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*BRIEF COMMUNICATION*

# SOME PHYSIOLOGICAL PROPERTIES OF THE 'MENSTRUAL STIMULANT' SUBSTANCES *A*1 AND *A*2

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**Summary.** The 'menstrual stimulant Component *A*' substances, which have now been identified as certain prostaglandins, generally stimulate smooth-muscle preparations but may inhibit the human myometrium in certain circumstances. A tentative re-assessment of their physiological significance is suggested.

The following is the substance of a Demonstration at the Physiological Society meeting on 12th and 13th July 1963. 'The menstrual stimulant' is the provisional name given to a group of myometrial stimulants found in menstrual fluid; a brief summary of the earlier work on these substances has been given by Pickles (1963).

The principal sub-group of stimulants, previously called Component *A*, has now been shown to contain several active substances of which the main ones are referred to here as *A*1, and *A*2; and they have been identified as certain *prostaglandins*. *A*1 is almost certainly identical with $PGF_{2\alpha}$ described by Ånggård & Bergström (1963), while *A*2 is almost certainly identical with $PGE_{2\alpha}$ (G. Eglinton, W. J. Hall, V. R. Pickles, R. A. Raphael and G. N. Smith, in preparation). The properties of the PGF and PGE series have been briefly summarized by Bergström (1963).

The *A*1 and *A*2 used in most of the tests described here were prepared by Dr G. N. Smith, using a method to be described (Eglinton *et al.*). *A*1 and *A*2 can however be partially separated from one another by a modification of the silica-gel chromatography used previously (Clitheroe & Pickles, 1961). For example, in one experiment lipids having the biological activity characteristic of *A*2 were eluted from a silica-gel column by 3% methanol in diethyl ether; a mixture of *A*1 and *A*2 was eluted by 4% methanol; and *A*1 alone by 5% methanol. Comparison of biological activity with weight showed that even the best 'Component *A*' preparations previously made by silica-gel chromatography were grossly impure.

*A*1 and *A*2 may also be distinguished by their different effects on smooth-muscle preparations. The rabbit jejunum, suspended in a modified Krebs' bicarbonate saline solution containing 3 mM $MgSO_4$, was more sensitive to the *A*1 ($PGF_{2\alpha}$) than to the *A*2 ($PGE_{2\alpha}$) in the amounts present in the partially-purified extracts; whereas the dioestrous guinea-pig uterus was relatively more



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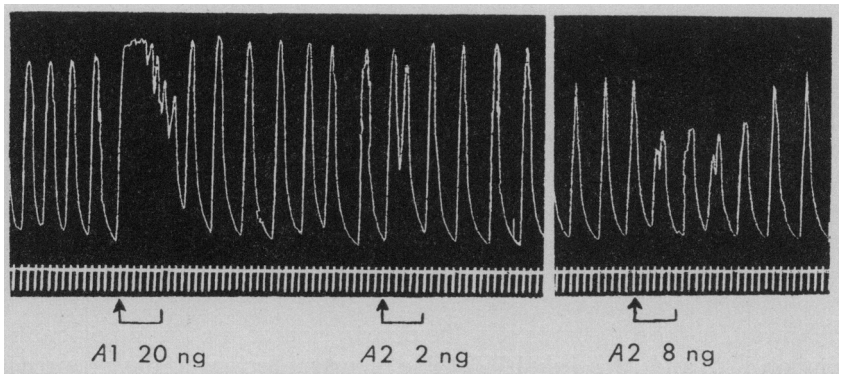
sensitive to *A*2 than to *A*1. Tests were also made on human myometrial preparations *in vitro*, after hysterectomy of pre-menopausal patients. Examples are shown in Text-fig. 1.

*A*1 invariably increased the contractions. The effective concentrations were within the range 2 to 20 ng/ml; but as these hysterectomy specimens were relatively insensitive to other stimulants (e.g. 'Pitressin' 5 to 10 m-u/ml, histamine 10 µg/ml), the sensitivity *in vivo* may well be greater than these figures suggest.




TEXT-FIG. 1. Effects of *A*1, and of *A*2 in two different quantities, on the contractions of a human myometrial preparation *in vitro*. The quantities quoted are only approximate, but they represent roughly the ratio of *A*1 to *A*2 in menstrual fluid. Time-marker, min; bath volume, 4 ml.

*A*2 slightly increased the contractions of some human myometria, desynchronized those of others, and decreased those of yet other preparations. Sometimes it was possible to show a change from stimulation to inhibition with increase of dosage, as shown by Eliasson (1959) for seminal prostaglandin. From the clinical data, the impression was gained that uteri under strong oestrogen dominance were the most likely to give the inhibitory type of response. Some showed complete inhibition. This again accords with Eliasson's observation (1963) for seminal prostaglandin.

Cruder extracts containing both *A*1 and *A*2 generally had an overall stimulant effect, which however varied from one uterus to another. The former observations that oestrogens decrease the normal excitatory response of the guinea-pig uterus to such extracts (Best & Pickles, 1963), and that mid-cycle human uteri frequently give indifferent responses even to large doses of crude 'menstrual stimulant' extracts (Pickles, 1959), can now be understood as further manifestations of the same effect.

A human Fallopian tube was stimulated by both *A*1 and *A*2.

The discovery of the prostaglandin nature of the menstrual stimulant Component *A* suggests a tentative re-assessment of its physiological significance. The process of menstruation may be thought of as subsidiary to the primary changes in the ovaries and endometrium; and the function of the endometrial prostaglandins (*A*1 and *A*2) during menstruation, for which there is now much circumstantial evidence, may likewise be physiologically subsidiary. Their

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hypothetical primary function might, for example, occur during implantation. The endometrial prostaglandins would seem likely to be released at the site of implantation, and a high concentration reaching the adjacent myometrium might significantly inhibit its contractions at that point, thus facilitating the implantation. In this way the endometrial prostaglandins would supplement the seminal ones, which have been implicated in fertilization.

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