multiple values were obtained from several attendances only the first complete set were analysed.

It has usually been suggested that portal systemic encephalopathy is more likely to occur in older patients (Rousselot *et al.*, 1963; McDermott *et al.*, 1968; Panke *et al.*, 1968). This was not so in the present series, for though the incidence of cerebral dysfunction tended to be greater in patients aged 40 and over there was no significant age distribution to the overall incidence of clinical encephalopathy.

The Reitan trail making test has afforded a useful tool for the objective assessment of cerebral dysfunction after portal decompression and has also been used sequentially to measure response to treatment of encephalopathy. At the moment the sociological significance of these alterations in cerebral function is uncertain. They may well be important in patients whose occupation demands a moderate intellectual capacity, and to clarify this point further work is being undertaken.

This group of patients had no other cause for cerebral dysfunction, such as alcoholism, and the use of these tests in assessing cerebral changes in patients who have undergone portal decompression may be limited in alcoholic patients.

We would like to thank Mr. Alan Hunt for allowing us to study patients under his care, and the Board of Governors of St. Bartholomew's Hospital for financial support.

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Placental Localization by Isotope Scanning with ^{113m}In. Results in 200 Patients

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Summary: Placental scanning was carried out in 200 patients over a period of 22 months with ^{113m}In. It was found to be a reliable method of demonstrating the placenta, with a smaller radiation dosage than by x-ray methods.

Introduction

Placental localization is now being carried out more frequently either to confirm placenta praevia or, if this is excluded, to allow the expectant mothers who have been admitted to hospital to return home for social reasons or to free hospital beds for others. If reliance is to be placed on the localization then it must be accurate and should be convenient and without risk to mother and fetus.

Methods

X-ray Methods.—Soft-tissue radiography may demonstrate the placenta by visualizing fine calcification within it in 30-50% of patients with a whole-body radiation dose to the fetus of 100 to 2,000 mrads. Erect lateral pelvimetry will usually exclude a major degree of placenta praevia if the fetal head is engaged in the pelvis (Reid, 1949, 1951; Vickers, 1965). This method can give rise to false-negative and false-positive diagnoses, and the engaged head may not exclude a major degree of placenta praevia (Macafee, 1956). The most reliable *x*-ray methods are angiography and amniography. In the former a catheter is inserted from the femoral artery up to the bifurcation of the aorta, and after injection of contrast medium one or two radiographs are taken of the whole abdomen or pelvis (Fernström, 1955, Brink, 1960; Sutton, 1966; and Herlinger, 1968). In amniography the contrast medium is injected into the amniotic sac.

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‡ The Radiochemical Centre, Amersham.

Thermography and Ultrasound.—I have not found thermography to be of value. Unless the placenta is anterior there seems little chance of its detection by this method. Doptone examinations have confirmed the position of the placenta in some patients. Compound B scans are capable of showing the placenta even in the first trimester and are considered by Donald (1969) and Secker Walker *et al.* (1969) to be the method of choice. More recently, Cryer *et al.* (1970) stated, "at present, it would appear that neither ultrasonics nor thermography is a serious competitor to radio-isotope and radiographic methods," and also suggested that detailed follow-up studies should be made in order to detect any possible harmful effects of the diagnostic use of ultrasound.

Isotope Methods.—All isotope methods depend on labelling the maternal blood and detecting the placental blood pool. Browne (1951) used ^{24}Na, and others have used ^{131}I and ^{99m}Tc serum albumin with physical half-lives of 8 days and 6 hours respectively, and have used thyroid-blocking agents to help prevent uptake of isotope in maternal and fetal thyroids. Inhaled gases, such as ^{11}CO, with physical half-life of 20 minutes (Jacoby and Arnot, 1969), may also be used to label the blood, if there is a nearby cyclotron to produce the isotope. The present isotope of choice is ^{113m}In (physical half-life 1·7 hours), which is derived from a ^{113}Sn generator column. The gamma energy is 393 KeV, which means that little radiation is absorbed or scattered in the tissues as may occur using ^{99m}Tc (140 KeV) with a posteriorly situated placenta.

Technique.—The column is eluted with 4 ml. of N/20 HCl, 0·5 ml. of 20% gelatin is added, and the mixture autoclaved. Then 250-500 μCi is injected intravenously at about *p*H 1·6—a modification of the original method of Stern *et al.* (1967) (see also Wagner, 1968). Scans are made with the patient first supine, after she has emptied her bladder, and subsequently lateral, if the placenta is not fundal or is poorly seen. A dual 5-in. (12·5-cm.) SELO† scanner is used, summing the outputs of the detectors (above and below the patient) in the

display. The scanning speed is 20 mm./sec. with a line spacing of 4 mm., each view taking about 25 minutes.

Radiation Dosage and Clinical Hazards

The breakthrough of ^{113}Sn (physical half-life 115 days) from the generator columns‡ is very low, being about 10^{-6} of the total column activity (Wright *et al.*, 1969). ^{113m}In bound to transferrin does not appear to cross the placenta to any extent (Huddlestun *et al.*, 1969; Johnson *et al.*, 1969). The maternal and fetal whole-body doses are estimated at 5 and 4 mrads/500 μCi respectively, which is roughly equal to about a week's naturally occurring background radioactivity from the environment. Chemical dosage of indium is of the order of 10^{-12} g., and is negligible. A few pyrogen reactions occurred early in this series but have not occurred since the bottles in which the isotope is autoclaved had their rubber washers in the metal cap lined with aluminium foil (Wright, 1969).

Patients and Results

Between March 1968 and January 1970 200 patients were examined, two being examined in subsequent pregnancies. Patients were examined between 28 and 42 weeks of pregnancy, and the clinical presentations varied from a primigravida of 15 with repeated slight bleeding to a para-4 with transverse lie. Forty-three patients had caesarean sections.

Position of Placenta (202 Scans)

Fundal		103
Anterior body		60
Posterior body		12
Placenta praevia	Grade I (posterior)	11
	Grade II–III (down to cervix)	11
	Grade III–IV (across pelvis)	4
Succenturiate lobe (praevia)		1
Twin pregnancies (both placentae shown) (see Fig. 1)		2

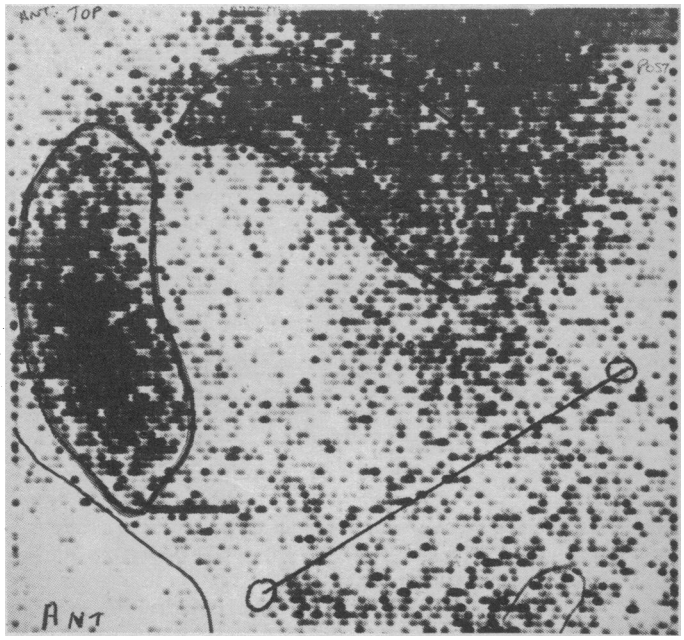

FIG. 1.—Twins; one placenta anteriorly in the body and the second posteriorly in the fundus.

Discussion

Comparison of scans was made in a few cases with a point-to-point counting system termed "simplified placental localization" by Hibbard (1969), for which 50 μCi of isotope may suffice. This method may reliably demonstrate an obviously fundal placenta, but seems to be unreliable unless the placenta is partly "sideways on." If the placenta lies across the front or back of the uterus like a "flat pancake" the blood pool in it will appear rather thin to the detector and the difference in count rate between the area of the placenta and surrounding tissues (also containing labelled maternal blood) will not be very great. In some patients we have not been able to localize the placenta either with a hand counter or the scanner in the supine position, though it was very clearly seen on the scan in the lateral.

The only major error occurred with the fourth patient we examined, when there appeared to be increased activity both in the fundus and in the pelvis. Radioactivity was found in the urine (450 ml.) and as this seemed to account for the pelvic activity it was assumed that the placenta was fundal, though it was found to be praevia at subsequent caesarean section following a further antepartum haemorrhage. Four relatively minor differences in the position of the lowest part also occurred. It is interesting to compare the results of clinical palpation of the placenta through the cervix under anaesthesia. In this series three grade II or III placentae praeviae were not felt, and one patient had a breech diagnosed in error as a placenta praevia.

The scan is easy to interpret if the placenta is obviously fundal (Fig. 2) or grossly praevia (Fig. 3), but lesser degrees of praevia may be of serious clinical importance, especially if posterior, since if the cord has a low insertion the placental circulation may become impaired as the presenting part presses against the lumbosacral junction during uterine contractions in labour (Stallworthy, 1950). Such an example occurred in the present series. The lateral view is important in showing this and also the position of the anteriorly situated placenta, which if it extends down only to the symphysis pubis should not be considered praevia. Twenty-nine were in this category, and in one patient, though the lower edge was felt at examination under anaesthesia, it was not significantly praevia at subsequent section for disproportion.

To determine the plane of the pelvic brim and the lower segment, the old-fashioned external conjugate diameter (Baudelocque, 1789) may be used. This is on average 8 cm. longer than the internal diameter. The symphysis pubis and

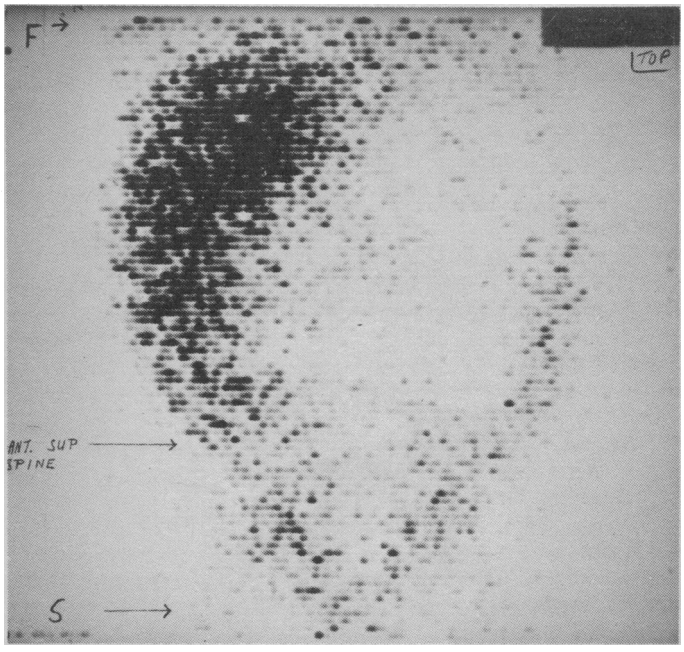

FIG. 2.—An obviously right fundal placenta (anteroposterior view). S = symphysis pubis. Plane of anterior superior iliac spines is also indicated.

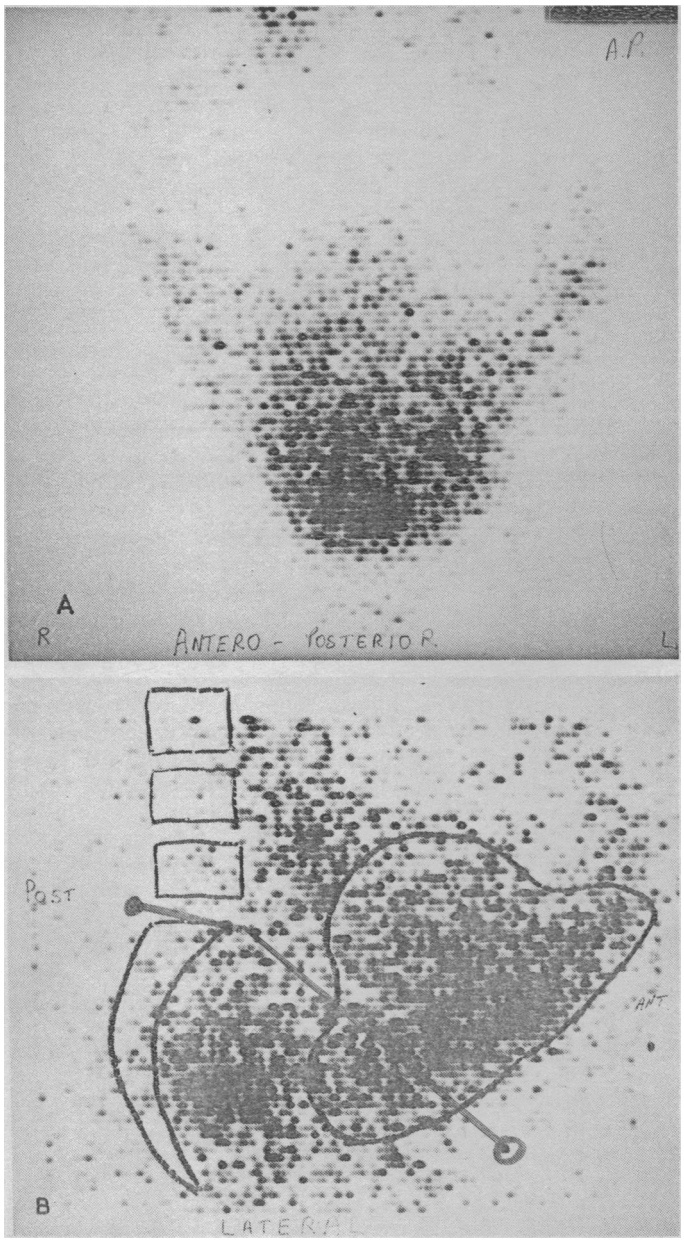

FIG. 3.—Grade IV placenta praevia: (a) anteroposterior view, (b) lateral. Note: isotope in maternal liver and pelvic vessels, etc.

upper sacrum may be palpated and their positions marked on the scan and the approximate position of the sacral promontory derived (Fig. 4).

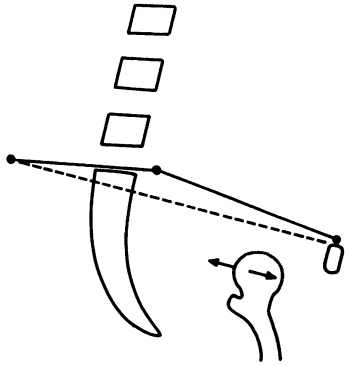

FIG. 4.—Diagram to show the expected position of the cervix and the method of deriving the plane of the internal conjugate. The arrows show the approximate position of the cervix (Nelp and Larson, 1969).

Technical Problems

Contrary to the experience of reported series from the U.S.A. (Huddlestun *et al.*, 1969; Johnson *et al.*, 1969) our main problem has been urinary excretion of the isotope and a failure to bind to plasma proteins. In gross cases one may obtain a pyelogram and not see the placenta at all, as occurred in three patients, though a repeat examination was successful in two. In 10 patients the placenta was visualized despite the pronounced urinary excretion. In about 25% of all scans the renal pelvis was faintly seen. The urinary bladder is usually distinguished from a placenta praevia by its shape and position, though inexperience may cause problems as in the mistake discussed above.

Stern *et al.* (1967) and Hosain *et al.* (1969) showed that the isotope binds to transferrin and we have also found by electrophoresis that the labelled band is in the β-globulin region. We had initial success using ^{113m}In Cl at *p*H 4, but then experienced a considerable amount of urinary excretion until we reduced the *p*H to 1·6 by omitting the titration with NaOH, though we still find the occasional patient who has urinary excretion of the isotope. We experimented with the use of in-vitro labelling of the maternal blood (by mixing the isotope with blood in the syringe for a few seconds, and also tried incubating 10 ml. of blood at room temperature for 10 minutes with the isotope preparation and 100 units of heparin), but though we were able to visualize the placenta in one case in which we had previously seen only urinary excretion we now feel that a recent intravenous iron injection may have been the cause of the first failure, and this method does not seem to have any real advantage. The omission of gelatin from the preparation as advised by Garnett and Bayly (1969) seemed to promote urinary excretion.

Recent intravenous iron injections have also been a feature of some of the other failed cases, and may have caused almost complete saturation of the metallic receptors on the transferrin. In those cases with partial excretion of isotope high oral iron ingestion may have been an important cause. It has been shown experimentally by Hayes *et al.* (1967) that gallium can saturate the indium-binding sites on proteins, and it is possible that the same happens with iron, as transferrin is the main iron transporter in the blood. Syncope, when supine, due to blocking of the inferior vena cava by the pregnant uterus occurred in three cases and was easily treated by turning the patient into the lateral position.

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Miosis during L-Dopa Therapy

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Summary: The pupillary diameter of 11 patients with Parkinson's disease was significantly decreased four hours after ingestion of L-dopa. It is suggested that this miosis may be caused by diminished noradrenaline output at sympathetic nerve endings, or alternatively by an action on the central nervous system.

Introduction

L-Dopa produces improvement in the manifestations of Parkinsonism and has an important therapeutic role in this common condition (Cotzias *et al*, 1968, 1969; Yahr *et al.*, 1968, 1969; Calne *et al.*, 1969a, 1969b; Godwin-Austen *et al.*, 1969b). Both hypertension and, more commonly, hypotension may occur during L-dopa therapy (Cotzias *et al.*, 1968, 1969; Yahr *et al.*, 1968, 1969; Calne *et al.*, 1970). The most likely explanation of these observations is that L-dopa therapy interferes with sympathetic activity, which in turn leads to hypotension, particularly in the erect posture.

We have investigated the pupillary aperture in patients during and after L-dopa therapy as a convenient measure of peripheral sympathetic activity.

Patients and Methods

Eleven patients participating in a trial of L-dopa therapy in idiopathic Parkinsonism (Calne *et al.*, 1969b) were studied. Their ages ranged from 47 to 65 years and their initial Parkinsonian symptoms varied from mild to gross disability. The daily doses of L-dopa ranged from 1·0 to 6·8 g. (mean 3·2 g.). For each patient an ocular photograph was taken during maintenance with maximum tolerated doses of L-dopa. Photographs were taken at 12.30 p.m., four hours after the most recent dose of L-dopa. The second series of photographs was made several weeks after ceasing L-dopa therapy.

To ensure constant lighting and to minimize the effects of tremor the head rest and lighting system of a Leitz slit-lamp were used. Measured light intensities were reproduced between series of photographs. Photographs were taken with an Exakta Varex IIB 35-mm. camera, a Trioplan 10-cm. lens with focusing bellows and Ilford HP4 film being used. The back of the camera was 40 cm. from the bridge of the subject's nose. To avoid the effects of accommodation, patients looked "through" the camera lens without focusing. Three photographs were made on each occasion and negatives were projected on to the wall of a darkroom, giving a final magnification of ×15. Measurements of the horizontal diameter of the pupil were made. Observations were performed on the left eye: all three photographs in each patient were used and the mean of the readings was taken.

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Results

Variations in pupillary diameter within each set of three photographs were small (often less than 1 mm. on the magnified image), suggesting that fluctuations in accommodation were not affecting results.

Pupillary diameters during and after L-dopa therapy, and the percentage differences for each patient, are set out in the Table. In 10 of the 11 patients the pupil was smaller during L-dopa therapy than after its cessation. A Wilcoxon signed rank test showed that the difference in pupillary diameters is significant at the 0·1% level.

The extent of miosis in individual patients showed no correlation with the dose of L-dopa, the development of hypotension, or the response of the Parkinsonism to therapy. There was a similar lack of correlation between dose, hypotension, and therapeutic response.

Pupillary Diameters in mm. (× 15) *in* 11 *Patients During and After Therapy with* L-*dopa by Mouth*

During Therapy d_1	After Therapy d_2	% Increase After Therapy $\frac{d_2 - d_1}{d_2} \times 100$
53·7	71·7	25
79·7	111·0	28
53·0	58·3	9
47·7	60·3	21
85·7	82·7	-4
72·5	100·3	28
92·3	108·0	15
81·0	83·0	2
54·3	81·7	34
60·3	103·5	42
65·3	102·0	36

Discussion

The finding of a significant miosis during L-dopa therapy is compatible with the hypothesis that sympathetic tone is reduced by this treatment. The demonstration of orthostatic hypotension during L-dopa therapy also accords well with this view. Reduced sympathetic activity during therapy with a drug which is a precursor of noradrenaline may appear paradoxical. It has been shown, however, that both dopamine (Spiers and Calne, 1969) and L-dopa (Calne and Spiers, 1970) cause release of noradrenaline from sympathetic nerve endings, and may produce depletion of noradrenaline stores, even though both drugs are precursors of noradrenaline. That amine release by dopamine may outstrip synthesis has been shown in animal experiments (Harrison *et al.*, 1963; Eränkö and Räisänen, 1968). Administration of L-dopa restores the noradrenaline content of peripheral adrenergic nerves after reduction by reserpine (Pennefather and Rand, 1960), but apparently does not increase peripheral noradrenaline stores when these are initially normal. Though treatment with L-dopa increases the dopamine content of rabbit brain, changes in noradrenaline levels are slight or absent (Carlsson *et al.*, 1958).

During long-term therapy with L-dopa by mouth pupillary dilatation has sometimes been observed one to two hours after an oral dose of L-dopa (van Woert, personal commu-