patients treated after 28 weeks' gestation and three out of 12 patients treated before 28 weeks' gestation. This highlights the problem of severe disease early in pregnancy, when intrauterine transfusion remains extremely hazardous, yet plasmapheresis alone even using a cell separator to exchange over 20 l a week may fail to control the rate of fetal haemolysis.

Several points have emerged from our study of patients with exceptionally severe rhesus disease treated by intensive plasmapheresis with a cell separator. Firstly, the expected rise in anti-D level as pregnancy progresses can be prevented. Concentrations in seven of our eight patients actually fell ($P < 0.05$), and five had a final level below 4 mg/l (table II). Secondly, amniotic fluid spectrophotometry readings (Δ 450 nm) can be maintained at levels below those recorded in preceding pregnancies. This was achieved in six out of seven patients ($P < 0.025$). The apparent reversal of a rising trend in some patients (figs 2 and 3) presumably reflected reduced haemolysis. Thirdly, the fetus can be saved through plasmapheresis alone, even in cases severe enough to warrant treatment from 20 weeks' gestation. Two of the five mothers treated by this policy delivered live babies with cord blood haemoglobin concentrations of 10·0 and 15·4 g/dl. Both mothers had previously lost two babies as early as 28 weeks' gestation (table I). Lastly, plasmapheresis must be intensive. We were successful only when up to 7 l two or three times a week was exchanged. In cases in which we exchanged about 20 l weekly plasmapheresis eventually failed to control the rhesus disease (table III).

These preliminary observations suggest that fetal haemolysis may be reduced by intensive plasmapheresis using a cell separator and that in some cases this effect can be sustained by plasmapheresis alone until a viable fetus is delivered at 36-37 weeks. Unfortunately babies still die from prematurity and the idiopathic respiratory distress syndrome, in spite of lessening of haemolysis (table III), and in others haemolysis cannot remain controlled by plasmapheresis alone. These factors must be taken into account when considering a patient for this form of management. Only highly motivated patients should be selected, as fetal loss after prolonged treatment is particularly distressing.

If the effect of intensive plasmapheresis in reducing fetal haemolysis is accepted its optimum contribution to managing severe rhesus disease may still be to tide the baby over from about 24 weeks until 30 weeks' gestation or later, when intrauterine transfusion is less hazardous.

We thank Dr J Wallace, Dr R Mitchell, and the staff of the Blood Transfusion Service, Law Hospital, for anti-D antibody measurements; Professor I Donald and the obstetricians of the Queen Mother's Hospital for referring patients and for their continuing interest; and Tenovus, Scotland, for financial support. We particularly acknowledge the technical help of Mrs M Davie, Mrs I Kershaw, and Mrs B Pickering, of the department of haematology.

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Changes in breast sensitivity at puberty, during the menstrual cycle, and at parturition

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Summary

Sensitivity to pain and touch was measured in the nipple, areola, and cutaneous breast tissue of prepubertal boys and girls, postpubertal men and nulliparous women, and pregnant women before and after delivery. Before puberty there were no differences between the sexes, but after puberty the tactile sensitivity of all areas of the women's breasts was significantly greater than the men's. Tactile sensitivity of all areas also varied during the menstrual cycle, with maximal sensitivity at mid-cycle and at menstruation; the mid-cycle peak was absent when the women were taking oral contraceptives. But the most dramatic changes occurred within 24 hours of parturition, when there was a great increase in breast sensitivity. This may be the key event for activating the suckling-induced discharge of oxytocin and prolactin and inhibiting ovulation during lactation.

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Introduction

The breasts undergo volume changes in response to changing hormone concentrations at puberty,[1] during the menstrual cycle,[2] and during pregnancy.[3] Although the human breast serves a subsidiary function as an organ of sexual attraction,[4] its primary purpose is to nourish the newborn infant. Breast-feeding also establishes an intimate tactile bond between mother and child, which may be important in establishing and maintaining the mother-infant relationship.[5,6]

Afferent suckling stimuli from the breast have important endocrine consequences for the mother, as they initiate a

reflex discharge of oxytocin and prolactin from the pituitary.[7,8] Oxytocin stimulates the flow of milk initially, while prolactin ensures that lactation is sustained. Furthermore, the suckling stimulus inhibits maternal pituitary gonadotrophin secretion,[9] and lactational amenorrhoea ensures adequate natural spacing between successive births.[10]

If sensory nerve endings in the breast play such an important part in the reproductive process, it would be interesting to establish whether breast sensitivity is itself under hormonal control. We therefore decided to measure two aspects of breast sensitivity—namely, two-point discrimination and pain thresholds—at various stages in reproductive life.

Subjects and methods

Prepubertal children—A single set of observations was made on the breasts of 11 boys and 11 girls aged from 9-11 years.

Nulliparous women—Six healthy nulliparous female volunteers aged between 20 and 22 provided data from eight normal menstrual cycles and eight cycles controlled by a contraceptive pill (ethinyloestradiol 30 μg, norgestrel 500 μg; Eugynon 30). One woman recorded information during a normal cycle, followed two months later by three pill-controlled cycles.

Men—Six male volunteers aged between 23 and 28 each provided a single set of observations.

Pregnant women—Four healthy women (two of whom were nulliparous) aged from 25 to 39 were studied. All were in the final weeks of pregnancy. Data were collected weekly at an antenatal clinic and daily immediately after delivery. Two of the women breast-fed their babies; no drugs were administered to suppress lactation in the two women who were bottle-feeding.

BREAST MEASUREMENTS

Each quadrant of the nipple, areola, and cutaneous breast tissue was tested separately. As measurements were collected from both breasts, one day's data consisted of measurements from 24 breast areas.

The two-point discrimination test—The two points of a pair of geometric dividers initially widely separated, were brought closer together until two distinct sensations could no longer be discriminated when touching the skin. The distance between the divider points at this stage was recorded.

The pain threshold test—The apparatus used was a Semmes-Weinstein pressure aesthesiometer, consisting of 20 nylon monofilaments of varying diameter.[11] Each filament was pressed against the skin until it bent slightly, and the smallest size to cause a "jagging" pain was recorded.

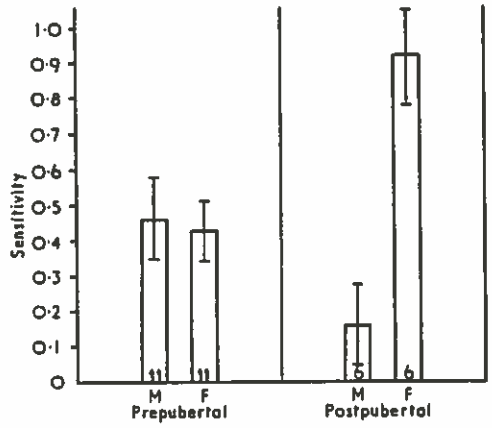

FIG 1—Tactile sensitivity of the cutaneous breast in prepubertal girls and boys and postpubertal men and women. Sensitivity was calculated from two-point discrimination data (TPD) according to the formula K-log$_e$ (1+ TPD). K is an arbitrary figure employed to portray low two-point discrimination values as peaks of sensitivity. One was added to TPD values to ensure a positive result for the natural logarithm. Numbers of patients given in each column. K = 1·2.

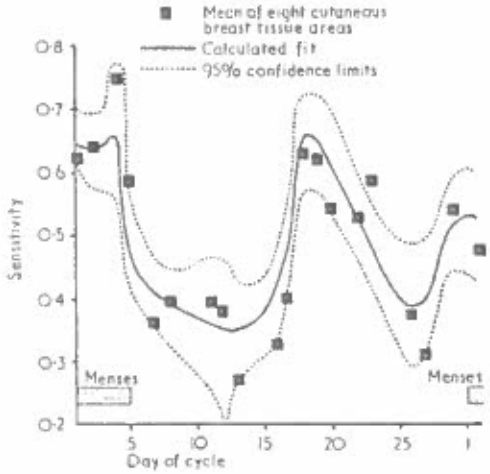

FIG 2—Changes in tactile sensitivity of cutaneous breast tissue in a nulliparous woman during normal menstrual cycle. Sensitivity was calculated as in fig 1. K = 1·2.

METHODS OF ANALYSIS

Pubertal data—The mean values for the cutaneous, areolar, and nipple areas were calculated separately and the absolute thresholds of the boys and girls compared using a *t* test. Since the means and variance of the two-point discrimination data were positively correlated, the results were transformed into natural logarithms to eliminate this.[12] An identical method was used to compare the single observations on the men with one day's data selected at random (using a table of random numbers) from each woman.

Menstrual cycle data—To quantify any changes in two-point discrimination or pain thresholds occurring during the menstrual cycle, the daily means of the eight cutaneous, areolar, and nipple areas were calculated and a Fourier analysis applied.[13] For each woman data from identical cycle lengths were matched day for day and pooled.

Pregnancy data—A factorial analysis of variance was carried out on data from each pregnant woman. This allowed the total variance to be partitioned between the effects of time, breast, and quadrant and their interactions. By comparing these mean squares with the residual, the significance of these effects was determined. As the effect of quadrants was insignificant, a slightly different partitioning was used to test each day after delivery with the days before.[12] The two-point discrimination data were transformed into natural logarithms.

Results

SEX DIFFERENCES

No significant differences could be detected in either the pain or two-point discrimination thresholds between the prepubertal boys and girls (fig 1). There was also no difference between the absolute pain thresholds of the breasts of adult men and women. When the two-point discrimination data for men and women were compared, however, all areas of the women's breasts were significantly more sensitive than the men's ($P < 0·01$). Women's breasts showed a significant increase in two-point discrimination sensitivity after puberty ($P < 0·025$), although there was no significant change between boys and men (fig 1).

CHANGES DURING NORMAL MENSTRUAL CYCLE

Two-point discrimination thresholds—Seventeen of the 24 separate breast zones which were analysed during the eight cycles studied showed a significant rhythmicity ($P < 0·05$). In these cases a peak of

sensitivity was always associated with the period immediately before menstruation or with menstruation itself. Seven of these cycles showed a second peak of sensitivity at mid-cycle (fig 2), and in five the nipple, areolar, and cutaneous areas all showed a similar rhythm.

Pain thresholds—Seven of the eight menstrual cycles studied showed a significant rhythm in pain thresholds ($P < 0.05$), but comparison of cycles within and between subjects showed few common features. In all but two cases peaks of sensitivity coincided with the menstrual or premenstrual period. Other peaks, however, appeared apparently at random throughout the cycle. Similar rhythms in the nipple, areolar, and cutaneous areas were found in only one case.

CHANGES ON ORAL CONTRACEPTIVES

Two-point discrimination thresholds—A significant rhythmicity ($P < 0.05$) was observed in the two-point discrimination thresholds in all eight cycles studied. There was a single peak of sensitivity that was related to the premenstrual period or to menstruation itself (fig 3). No mid-cycle peaks were observed. No cycles were seen in the pain thresholds of any subject.

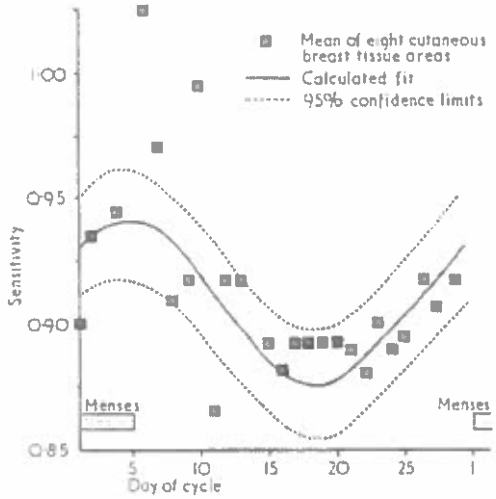

FIG 3—Changes in tactile sensitivity of cutaneous breast tissue in a nulliparous woman during menstrual cycle when taking oral contraceptives. Sensitivity calculated as in fig 1. K = 1·2.

CHANGES DURING LABOUR

When the total variance was partitioned, the effects of time and breast and their interactions were found to be significant. Thus data from the prepartum period were compared with each day's data after delivery in both breasts separately.

Two-point discrimination thresholds—Nineteen of the 26 cutaneous breast tissue results taken on postpartum days were highly significantly different ($P < 0.01$) from the days before delivery. Two of the results were significantly different at the 5% level and the remaining five results were not significant. Before delivery the nipple and areolar areas were so insensitive that none of the four subjects could discriminate two points; however, after delivery the sensitivity of these regions increased greatly. In all four subjects discrimination reached the maximum value possible for the test system in the immediate postpartum period. Both breasts showed similar patterns in all the women studied (fig 4). No differences were noted between women who were breast-feeding or bottle-feeding, nor between primiparous and multiparous women.

Pain thresholds—A significant change in pain threshold was detected between the pre- and postpartum periods ($P < 0.05$). The direction of this changing sensitivity was not consistent, however, either between or within subjects for either the cutaneous breast, nipple, or areola.

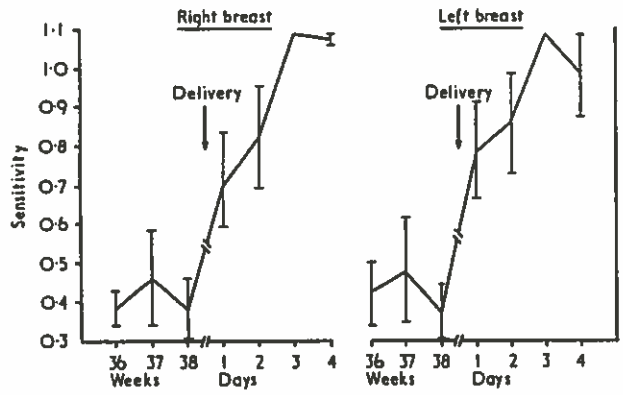

FIG 4—Changes in tactile sensitivity of cutaneous breast tissue in perinatal period. Sensitivity was calculated as in fig 1. K = 1·2.

Discussion

We were not surprised to find that the nipple was the most sensitive area of the breast to both touch and pain, followed by the areola, and then the cutaneous breast tissue. There was no difference in breast sensitivity between boys and girls before puberty, but women's breasts became much more sensitive after puberty and appeared to undergo rhythmic changes during the menstrual cycle, with maximal sensitivity just after mid-cycle and again at menstruation. This mid-cycle peak of sensitivity was absent in women taking oral contraceptives. During the latter weeks of pregnancy the breasts were relatively insensitive. There was an abrupt and spectacular increase in sensitivity 24 hours after parturition, however, and this was maintained for several days, regardless of whether or not the woman continued to breast-feed. The nipple and areola were so insensitive before delivery that accurate measurements became impossible; the two-point discrimination distance was greater than the nipple or areolar diameter.

Cutaneous pain sensitivity showed much less variability. There was no difference between prepubertal and postpubertal girls; changes in pain thresholds during the normal menstrual cycle were slight but statistically significant and were not seen during pill cycles, and there were inconsistent changes at the time of parturition. There did not appear to be an obvious correlation between changes in breast sensitivity and breast volume changes. Thus maximal sensitivity occurred at menstruation when volume is actually declining,[2] and the sensitivity change at parturition was not apparently related to any volume change at this time.[3]

These sensitivity changes are probably hormonally induced; increased sensitivity seems to coincide with falling hormone concentrations at ovulation, menstruation, and parturition. By far the most spectacular sensitivity change was seen at parturition, and this could be of great physiological significance. Tyson *et al*[13] showed that stimulation of the nipple of women on oestrogen treatment would not induce prolactin release, whereas it was effective after withdrawal of oestrogen. If the nipple is the focal point of communication between mother and infant, it makes sense that it should only begin to transmit relevant information after the mother has given birth. The acquisition of postpartum nipple sensitivity might therefore be the key mechanism controlling the infant's present and future food supply, the mother's behavioural response, and her reproductive cycle.

We thank all those who kindly volunteered to take part in this study, the staff of the Simpson's Memorial Maternity Pavilion for their co-operation, and Maurice Dow and Len Nunney for their statistical advice. Professor R A Hinde, FRS, kindly lent us the aesthesiometer.

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Intravenous tyramine response in migraine before and during treatment with indoramin

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Summary

We studied the response of 31 migraine sufferers (20 women, 11 men) to intravenous tyramine (the tyramine-dose/pressor response test). Patients were treated either with placebo tablets or indoramin, an alpha-adrenergic blocking agent, in a double-blind crossover trial. We found that patients with migraine required significantly less tyramine to increase their systolic blood pressure by 30 mm Hg when compared with matched controls. Indoramin significantly increased the amount of tyramine needed to raise the systolic blood pressure among migraine sufferers and reduced the incidence of post-tyramine migraine from 46% while patients were on placebo tablets to 8% when they were receiving indoramin. There was no association between tyramine sensitivity and a history of premenstrual or dietary migraine, nor was there a significant difference in the incidence of post-tyramine migraine between men and women. We conclude that the intravenous tyramine test may be valuable in assessing migraine sufferers who will respond to an alpha-advenergic blocking agent such as indoramin.

Introduction

There are conflicting reports both about the role of the biogenic amines and their receptors in the aetiology of migraine,[1-4] and about the sensitivity of patients with migraine to tyramine given by mouth.[5 6] Secutari[1] reported decreased central serotonin activity in migraine sufferers and postulated that a supersensitivity to monoamines may be associated with the complaint. Herraro and Marino[2] postulated increased concentrations of circulating noradrenaline and tyramine during migraine attacks. Sandler *et al*[7] have reported decreased platelet monoamine oxidase activity in patients with migraine. Hence, if migraine is associated with either increases in circulating monoamines, or receptor sensitivity, or decreased monoamine oxidase activity, drugs which block the adrenergic receptors may be effective in the prophylaxis of migraine.

Indoramin (fig 1) is a selective alpha-adrenoceptor blocking drug[8] and is being investigated for its possible prophylactic value in migraine.[9] In addition to alpha-adrenoceptor blockade, indoramin in higher concentrations also blocks the reuptake of released noradrenaline in the synaptic cleft.[10] Tyramine is an indirectly acting sympathomimetic amine which releases noradrenaline from nerve terminals.[11] Recently tyramine has been used to study the reuptake blocking-effect of tricyclic and related antidepressive drugs.[12] One index of the various pharmacological actions of tyramine that can be conveniently studied is the increase in blood pressure (BP) induced by the released noradrenaline (tyramine-dose/pressor response test).[13]

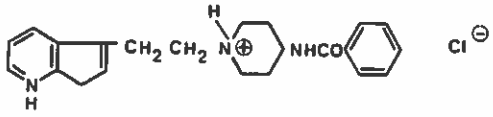

FIG 1—Structural formula of indoramin.

There were three main objects of the present investigation. Firstly, to compare the reaction of untreated migraine sufferers with control subjects to the intravenous tyramine-dose/pressor response test. Secondly, to evaluate the pharmacological interaction of indoramin on the tyramine-dose/pressor response test. Thirdly, to investigate the incidence of migraine after intravenous tyramine among migraine sufferers both before and during indoramin treatment.

Patients and methods

Thirty-one patients with migraine (20 women, 11 men), were selected according to the criteria of the World Federation of Neurology Research Group on Migraine and Headache.[14] A full medical history was taken and particular attention was paid to possible precipitating factors of migraine, including diet and the relation of migraine to the menstrual cycle. Patients with a history of psychiatric and cardiovascular disorders and those with clinical electrocardiographic and electroencephalographic evidence of cardiovascular or other neurological illnesses were excluded from the study. The 27 control subjects

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