and therefore did not fall within the definition of premature (of these 106 infants, two-thirds were over 3,000 g.), and 19 weighed between 2,000 and 2,500 g.; among the latter there were cases with distinct obstetrical signs (renal symptoms) and cases with an extremely bad history or signs of foetal distress.

The total results thus appear better in infants delivered by induction of labour before term; however, the above comparison is open to criticism. On the one hand, a small number of the infants delivered spontaneously were not seen immediately after birth, and, on the other, in the group of children delivered by induction of labour before term there are a greater number of cases where there was a previous history or the maternal serology gave cause for anxiety. In an attempt to examine two comparable and *a priori* severely affected groups of infants differing only in the manner of delivery, we have selected only infants born alive, with one or more elder sibs dead either *in utero* or in the neonatal period from haemolytic disease of the newborn due to Rh-immunization; we retained only infants known before birth to be exposed to danger and consequently treated with equal promptness.

TABLE II.—*Influence of Method of Delivery Among Live-born Infants Having at Least One Elder Sib Dead from Haemolytic Disease of the Newborn Due to Rh-immunization and Treated Promptly*

	Total	Deaths	Kernicterus	Recoveries
Delivered by spontaneous labour	26	7 (26.9%)	0 (0%)	19 (73%)
Delivered by labour induced before term	51	3 (5.9%)	2 (3.9%)	46 (90.2%)

It is clear from Table II not only that the induction of labour before term has enabled us to prevent deaths *in utero* towards the end of pregnancy, sometimes in the final stages (Gaucherand *et al.*, 1952), but that even in the case of live-born infants the degree of affection is less when labour has been induced before term. This corresponds to the fact that the severest pictures at birth are encountered most often in infants delivered spontaneously.

Although it has been possible in the past to accuse induction of labour before term of increasing the number of cases of kernicterus—as indeed would appear from Table II—the criticism is now without foundation, since we know how to avoid this complication. Since May, 1954, observation of bilirubin levels has, as is explained below, guarded against kernicterus. From this date, in 13 women bearing an Rh-positive child still alive at the end of the eighth month, who had previously had at least one death *in utero*, induction of labour before term enabled us to obtain 13 living children and 13 complete recoveries.

Prompt Exchange Transfusion Criteria

We have adopted broad criteria for carrying out exchange transfusion immediately after birth; in establishing them, regard was paid both to clinical and to laboratory information. Faced with even one clinical sign of affection, we carried out the treatment at once. In cases where the infant showed no clinical signs at the moment of birth, the results of the laboratory investigations were interpreted cautiously.

TABLE I.—*Influence of Method of Delivery Among Live-born Infants*

	Total	Deaths	Kernicterus	Recoveries
Delivered by spontaneous labour	236	33 (10 from kernicterus)	21	192 (81%)
Delivered by labour induced before term*	125	7 (none from kernicterus)	3	115 (92%)

*Or, exceptionally, by caesarean section.

Serological tests, whether on the mother or on the infant, are of diagnostic value, but only to a much less degree are they prognostic. In cases where the haemoglobin is low, clinical evidence will already have indicated as much; where it is normal it is known to be deceptive. Walker and Mollison (1957) state that 40% of infants dying from kernicterus had a cord haemoglobin above 15 g./100 ml. Erythroblastæmia and reticulocytosis are no more reliable as a guide. The information supplied by the cord bilirubin level is somewhat of the same order as that supplied by the haemoglobin: a high level tells us nothing, and it is not uncommon for a low one to rise later to a dangerous level.

It is possible that indications drawn from the pigment "heme" of Abelson and Boggs (1953) may have a greater accuracy.

In practice, we have invariably carried out exchange transfusion on infants with a positive direct Coombs test, except in cases where the six following conditions prevailed: absence of any clinical signs, infant weighing over 3,000 g., absence of previous history, satisfactory cord data (Hb above 15 g., bilirubin below 3 mg.), serological findings giving little cause for alarm (titre of maternal antibody below 1/32), and the assurance of adequate supervision by means of bilirubin estimations.

Our criteria have thus been wider than those of Boggs (1956), who, relying on the cord level of the pigment "heme," was able to refrain from intervention in 30% of erythroblastotic infants, and also than those of Walker (1958), who considers that the information supplied by the cord blood haemoglobin and bilirubin levels is in practice by itself sufficient to distinguish at birth infants who need (or will need) transfusion and those (40%) for whom no treatment will be necessary. In our own series only 10% of the infants seen at birth with a positive direct Coombs test recovered without treatment.

In the case of infants seen at birth, however, it is the immediate necessity which must be decided: we do not believe that the initiation of hourly bilirubin estimations constitutes a valid reason for delaying immediate exchange transfusion in cases where it is not independently demanded by the clinical condition. By delaying there is a risk of depriving the infant of the advantage of prompt exchange transfusion, which would prevent the haemolytic crisis that comes immediately after birth. Moreover, bilirubin estimations performed on small samples of capillary blood cannot be accurate enough to allow the rise which occurs in a few hours to be followed precisely. Finally, even if it is possible to appreciate the rate of the rise (which reveals the intensity of the haemolysis), its duration, which is a function of the efficiency of the eliminating processes in any given case, can hardly be foreseen. Cases do occur where a rapid increase ceases abruptly, and, conversely, where a slow rise later becomes dangerous. Although the highest serum bilirubin levels are generally attained in infants with the highest cord bilirubin levels, it is also true that the premature infant often has a low cord level but a prolonged rise later. The criteria of cord blood may thus lose some of their value in infants born before term, and the practice of induction of labour before term may lead one to the necessity of treating a greater number of infants. We do not, however, think that this inconvenience can be weighed against the reduction in general mortality effected by it.

Blood Used for Transfusion

The blood used was in all cases of the same ABO group as the infant, and non-antigenic—that is, free from the antigen, usually Rh (D)—to which the mother was immunized. An examination of the mother's blood is thus implicit. There was, however, one exception in the case of a newborn infant admitted several years ago by a paediatric unit, when the mother's blood was not available. The child was referred as a case of haemolytic disease of the newborn, and, in addition to showing very suggestive clinical signs, was Rh-positive and had a positive direct Coombs test. It died during an exchange transfusion carried out urgently with Rh-negative blood. When later it became possible for us to obtain a sample of the mother's blood, she was found to be Rh-positive C/CDe, with an anti-c antibody. Since then she has borne two more affected children, on whom we have carried out exchange transfusions using Rh-positive (C/C) blood, and both of whom have recovered completely.

We use stored blood, as being more readily available, selecting bottles taken not more than three days previously, which have had time to settle. An amount of citrated plasma, equal to one and a half times the amount of acid-citrate-dextrose solution in the bottle before taking the blood, is drawn off. This allows us to inject somewhat less blood than is withdrawn, and thus to avoid or correct any circulatory overloading, while still relieving the anaemia. On an average, we thus create, at the beginning of the exchange transfusion, a deficit of 10 ml. per kg. of body weight, and sometimes more in cases of dyspnoea or cyanosis with raised venous pressure.

We believe that it is of value to use heparinized blood for the exchange; any risk of coagulation is thus avoided, and, more important, it provides an opportunity of adding directly to the bottle the calcium necessitated by the use of citrated blood. Electrocardiographic studies carried out by Gustafson (1951) by Furman, *et al.* (1951), and Joos *et al.* (1954) during the course of exchange transfusions, and those of Berliner (1936) after the injection of calcium, show on the one hand the dangers of hypocalcaemia and on the other those of massive injections of calcium. We therefore add 2.5 mg. of heparin followed by 1.5 ml. of 10% calcium gluconate to each 100 ml. of blood. At the end of the exchange the heparin remaining in the infant's circulation (about 5 mg.) is neutralized by the addition of 0.5 ml. of 1% protamine sulphate to the last few millilitres of blood given.

The amount of blood used for the exchange is based on the body weight of the infant or, more accurately, on its total blood volume, this being calculated as one-thirteenth of the body weight. Although in our first cases this amount was two to three times the total blood volume, we have received the impression that better results were obtained when four times the total blood volume was given, although it is difficult to produce clear statistical evidence for this. Whenever the state of the child permits, the latter is the amount used. There are, however, cases where, faced with a disturbing picture, one is obliged to confine oneself, as an emergency measure, to the correction of the anaemia and the reduction of the blood volume, and to attempt a complete exchange only in several stages.

The blood is warmed before and during the exchange in a water-bath at 37° C., and in addition the infant is

kept during the operation in a special thermostatically controlled incubator (Jouvencaux, 1958).

Technique of Exchange Transfusion

In the 418 exchange transfusions which we have carried out on newborn infants with haemolytic disease of the newborn caused by both Rh- and ABO-immunization, and also in cases where there was no blood-group incompatibility, we were able to use the umbilical route in all cases, except 13 (3%) in which we were obliged to cut down on the saphenous vein in the thigh. Often we were able to use the umbilical route on children over 4 days old, on premature infants (among them one weighing 900 g.), and up to three times on the same infant.

The efficacy of the exchange transfusion of a given amount of blood depends both on the capacity of the tubing from the syringe to the infant and on the amount of blood mobilized by each individual exchange. For this reason we have the syringe as near as possible to the umbilicus and use a 23-ml. syringe. The successive withdrawal and injection of this amount is perfectly well tolerated in the great majority of cases, but it may be reduced if the infant is small or if pallor develops on the withdrawal.

The speed of the operation also depends on the child's condition and its state during the exchange. Although for a long time we completed most of our exchanges in one hour, we have now adopted a slower rhythm.

Risks of Exchange Transfusion

It is impossible to reproduce the results of immediate exchange transfusion in figures, since it is not possible to compare the results obtained in infants who were so treated with those who were not, as the latter consists of infants either seen only at a late stage or who showed a mild affection, where intervention was not indicated. It is, however, possible to examine the risks of accidents during the operation.

In our 418 cases there were 14 deaths during or at the end of the operation, but an analysis of these cases shows that very few can be attributed to it. Among the 14 were a set of triplets whose four elder sibs had died from haemolytic disease of the newborn, three cases of hydrops, three cases of kernicterus, and one child delivered by caesarean section who had required resuscitation before the exchange. Another infant, already mentioned, died during an exchange carried out with Rh-negative blood, when the haemolytic disease of the newborn was in fact due to anti-c. Two others, rather heavily anaemic, died at a stage when the amounts of blood withdrawn were not greater than those injected. Finally, one infant died during the exchange transfusion of stored blood over one week old.

In no case was there post-operative infection or thrombosis. For a short period, however, we did encounter post-transfusional haemorrhages, and were led to wonder whether they had a connexion with the large amounts of blood—over three times the total blood volume—which we had begun to use at that time. In three infants who had not previously shown any haemorrhagic tendency exchange transfusion was followed, some 24 hours later, by purpura, prolonged bleeding at the sites of injection, or intestinal haemorrhage, the latter being followed by rapid death with a picture corresponding to that of cerebromeningeal flooding, although necropsy for the purpose of confirming this could not be performed.

We then carried out blood-coagulation tests on a series of infants treated by exchange transfusion. A reduction in the number of the platelets, previously reported after exchange transfusion or massive transfusion (Krevans and Jackson, 1955; De Bruijne *et al.*, 1956) was found. However, we have never found a thrombocytopenia severe enough by itself to explain the bleedings; in no case has the platelet count been below 50,000 per c.mm. But it is possible for massive exchange transfusion to have other consequences in the newborn besides a lowering of the platelet count. The most striking complication which we have met is hypoprothrombinaemia, and especially hypoproconvertinaemia, which must have been present before the exchange, with proconvertin times reaching 300 seconds when normal controls were giving times of 60 seconds. A state of hypoprothrombinaemia and hypoproconvertinaemia is physiological in normal newborn infants (Loeliger and Koller, 1952; Van Creveld, *et al.*, 1954) and is exacerbated by haemolytic disease of the newborn. It is generally largely corrected by the compensating effect of a great number of thromboplastic factors of placental origin, as Larrieu *et al.* (1952) and Masure and Schonne (1956) have shown. Under these conditions massive exchange transfusion could have the effect of temporarily correcting the two deficiencies for about 24 hours only, after which they would reappear rapidly, while at the same time draining off the compensating thromboplastic factors which would until then have protected the infant.

Since then all infants receiving exchange transfusion have been routinely treated with vitamin K₁, and we have been able to carry out 204 exchanges, normally involving over four times the total blood volume, without the appearance of any bleeding.

We have not used "synthetic" preparations of vitamin K, which are much less effective and which have been said to increase hyperbilirubinaemia and encourage kernicterus (Allison, 1955; Moore and Sharman, 1955; Crosse *et al.*, 1955; Meyer and Angus, 1956; Bound and Telfer, 1956). Allison *et al.* (1956) and Marusich *et al.* (1956) have shown that in rats deprived of vitamin E, haemolysis with haemoglobinuria can be induced by intramuscular injection of several synthetic preparations of vitamin K but not by the injection of vitamin K₁.

Control of Bilirubinaemia, and Drainage by Exchange Transfusion

Until May, 1954, once exchange transfusion had been carried out at the earliest possible moment, subsequent supervision was in practice limited to clinical observation and control of the haemoglobin. The direct Coombs' test had generally been rendered negative as a result of the exchange, and the erythroblastemia brought within fairly normal limits. From this date, however, a daily estimation of the serum bilirubin has been performed routinely on all infants by a micro-method requiring the use of only a small amount of capillary blood (Jouvencaux and Revol, 1957) and any showing hyperbilirubinaemia above 20 mg./100 ml. of serum have been regarded as requiring drainage by exchange transfusion.

Results during these two periods on infants coming into our hands, either immediately after birth or at any rate before the appearance of kernicterus, are given in Table III.

TABLE III.—Incidence of Kernicterus and Death Before and After Initiation of Regular Bilirubin Estimations (May, 1954)

	Live-born Infants Seen Before Appearance of Kernicterus	Kernicterus	Deaths	Recoveries
Before May, 1954	74	9 (12%)	12 (16%)	74.3%
After May, 1954	272	0 (0%)	20 (7%)	93%

A contrast is furnished by infants coming into our hands after May, 1954, with kernicterus already established and having bilirubin levels known or assumed to be well above 20 mg. We have on no occasion seen kernicterus following "direct" bilirubinaemia with levels reaching 30 mg. or lasting for a month which was not accompanied by "indirect" bilirubin levels above 20 mg.

Drainage by exchange transfusion is effective only to a relatively small extent, since the exchange affects only the blood, while bilirubin is diffused throughout the tissues. For this reason it is important to carry out the operation slowly, taking at least two hours and using large quantities of blood. We have found by experience that at the end of an exchange performed under these conditions the blood withdrawn in the last syringe still contains considerable amounts of bilirubin. The effectiveness of the tissue drainage effected by slow and massive exchange transfusion is apparent if the calculated amount of circulating bilirubin before draining is compared with that found in the total amount of blood withdrawn. We have found that the total quantity of bilirubin withdrawn is at least double that previously circulating in the infant's blood, and may be up to four times this amount.

The marked decrease in kernicterus in haemolytic disease of the newborn due to Rh-immunization, following regular bilirubin estimations and the effectiveness of drainage by exchange transfusion have led us to observe and treat all cases of profound jaundice occurring in the neonatal period in this way.

One wonders whether there will in the future be a better method than drainage for reducing a dangerous hyperbilirubinaemia. This would presuppose some action on the enzymatic processes which at the hepatic level transform bilirubin into the form in which it can be eliminated—that is, direct glycuco-conjugated bilirubin. These processes are temporarily deficient at birth in the normal and to an even greater extent in the premature infant. The substances—sulphobromophthalein (Yudkin and Gellis, 1949; Obrinsky *et al.*, 1952) the corticosteroids (Bongiovanni *et al.*, 1958), and bilirubin (Grodsky *et al.*, 1958; Brown and Zuelzer, 1958)—which are known to require glycuco-conjugation before elimination, are eliminated more slowly at birth, and the excretion of glycuronides is diminished during this period (Brown, 1957). It still remains to determine whether it is the glycuco-conjugation mechanism which is deficient, or any of the vital intermediate stages.

An extremely slow rate of elimination of bilirubin (and also of the corticoids) appears to be very frequent in thyroid insufficiency. The frequency with which prolonged neonatal jaundice, which may result in kernicterus, occurs in congenital myxoedema has been pointed out by Akerrén (1954), Christensen (1956), and Bialkin and Harris (1958). It is quite conceivable that this congenital condition may cause late maturity of the

organs. Conversely, where this immaturity exists as in the premature infant, it has been found that ¹³¹I fixation is lower than in the full-term infant (Van Middlesworth, 1954; Martmer *et al.*, 1956). It therefore appeared logical to look for some stimulating action of the thyroid hormone on enzymatic processes still insufficiently developed at birth, and we have recently been trying this line of approach in cases of neonatal jaundice not accompanied by exaggerated haemolysis. We are not at the moment in a position to draw any conclusions.

Additional Treatments

The only additional treatment which we use is the routine administration of 100,000 units of penicillin per kg. of body weight after exchange transfusion, and half an ampoule of vitamin K₁ a day intramuscularly during the first three or four days.

After transfusion, using blood with a high haematocrit, anaemia reappears only slowly and in a very small number of cases. We ourselves never give prophylactic anti-anaemic treatment, as this is often badly tolerated by the digestive system and is usually of no value. Under these conditions, in about 7% of infants treated by exchange transfusion we have been obliged to give one injection of packed red cells, usually round about the age of one month.

A condition which may occur, as in 52 of our cases, is the "inspissated bile syndrome," clinically evident in varying degrees and invariably revealed by the presence of a strong "direct" bilirubinaemia. It may also be observed in two forms: present at birth, it usually accompanies severe affection with a wide symptomatology; and, appearing later, it may assume a form which is not particularly severe, perhaps with a familial predisposition. The most usual consequence is the prolongation of jaundice, but not of jaundice leading to kernicterus. Is it possible that the condition may lead to affection of the hepatic cells? We are of the opinion that if this is so it would pre-exist at birth, and would be seen only in the very severe cases, where the syndrome is present from the start. We have seen one such case where the child died at 2 weeks, with a picture reminiscent of cirrhosis. It is for cases such as these that there may be some indication for the use of cortisone; in less severe cases we have been able to obtain some improvement with one tablet of icteryl daily.

Conclusion

The treatment of haemolytic disease of the newborn has grown steadily in effectiveness and is continuing to do so. It is certain the existence of a previous history worsens the prognosis of a given case, but even in these cases there is now a high percentage of recoveries. Since May, 1954, we have seen 74 women with at least one previous child dead, either *in utero* or after birth, from haemolytic disease of the newborn due to Rh-immunization, who were pregnant with a further Rh-positive child. Among these 75 infants (one case of twins) our results have been 16 deaths *in utero* (21%), 3 deaths immediately following birth (4%), and 56 complete recoveries (75%).

The above shows that the real therapeutic problem of haemolytic disease of the newborn due to Rh-immunization is now one which arises before delivery, and to which the answer consists in obtaining a live

infant, viable for the first few hours, which will then have every chance of recovery.

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Toothbrushes have been issued at a cost of threepence each to children in 170 schools of Fiji's main island of Viti Levu in a campaign to encourage children to preserve their teeth. At each school the children brush their teeth every lunch-time under the supervision of a teacher. The brushes they are using have been bought in bulk by the dental section of the Medical Department. Some of the children now brushing their teeth every day had never used a toothbrush before. It is hoped that they will get into the habit of cleaning their teeth at home as well as at school, and that, through them, parents who are not in the habit of cleaning their teeth will learn elementary dental hygiene. It is aimed, eventually, to introduce the scheme into every school in the islands.

BIOSYNTHESIS OF CHOLESTEROL IN FAMILIAL HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

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Hypercholesterolaemia occurs in pregnancy, hypoparathyroidism, the nephrotic syndrome, obstructive jaundice, and diabetes, as well as in a number of relatively rare familial conditions of unknown aetiology. When persistent the condition is often associated with xanthomatosis, and the forms of the disease which are not secondary to some known disorder have been extensively studied by Thannhauser (1958). The mechanism whereby the concentration of cholesterol in the plasma is maintained at a higher level than normal is unknown, although experiments with labelled acetate have suggested that in some cases increased biosynthesis from acetate may be responsible.

Cholesterol is synthesized from acetate units in the body (Bloch and Rittenberg, 1942), and a number of workers have investigated the incorporation of labelled acetate into the plasma cholesterol of patients with a variety of conditions associated with hypercholesterolaemia (Hellman, Rosenfeld and Gallagher, 1954; Hellman, Rosenfeld, Eidinoff, Fukushima, Gallagher, Wang, and Adlersberg, 1955; Gould, LeRoy, Okita, Kabara, Keegan, and Bergenstal, 1955). The present paper describes a similar investigation of a patient with familial hypercholesterolaemic xanthomatosis. It has been shown that in this patient the biosynthesis of free cholesterol and its turnover rate are greatly increased, although the rate of esterification is normal.

Clinical History

The patient was an engineer aged 36. In 1943 he had a thyroidectomy which left him with some hoarseness. In 1953 he was investigated for a blackout and gave a history of continuous tinnitus for the previous 12 months and the development of small nodules on the back of the hands for the previous three months.

Examination showed him to be a tall and well-built man, with a dry skin, heavy features, and a slow and husky voice. Blood pressure was 130/90 mm. Hg and the pulse rate 60 a minute. The heart and lungs were normal. The blood count was normal. Chest x-ray examination revealed no abnormality. Laryngological examination showed paralysis of the right vocal chord; the tinnitus was found to be central and fixed. The electrocardiogram showed depression of the ST segment and inversion of the T₃, suggesting myocardial damage. The B.M.R. was -38% of normal. The plasma cholesterol was 860 mg./100 ml., and a biopsy