

COMMUNICATIONS

HORMONAL INFLUENCE IN SIMPLE GLAUCOMA*

A PRELIMINARY REPORT

BY

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The incidence of chronic simple glaucoma before the age of about 50 years is greater in men than in women. Above this age the difference between the sexes becomes much less. Perkins and Jay (1960) considered two possibilities for this sex difference. They thought that some cases in the male might be delayed juvenile glaucomas and that others were possibly pigmentary glaucomas of the type described by Sugar and Barbour (1949).

It seemed logical to consider the incidence of chronic simple glaucoma in relation to hormonal state, since the menopause occurs at about this critical age. The purpose of the present investigation was to discover a possible hormonal influence on the outflow channels in the eyes of women during the pre-menopausal years.

In the first place, eyes of women were examined under differing physiological conditions. Subsequently hormone blood levels were altered experimentally.

PART I. INVESTIGATION OF OUTFLOW CHANGES DURING DIFFERENT PHASES OF THE MENSTRUAL CYCLE IN NORMAL WOMEN AND IN MALE CONTROLS.

Methods

Ten young women medical students (aged 19 to 28) with regular menstrual cycles volunteered for this part of the study. At a preliminary interview a menstrual history was taken and the presence of eye disease was excluded.

The following tests were carried out on the left eye only at the same time of day for 6 weeks at weekly intervals:

- (1) Applanation tonometry.
- (2) Tonography, using the Schiötz tonometer.

The coefficient of outflow was corrected for scleral rigidity on the Friedenwald nomogram.

The tests were also carried out on three males acting as controls.

Each of the women subjects was given a chart on which to record details of her menstrual cycle and of her basal temperature taken each morning before rising.

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This was the method chosen to confirm that ovulation had taken place and that a corpus luteum had been formed.

All the tests were made with "blind" technique so that the experimenter had no knowledge of the stage of the menstrual cycle of the subject under investigation.

Results

Fig. 1a shows the average oestrogen and progesterone levels throughout the normal menstrual cycle and Fig. 1b shows the outflow coefficient in the ten women with normal regular menstrual cycles. Since all the subjects did not have cycles of the same length, the stage of cycle is expressed as a percentage of the duration in each subject.

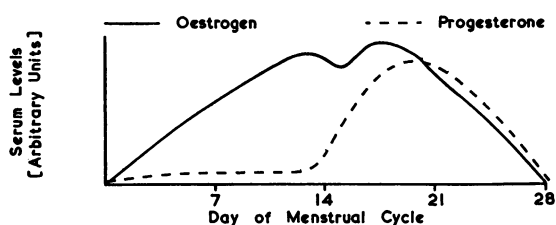


FIG. 1a.—Oestrogen and progesterone levels in the normal menstrual cycle.

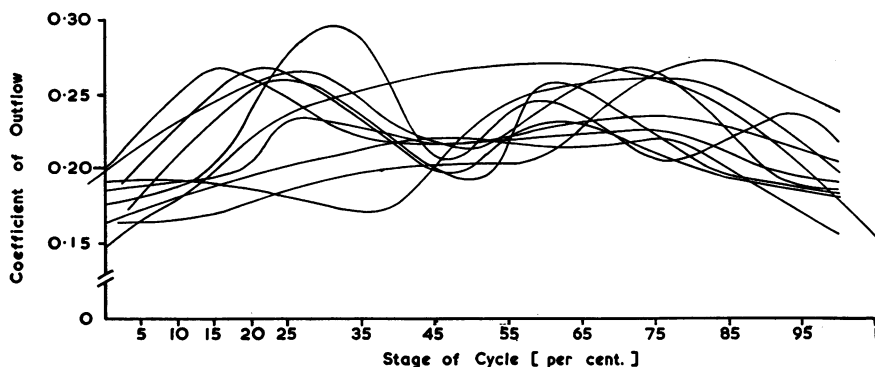


FIG. 1b.—Outflow coefficient in ten normal women.

The rate of outflow of fluid from the eye is seen to vary during the different phases of the cycle. Two peaks occur, the first during the first quarter of the cycle and the second during the third quarter. The outflow facility is lowest at the start of the cycle and drops again at mid-cycle.

The three males showed very little change in the facility of outflow over a period of 6 weeks. Table I (opposite) shows the results in one of the male controls.

It is hoped to extend this study in the future to a series of post-menopausal women.

TABLE I
TONOMETRY READINGS IN A NORMAL MALE

Sex	Test	Week					
		1	2	3	4	5	6
Male	Applanation	16	16	16	16	16	16
	C	0·17	0·18	0·17	0·17	0·17	0·18
	P _{o/c}	94	89	94	94	94	89

PART II. INVESTIGATION OF OUTFLOW CHANGES DURING PREGNANCY

Methods

Seven primigravidae without ocular abnormality agreed to have tonographic studies made on their left eyes throughout their pregnancies. Readings were taken as early in pregnancy and as often as possible. The first was usually taken at about 8 weeks and the average interval between readings was a month. In one case weekly readings were taken. At least one post-partum reading was taken in each case after breast feeding had been discontinued.

Results

Table II and Fig. 2 (overleaf) show the results in the seven pregnant women. There was an initial and sometimes very steep rise in outflow facility to about 20 weeks, then a drop followed by a slower recovery with a second peak at about 26 weeks and a fall towards the time of parturition. The subjects who have attended so far for post-partum readings show much lower facility of outflow values in the non-pregnant state than at the height of the pregnancy, though not all have returned to normal. This may be due to a continuation of a flow-promoting effect. Becker and Friedenwald (1953) reported an increase in facility of outflow in one case during pregnancy and this result has been confirmed.

PART III. ADMINISTRATION OF SEX HORMONES

The positive findings in the first two stages of investigation led us to extend the study to see whether it was possible to influence the intra-ocular pressure or facility of outflow by the systemic administration of female sex hormones.

At the start of the menstrual cycle, when the low values for outflow facility were recorded, the blood levels of oestrogen and progesterone are at their lowest (Fig. 1*a*). The oestrogen level gradually rises to mid-cycle, then drops slightly, and with the formation of the corpus luteum following ovulation the progesterone level starts to rise and the oestrogen level gradually rises again until they both reach a peak towards the end of the third week, after which they fall until a day or two before the start of the next cycle. Thus

TABLE II
COEFFICIENCY OF OUTFLOW DURING PREGNANCY AND POST PARTUM
IN SEVEN WOMEN

Case No.	Month of Pregnancy								Post Partum
	1-2	3	4	5	6	7	8	9	
A	0.22	0.20	0.24	0.17	0.22	0.23	0.23	0.18	0.26
B	0.27	0.45	0.39	0.23	0.36	0.31	0.32	0.31	0.27
C	—	0.40	0.40	0.37	0.39	0.32	0.32	0.31	0.24
D	0.26	0.32	0.30	0.21	0.25	0.27	0.30	0.24	0.18
E	0.27	0.33	0.31	0.22	0.34	0.22	0.42	0.34	—
F	—	0.20	0.33	0.15	0.21	0.14	0.18	0.13	—
G	0.21	0.25	0.45	Did not attend		0.49	0.27	0.28	0.41

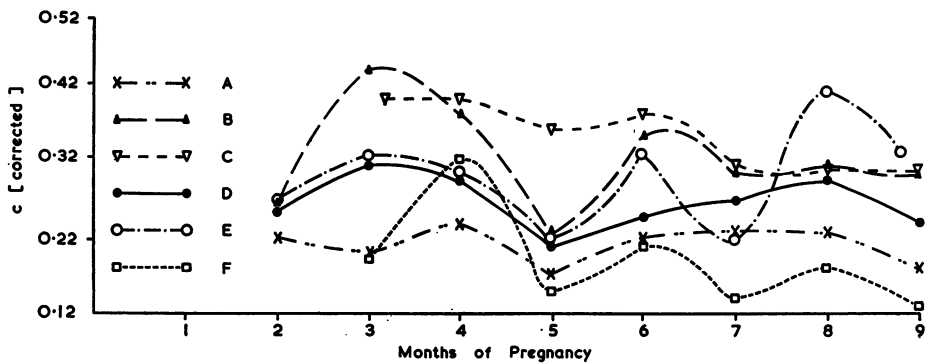


FIG. 2.—Outflow levels in six women during pregnancy.

the first peak in the outflow facility curve corresponds to the first rise of oestrogen and the second peak to the rise of oestrogen and progesterone.

Throughout pregnancy the oestrogen and progesterone levels gradually rise and reach a peak at 40 weeks. Occasionally the progesterone level tails off at 38 weeks but this is not constant. In pregnancy a third hormone, relaxin, is also present. This substance is particularly interesting because its level in the blood rises to a peak at 20 weeks and then falls off completely (Zarrow, Holmstrom, and Salhanick, 1955). It is absent from the blood from 20 to 24 weeks, and then reappears, rises to a maximum at parturition, and completely disappears again 48 hours later. This pattern seemed to follow closely that of the facility of outflow observed during pregnancy, when the drop in outflow facility consistently occurred in all the cases examined at approximately 20 weeks.

(1) *Progesterone*.—In view of the difficulties of oestrogen administration, with the attendant risk of influencing the menstrual cycle in pre-menopausal subjects and of causing post-menopausal bleeding in older women, it was decided to make initial experiments with progesterone. Both the natural hormone and a synthetic progesterone-like substance, norethisterone acetate, (Norlutin-A), were tried.

Several workers have already reported the ocular hypotensive effect of progesterone and some have even used it in the treatment of different types of glaucoma.

No definite knowledge was available of the rate of any possible action it might have, and the studies were therefore confined to appplanation tension readings at definite intervals after administration. Because tonography upsets the mechanics of the eye for at least 2 hours it was impracticable at this stage.

Method

50 mg. progesterone were injected intra-muscularly in three normal males, three premenopausal females, two normal post-menopausal females, two post-menopausal females with chronic simple glaucoma, and one post-menopausal female with aphakic glaucoma.

10 mg. Norlutin were administered orally to a post-menopausal subject with chronic simple glaucoma and a placebo was given as a control the next day. This was a "double-blind" experiment as neither experimenter nor patient knew on which day the Norlutin was administered.

Results

Table III (overleaf) shows that progesterone, in the dose given, seems to cause a small but consistent fall in intra-ocular pressure. The drop is greater in post-menopausal subjects both normal and glaucomatous. Males are affected least but it is interesting to note that the male subject showing the greatest fall was over 50 years old. The other two were aged 30 years.

When administered intra-muscularly, progesterone takes about 2 hours to act on the intra-ocular pressure and the action lasts for 4 hours. It is impossible without further investigation to say whether the fall in pressure is due to a reduction in the formation of aqueous humour or an increase in its outflow. Experiments involving administration of hormones to human volunteers naturally have to be limited, but it is hoped to be able to extend this work in the future and follow up the possible mechanism of action of progesterone.

In the last experiment Norlutin caused a rise in pressure of 5 mm. Hg after 2 hours, and the same thing happened when it was repeated 1 week later. Its use was therefore discontinued.

All the injections were given in the morning so that the falls recorded could have been partly due to the diurnal variation of tension.

(2) *Relaxin*.—This is described as the third ovarian hormone and was discovered by Hisaw (1926). It is a polypeptide of low molecular weight and is present in blood serum as conjugates which vary with species, *e.g.* human relaxin softens the symphysis pubis of the guinea-pig but not that of the mouse. It is completely inactivated by digestion with proteolytic enzymes, rendering oral administration useless. It has an action on connective tissue which is presumably effective throughout the body, including the eye. Using sponge biopsy technique, Elden, Sever, Noble, and Boucek (1957) showed that relaxin produced dilatation of the blood vessels in the connective tissue—followed by oedema and splitting of the

TABLE III
FALL IN OCULAR TENSION (mm. Hg) AFTER ADMINISTRATION OF
50 mg. PROGESTERONE INTRAMUSCULARLY

Subjects		Day of Cycle	Hours after Injection												
			1		2		3		4		5		6		
			R	L	R	L	R	L	R	L	R	L	R	L	
No Ocular Disease†	Post-menopausal	—	1	1	2	2									Recovered
		—	3	6	5	7									
	Pre-menopausal	25	1	1	2	2									
		14	2	1	2	5									Recovered
	Male	Age 30 yrs	—	1	1	1	1								
		Age 30 yrs	—	1	1	1	1								Recovered
Age 50 yrs		—	2	2	3	3									
Chronic Simple Glaucoma	Post-menopausal	—	—	—	—	—	3	5	3	5	5	6		Recovered	
		—	—	—	—	—	3*	5	3*	7				Recovered	

* Right eye more severely affected

† All recovered after 6 hrs

collagen fibres. Chemical studies showed that the ground substance of the collagen fibres became polymerized. The significance of this action need hardly be stressed when one considers the histology of the trabecular meshwork. Relaxin exerts its action only in the presence of oestrogen and thus subjects have to be oestrogen primed before the administration of relaxin. Preliminary studies with this hormone are described below.

Methods

20 mg. relaxin were injected intra-muscularly into seven subjects:

- (i) A pre-menopausal female on the 21st day of her cycle, *i.e.* when fully oestrogen primed.
- (ii) A non-oestrogen primed male.
- (iii) An oestrogen primed male receiving treatment for carcinoma of the prostate.
- (iv) and (v) Two post-menopausal oestrogen primed females with chronic simple glaucoma.
- (vi) A male receiving relaxin for treatment of scleroderma.
- (vii) A female receiving relaxin for treatment of scleroderma.

Tonography was performed on two successive occasions before the administration of relaxin so that a base line was obtained. It was repeated on the morning of the injection and 6 hours after it (*i.e.* when the effect on the symphysis pubis of the guinea-pig is known to be maximal).

Results

Table IV shows that the results were positive in all seven cases. A small fall in pressure occurred with an increase in outflow of fluid from the anterior chamber. The fall was greater when measured with the applanation tonometer, which showed an increase in scleral rigidity due presumably to the uptake of water by the scleral tissue. This masked to some extent the real increment as shown by the increase on the tonometer scale over the 4 minutes.

TABLE IV
RESULTS OF ADMINISTERING RELAXIN ON OUTFLOW FROM
ANTERIOR CHAMBER IN SEVEN CASES

Case No.	Sex	Condition	Test	Before Injection	6 hrs after Injection
(i)	F	No ocular disease Physiologically oestrogen primed	Applanation Schiotz Tonography c P _{o/c}	16 17 5 to 7.5 (5.5 g.wt.) 0.19 84	11 15 6 to 9 (5.5 g.wt.) 0.17 64
(ii)	M	No ocular disease Not oestrogen primed	Applanation Schiotz Tonography c P _{o/c}	12 15 6 to 9 (5.5 g.wt.) 0.18 67	9 15 6 to 10 (5.5 g.wt.) 0.20 45
(iii)	M	Oestrogen primed Receiving treatment for carcinoma of prostate	Applanation Schiotz Tonography c P _{o/c}	18 19 4.5 to 7.5 (5.5 g.wt.) 0.26 69	15 16 5.5 to 9 (5.5 g.wt.) 0.28 54
(iv)	F	Chronic simple glaucoma Oestrogen primed	Applanation Schiotz Tonography c P _{o/c}	23 26 5 to 7 (7.5 g.wt.) 0.10 230	20 26 5 to 8 (7.5 g.wt.) 0.13 153
(v)	F	Chronic simple glaucoma Oestrogen primed	Applanation Tonography	R.E. 48 L.E. 52 Tensions too high	R.E. 45 L.E. 48
(vi)	M	Scleroderma Oestrogen primed	Applanation Schiotz Tonography c P _{o/c}	14 19 4.5 to 7.5 (5.5 g.wt.) 0.16 87	14 15 5.75 to 9 (5.5 g.wt.) 0.25 56
(vii)	F	Scleroderma Oestrogen primed	Applanation Schiotz Tonography c P _{o/c}	13 15 6 to 10.25 (5.5 g.wt.) 0.33 39	12 16 5.5 to 11.5 (5.5 g.wt.) 0.39 31

These results followed a single injection of relaxin and the next day all readings had returned to normal. The next stage should be to investigate its action over

a prolonged period to see if a greater effect could be obtained. Our limited supplies of the hormone, which is very expensive, prevented our doing this, but we were fortunate enough to be able to make serial tonographic studies of a patient previously oestrogen primed receiving relaxin for the treatment of scleroderma. Here again an increase in outflow was maintained throughout the relaxin therapy period.

Discussion

Enough work has not yet been done to draw firm conclusions, but the results recorded suggest that a hormonal influence may be acting in the female to protect the outflow channels of the anterior chamber. It is possible that this influence may derive from relaxin which seems to be active only in the presence of oestrogen. At this stage it is interesting to note that Emery and Lawton (1947) reported relaxation of the symphysis pubis in guinea-pigs treated with oestrogen and neostigmine.

The question also arises whether or not relaxin is released during each menstrual cycle in amounts too small to be detected by our present rather insensitive assay techniques. Goldthwait and Osgood (1905) reported that relaxation of the symphysis pubis occurs in human subjects during menstruation as well as in pregnancy. If relaxin is released during the menstrual cycle, it may be the agent responsible for the changes in outflow reported in an earlier section. A more likely state of affairs would seem to be that a balance is maintained by the three hormones working together, oestrogen and progesterone providing a background against which relaxin can take effect.

It is proposed to extend these studies and to investigate the possible application of relaxin in the treatment of glaucoma. Parenteral administration limits its usefulness, but as its molecular weight is fairly low it is worth exploring its absorption by mucous membrane routes, with particular reference to the conjunctiva, possibly in combination with a locally-administered oestrogen priming agent.

Summary

Studies have been made on changes in intra-ocular pressure and the coefficient of facility of aqueous outflow during the menstrual cycle, during pregnancy, and after the administration of progesterone and relaxin.

Results indicate that relaxin may increase the facility of outflow in the presence of oestrogen, and it is proposed to extend the study to see if this can be confirmed.

We should like to acknowledge Messrs. Parke, Davis, and Co. for the gift of the progesterone, Norlutin, and relaxin, and in particular Dr. J. A. L. Gorringer for his helpful co-operation. We should also like to thank Sir John Peel for allowing access to his ante-natal patients from King's College Hospital, and Dr. T. M. Chalmers for access to his scleroderma patients from the Middlesex Hospital.

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