palpating the pulsating graft in the femoral triangle and in the popliteal fossa or by arteriography. Arteriography was used in only four cases.

Failure to improve after grafting procedures, or failure to maintain improvement, may be ascribed to two causes. Either the graft or the host artery may thrombose. Early failure which occurs immediately or a few hours after operation may be due to technical error, one of these being inadequate washing with heparin solution so that a clot is swept onwards after restoration of blood flow to lodge distally. Late failure may be the result of thrombosis in the graft or in the host vessel. Fig. 3 is an example of the occurrence of thrombosis in a graft two months after the operation. Most of the graft is occluded and only the proximal and distal portions are patent. We cannot determine the reason for the late graft thrombosis, but it may be that immunological reactions are responsible in some instances. There is little doubt that most of the late failures are due to thrombosis of the host vessels: atherosclerosis is a progressive disease.

We have one clear instance of the failure of a graft because of thrombosis in the host vessel. A graft was inserted in a man aged 74 for incipient gangrene. The clinical improvement was remarkable, but five weeks later gangrene set in and an above-knee amputation was performed. Fig. 10 shows the graft to be patent and the host vessel thrombosed.

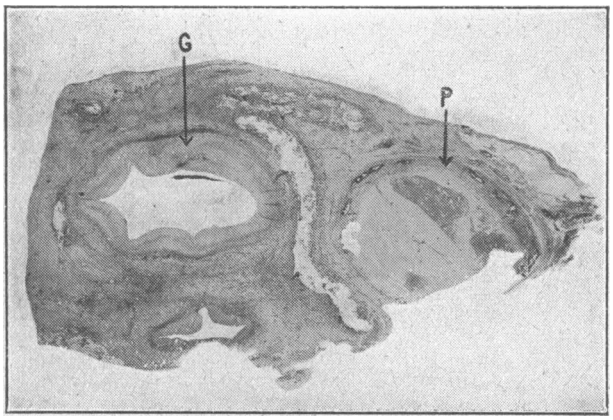

FIG. 10.—Photomicrograph of the popliteal artery (P) and arterial homograft (G) in an amputated leg. The graft is patent, but the popliteal artery is occluded by both recent and old thrombosis. (H. and E. ×3½.)

Because of the progressive nature of atherosclerosis grafting procedures are palliative rather than curative, but there is no doubt that the palliation achieved is far greater than that afforded by any other method of treatment. Although the series of cases presented is small, and the follow-up period is short, the results indicate that when possible bypass grafting, using the end-to-side anastomosis, should be carried out when other simpler methods of treatment have failed.

Summary

The materials available for peripheral artery grafting are discussed, and, of these, autogenous vein or human artery has proved to be superior to any synthetic substance. In atherosclerosis autogenous vein of sufficient length and diameter is rarely available, and so the latter is now used by us exclusively.

Grafting should be considered in all patients suffering rest pain or incipient gangrene, and also in those who are incapacitated by intermittent claudication. Coronary disease may make the operation a risky one, but this risk is probably no greater than that of an amputation.

The end-to-side graft is best in our hands, the reason being possibly because of the turbulence of blood flow induced at the site of anastomosis. The graft should always extend from the common femoral artery above to the distal part of the popliteal artery below, even if the length of femoro-popliteal artery obstructed is minimal. No other graft is now considered.

The results show a success rate of over 80% for periods up to 18 months, and in the state of our present knowledge the operation seems well worth while.

Failure may occur from extension of disease in the host arteries, from clotting in the graft, or sometimes from clotting at the site of anastomosis. An operation for grafting is described in detail.

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LIQUOR AMNII STUDIES IN THE PREDICTION OF HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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In a review of the deaths from haemolytic disease of the newborn in England and Wales during 1953 and 1955 Walker and Mollison (1957) stated: "It is suggested that, if all cases of haemolytic disease of the newborn (due to anti-Rh(D)) were predicted antenatally and were treated when necessary by early adequate exchange transfusion, the present death rate could be greatly reduced. Each year, in England and Wales, more than 150 infants would be saved."

The following preliminary report on liquor amnii studies shows that it is possible to predict haemolytic disease of the newborn antenatally.

Bevis (1956) described his investigations on liquor amnii carried out during and after his tenure of a Leverhulme Research Scholarship from the Royal College of Obstetricians and Gynaecologists. In an effort to arrive at a prognosis for the baby yet to be born of a sensitized rhesus-negative woman, he obtained specimens of liquor by abdominal paracentesis, and using a spectrophotometer produced a spectral absorption curve for each specimen by plotting its optical density against the wavelength. It was Bevis's experience that when the baby was unaffected by haemolytic disease the graph of optical density at various wavelengths was virtually a straight line between 600 and 400 mμ. When the baby was the subject of haemolytic disease, Bevis noted a rather consistent deviation attributable to increased optical density at 450 mμ. This deviation is referred to hereafter by the somewhat colloquial term of "the bulge," and its appearance has been attributed by Bevis to the presence of bilirubin, the concentration of which it reflects quantitatively. He has also identified a less consistent deviation attributable

to oxyhaemoglobin. In Bevis's report there is a rough correspondence between the severity of the haemolytic disease and the concentration of bilirubin as indicated by the height of the " bulge."

While there is still indecision on the best method of management of sensitized rhesus-negative women, there is no doubt that there is a place for timely intervention in selected cases. It was thought that the liquor amnii test might help to decide the best time for such intervention, if its accuracy could be proved. In January, 1956, the Medical Committee of St. Mary's Hospitals, Manchester, decided that all rhesus-negative cases with antibodies should be seen by one obstetrician after the 30th week, and I was invited to undertake this. Aspiration of the liquor amnii was performed at the 32nd week, and, as suggested by Bevis, at fortnightly intervals thereafter. This entailed as many as three or four tests on booked cases, but in many patients referred late in pregnancy from outside clinics there was time for only one test. In the first 74 cases, 134 specimens of liquor were tested, the aim immediately being to see how accurately it was possible to predict that the baby would be affected or unaffected.

Results

An analysis of the first 74 cases revealed a correct forecast in 52 (70.3%). The predictions were correct in 35 of the 55 affected cases (63.6%) and in 17 of the 19 unaffected cases (89.5%). The incorrect forecasts were examined with the clinical pathologist (Dr. R. F. Jennison). Of the 20 affected cases which had not been predicted there were 11 whose

Table of Results

	Cases	Correct Forecasts
Tested before 35th week ..	61 ..	56 (91·8%)
„ after 35th „ ..	40 ..	20

babies were only serologically affected (Coombs test positive) but did not require treatment. These results were encouraging, but further examination was indicated.

It had been noticed that towards the end of pregnancy the liquor amnii obtained by aspiration tended more often to be turbid, owing probably to vernix caseosa, and that in such cases the results were unreliable. This led to an analysis of the predictions according to the week of pregnancy during which the liquor had been tested. This showed (Fig. 1) that when the test had been carried out before the start of the 35th week, 37 out of 40 cases had been accurately predicted (92.5%), whereas after and including the 35th week there were only 15 correct forecasts in the other 34 cases (44.1%).

These results would suggest that if the liquor is tested in the same case before and after the 35th week different and conflicting curves might be obtained. This is true, and Fig. 2 shows three curves, the earlier test at the 32nd week showing the child to be affected, and the later ones at the 37th and 38th weeks suggesting that it would be unaffected. The forecast at the 32nd week was the correct one.

It has been mentioned that a turbid liquor was more frequently encountered late in pregnancy, but it must be stressed that late in pregnancy the liquor is just as frequently clear, yet the resultant curve erroneously predicts an unaffected baby (Fig. 2). Turbidity can be present before the 35th week, and if it were true that it was always responsible for false negatives one would expect turbidity to mask the presence of bilirubin before the 35th week. This is not so, as was demonstrated in several cases in this series. One cannot therefore blame turbidity alone, and the conclusion drawn is that towards the end of pregnancy there is in affected cases much less bilirubin in the liquor. One can only surmise that perhaps a more mature baby may be able to deal with this excess bilirubin in its own liver.

Since appreciating the importance of an early paracentesis, much better results have been obtained. Only one test on each case has been found to be necessary. There were 23 consecutive correct forecasts in the next 27 cases. The final analysis of all cases (See Table) shows an accurate prediction in 56 cases (91.8%) out of the 61 where the test had been performed before the 35th week. On reviewing the five incorrect forecasts based on early paracentesis alone, it was found that in two cases there had been a delay of respectively 11 and 16 days in testing the liquor owing to a breakdown of the spectrophotometer. In both instances the infant was predicted to be affected only mildly. The bilirubin detected was presumably due to haemolysis during this delay of a few red cells remaining in the liquor after filtering and centrifuging. A heavily blood-stained liquor must be discarded, but it is obvious that other specimens must be tested immediately if false positives are to be avoided. If these two cases are eliminated from the series the accurate prediction rate is 94.9%. Of the remaining three cases, one was found to have given incorrect dates, so that the liquor test was in actual fact performed after the 35th week, and in the other two unaffected babies were predicted. This was correct in so far as neither required treatment, but the cord blood was Coombs-positive.

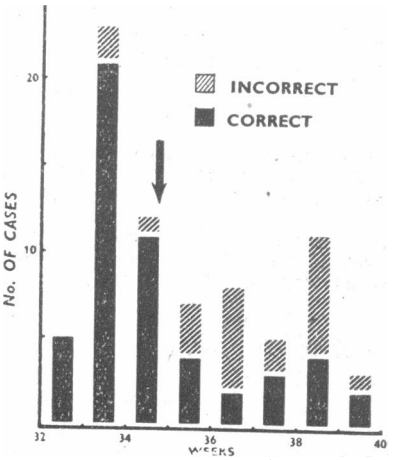

FIG. 1.—Number of cases predicted in each week of pregnancy, showing correct and incorrect forecasts. The arrow indicates the end of the 34th week.

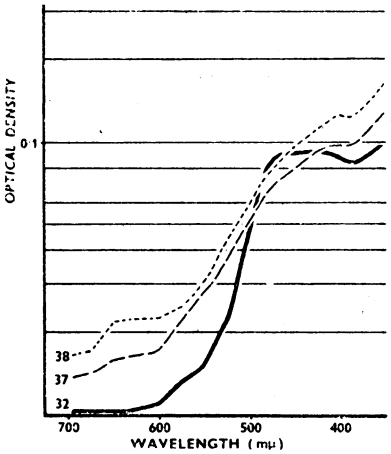

FIG. 2.—Showing three spectral absorption curves at 32, 37, and 38 weeks. The one at 32 weeks suggests that the infant will be affected (bilirubin at wavelength of 450 mμ), whereas the other two suggest an unaffected infant (no bilirubin). All specimens of liquor were pale and clear.

It is now felt that the increased accuracy of the early liquor test makes it highly desirable that the test be offered to all patients at risk. A plea is therefore made for the customary retesting of the serum of rhesus-negative patients to be carried out at the 32nd week, and very promptly reported, so that a liquor test can be performed in good time.

At a meeting of the Paediatric Section of the Royal Society of Medicine held at Queen Charlotte's Hospital in February, 1957, a report was given of 30 caesarean sections being performed between 32 and 36 weeks on patients who had had two or more stillbirths, irrespective of whether the husband was homozygous or heterozygous. In this group seven unaffected children were delivered. If a liquor test had been performed on these patients before the 35th week, an alternative management might have been considered in seven instances.

There have been no accidents as a result of the test, and the patients are not distressed by it. Indeed, when a patient is given a good prognosis concerning her baby, considerable peace of mind is derived from such news.

Summary

A report is given of liquor amnii tests on 101 sensitized rhesus-negative women. It has been found that: (1) the liquor must be tested fresh before the 35th week; and (2) an accurate prediction can be obtained in at least 94.9% of cases.

This work has been made possible by the willing co-operation of all members of the medical and nursing staffs of St. Mary's Hospitals, Manchester. I wish to thank Professor W. F. Gaisford, Dr. G. M. Komrower, and Dr. R. F. Jennison for their constant advice and enthusiasm in this research; and also my obstetrical colleagues who so kindly entrusted their patients to my care, and to Dr. D. C. A. Bevis for much generous assistance.

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TOXAEMIA OF PREGNANCY TREATED WITH PROGESTERONE DURING THE SYMPTOMATIC STAGE

BY

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While investigating the use of progesterone for the relief of premenstrual syndrome (Greene and Dalton, 1953) a high incidence of toxaemia of pregnancy (19.1%) was recognized among sufferers from this syndrome. A further investigation, undertaken to ascertain the incidence of premenstrual syndrome in those who had previously suffered from toxaemia of pregnancy, revealed that 86% of the 237 women thus affected at one time or another during the previous twelve years also suffered from premenstrual syndrome (Dalton, 1954). Furthermore, direct questioning and a scrutiny of records of these patients showed that before the full development of the signs of toxaemia—that is, oedema, hypertension, and albuminuria—most had earlier in the pregnancy experienced a symptomatic stage characterized by relatively minor afflictions—for example, lethargy 43%, headache 48%, visual aura 37%, vertigo 29%, nausea and vomiting 16%, irritability 14%, depression 9%, and backache 6%. In fact, only 7% disclosed freedom from these symptoms during a toxaemic pregnancy. Of the 237 women, 92 (38.8%) had experienced both a normal and a toxaemic pregnancy, and 72 (78%) contrasted the sense of well-being associated with a normal pregnancy with the malaise and minor symptoms characteristic of the toxaemic condition.

The striking feature of these early minor symptoms of toxaemia was their close resemblance to those of premenstrual syndrome noted in an earlier investigation (Greene and Dalton, 1953), most patients confirming that the minor symptoms during their toxaemic pregnancy were similar, though of increased severity, to those experienced in the premenstruum, irrespective of whether the onset of premenstrual syndrome had preceded or followed the toxaemic pregnancy.

Apart from the similarities of these minor symptoms in the two conditions, other points in common were noted. For example, day-to-day observations of sufferers of premenstrual syndrome had shown that, apart from minor symptoms, some developed oedema, hypertension, and albuminuria during the premenstruum, with spontaneous improvement during menstruation. This appeared to be analogous to the spontaneous resolution of oedema, hypertension, and albuminuria following delivery. Furthermore, if symptoms remain untreated either in premenstrual syndrome or in toxaemia both diseases may culminate in fits, epileptic in the one case, eclamptic in the other.

In an earlier investigation one of the reasons for using progesterone in the treatment of premenstrual syndrome had been that some patients suffering from this condition were symptom-free during pregnancy. It was considered that the corpus luteum and placenta supplied enough progesterone during pregnancy to keep these patients symptom-free. Others were not only unrelieved of their premenstrual symptoms during pregnancy, but, as already indicated, developed symptoms closely resembling those of the premenstruum and culminating in toxaemia. It was therefore thought possible that the development of toxaemia might in such cases arise from failure of the corpus luteum and placenta to produce sufficient progesterone.

In the light of similarities between premenstrual syndrome and toxaemia, and the fact that treatment of the former with progesterone not only relieved the symptoms (Greene and Dalton, 1953) but also prevented the development of oedema, hypertension, and albuminuria in the premenstruum (Dalton, 1954, 1955), it was decided to carry out a trial, employing large doses of progesterone in patients disclosing early minor symptoms of toxaemia, in an attempt to arrest full development of that condition.

Methods and Material

This investigation was carried out in a maternity hospital and midwifery training centre with 71 beds. Here a clinic for mothers up to the 28th week of pregnancy is run by the midwives, who were asked to devote particular attention to those patients who, in the middle trimester, showed a deterioration in general health. Those complaining of nausea and/or vomiting, lethargy, irritability, depression, vertigo, fainting, and paraesthesia (generally between the 16th and the 28th weeks but sometimes earlier) were referred to me. After interviewing them, but without clinical examination, I recommended a test dose of progesterone. Patients responding to the test dose were subsequently treated with progesterone or ethisterone in a dosage individually determined. Those showing toxaemic or other signs after the 28th week were referred directly to the consultant, with whom any decision to admit such patients for routine toxaemic treatment rested.

Test Dose of Progesterone.—As at this stage there is no reliable biochemical test for detecting progesterone deficiency or potential toxaemic symptoms, a therapeutic test with progesterone was made. A controlled investigation into the value of this test injection is in progress at a London teaching hospital, where progesterone test injections and similar injections containing inert oil are being used. These results will be embodied in a subsequent paper. In the preliminary investigations a test dose was given for such toxaemic symptoms as occurred at any time before the 28th week. Initially 50 mg. of progesterone in oil was used, and if the symptoms were not relieved the test was later repeated, the dosage being doubled. It soon became apparent that better results were obtained with an initial dose of 100 mg., and this was subsequently adopted as standard. This test dose was injected deep into the buttock. If the symptoms were not relieved when the patient was seen two days later it was