

with having "done their bit." The older men in Group 4 (no previous history) were discharged; but most of the younger half returned to duty, many to full service.

External factors had also to be considered in disposal; for instance, though some men might have been regarded as fit for a lower grade of service, subsequent breakdown was likely if recategorization meant doing work which did not employ their talents in some useful way, or which, in an ambitious conscientious man, would interfere with promotion.

Of those men returned to a lower grade of service it was learned from follow-up inquiries that 4 were afterwards discharged from other hospitals. Follow-up replies were not obtained for all cases, but from those received about half the men were stated to be serving satisfactorily. Thirteen men were transferred to other hospitals: 7 because of psychosis or suicidal impulses, 3 for anti-syphilitic treatment, and another 3 for other treatments. It is probable that 10 of these were eventually discharged (the 7 with psychosis or suicidal impulses, plus 3 of the others) and that the remainder returned to duty in a lower category.

The final results, then, might be stated thus: 72 men were discharged from service, 19 returned to a lower grade of service, and 9 returned to full duty.

Summary

Observations on 100 men suffering from psychoneurosis following combatant service showed that 80 of them had had previous traits indicating emotional instability. The illness of 36 men was merely an aggravation of previous psychoneurosis, and in 33 it was associated with a definite predisposition to breakdown. Temperamental instability, revealed by frequent changes of job, was present in 11. Of the 20 men with no previous history one-half were much older than the rest of the group, and the disturbances in the younger half were mild.

Some observations are made on the possible selection of these cases and on their treatment and psychopathology.

When the liability to further breakdown was taken fully into account the recommendations for future disposal led to 72 of the group being discharged, 9 returned to full duty, and 19 returned to a lower grade of service.

[Since the above paper was written a new scheme has been developed whereby it will be possible to have psychoneurotic soldiers placed in work suited to them and, if necessary, near their homes. This highly commendable innovation will be followed with much interest.]

I wish to express gratitude to the Department of Health for Scotland for permission to refer to these cases; to Dr. C. D. Bruce, physician-superintendent of the hospital, and to my colleagues, for much helpful criticism; and to my wife for most of the work involved in tabulation.

REFERENCE

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J. V. Greenebaum, W. Felson, and M. Zeligs (*J. Pediat.*, 1941, **18**, 799), who give the history of a fatal case in a female infant aged 1 year, recall that acute interstitial myocarditis is a rare form of heart disease which was first described by Fiedler in 1890. The clinical picture is one of progressive myocardial failure unassociated with the usual causes of myocardial damage. In 1929 Scott and Saphir were able to collect only 38 cases in the literature, the youngest of which was in a child aged 3 years. The diagnosis is very difficult, and according to Maslow and Lederer, writing in 1933, has never been made before death. The disease should be borne in mind in cases of prolonged tachycardia in infants and children in whom no other cause for it can be found.

FRAGARINE: AN INHIBITOR OF UTERINE ACTION

(Preliminary Communication*)

BY

Sir BECKWITH WHITEHOUSE, M.S., F.R.C.S.
F.R.C.O.G., F.A.C.S. (Hon.)

(From the Department of Midwifery and Diseases of Women,
University of Birmingham)

In certain areas of Herefordshire and Worcestershire, and probably elsewhere, it is a common practice for women to use an infusion of dried raspberry leaves to allay the pains of labour. The same "tea" is also employed empirically, with apparently satisfying clinical results, in severe cases of dysmenorrhoea. It seemed, therefore, that an investigation into the pharmacological aspects of raspberry leaves might be interesting, and in May, 1940, with this end in view I approached Mr. E. C. Bennisson, chairman of the Advisory Committee of the School of Pharmacy, Birmingham. Mr. Withell, head of the School of Pharmacy, kindly undertook to prepare extracts and to isolate, if possible, any active principle that might be present. This work was started in August, 1940, and when enough material was obtained the extracts were submitted to Prof. J. H. Burn, University Department of Pharmacology, Oxford, for pharmacological trial. In March, 1941, I received from Prof. Burn the following account of his observations.

"I began by making experiments in the spinal cat, in which relaxation of the uterus is readily observed. If an infusion of raspberry leaves is made in the same way as tea, and if this infusion is concentrated by evaporation under reduced pressure, then an injection of an amount of infusion equivalent to about 2 grammes of dried leaves produces a momentary fall in the blood pressure, followed by a conspicuous rise, and simultaneously a relaxation of the uterus of the non-pregnant cat. It will be remembered that the sympathetic innervation of the uterus is inhibitor.

"This effect resembled that which is produced when a dose of nicotine is injected, which simultaneously produces a rise of blood pressure and relaxation of the uterus. The action of nicotine is known to be due to stimulation of the suprarenal gland resulting in liberation of adrenaline, and also to the stimulation of sympathetic ganglia resulting in a discharge of inhibitory impulses down the hypogastric nerves. It was found that the initial fall in blood pressure played no part in the action on the uterus, because in cats anaesthetized with chloralose no initial fall of blood pressure was observed.

"In further experiments, in which the suprarenal glands were first excluded from the circulation and in which the hypogastric nerves were cut, the injection of raspberry extract produced no relaxation, and, indeed, the effect observed was a small but well-maintained contraction.

"Further experiments were then done on the isolated uterus removed from the body and suspended in a bath. It was found that the extract produced a contraction of the uteri of both the cat and the guinea-pig, fairly prolonged in action and much more likely to represent any effect which may be observed by patients drinking raspberry tea. It is interesting to observe that the amount of extract producing an effect in the bath on the isolated organ is about 1/100 part of the dose which is taken by a patient drinking 10 oz. of a 5% infusion of dried raspberry leaves. The dose of pituitary extract which must be added to the bath to produce a similar effect is also about 1/100 part of the human dose.

"Attempts are being made to concentrate and purify the active principle responsible for the action on the isolated uterus. We do not know at present whether this principle is the same as that which produces inhibition of the uterus in the anaesthetized

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cat. If one substance is responsible for both effects its properties resemble those of the alkaloid hydrastinine, which was shown by Laidlaw in 1911 to have similar effects to those we find exerted by raspberry extract.

"It remains to add that raspberry extract has no action on the isolated cat heart."

On June 14, 1941, Burn and Withell (1941) brought before the Physiological Society of Great Britain, at a meeting held in Birmingham, a more detailed account of the work so far accomplished. On that date also the first clinical observation was made in my department at the University of Birmingham.

To obtain a record of the clinical effect of "fragarine"—the name we propose for the active principle in question—the intra-uterine-bag method described by Bourne and Burn (1927) and modified by Chassar Moir was employed. It is unnecessary to describe in detail the earlier experiments,

diminish their frequency and strength and to eliminate secondary contractions. This is indicated in the lower tracing in Fig. 2.

Case 3.—An 8-para. Fifth day of puerperium. Uterus anteverted and fundus extended two inches above the symphysis pubis. The cervical canal admitted two fingers. At 3.15 p.m. the intra-uterine bag was adjusted. The blood pressure was 100/62. At 3.30 p.m. 10 units of pituitrin were given. At 3.50 p.m. the blood pressure registered 112/58, and 20 grains of extract (49a) were administered by mouth. At 4.10 p.m. the systolic blood pressure showed a slight fall to 106. A tracing of uterine contractions similar to that shown in Fig. 2 was obtained.

Discussion

These experiments, *inter alia*, seem to confirm in the case of the human puerperal uterus the observations made by Burn and Withell on the uterus of the non-pregnant cat. The main effect is one of relaxation of the uterine

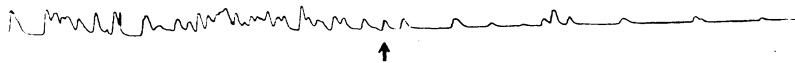


FIG. 1.—Showing the inhibitor effect of the administration of 40 grains of crude extract of dried raspberry leaves containing fragarine upon the spontaneous contractions of the human uterus on the fifth day of the puerperium. The arrow on the tracing marks administration of the extract. The divisions of the base line show intervals of one minute.

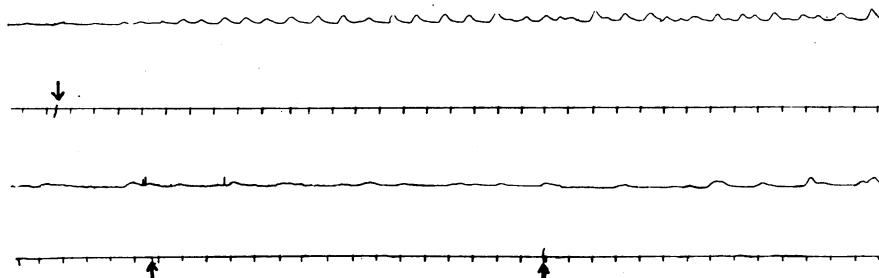


FIG. 2.—Uterine contractions after pituitrin are shown in the first tracing. The poor response of the uterus to pituitrin given after fragarine is shown in the second tracing. The arrow on the upper tracing marks administration of pituitrin 5 units. The first arrow on the lower tracing marks administration of raspberry-leaf tea 20 oz. 5%; and the second arrow, pituitrin 5 units. Divisions of the base lines show intervals of one minute.

but the following records provide in our opinion adequate clinical evidence of the inhibitory action of fragarine upon the human uterus.

Case Reports

Case 1.—A 1-para. Fifth day of puerperium. The uterus was anteverted and the fundus extended two inches above the symphysis pubis. The cervical canal admitted two fingers, and the intra-uterine bag was introduced without difficulty at 2.50 p.m. Spontaneous contractions of the uterus were recorded as shown in Fig. 1. The blood pressure registered 110/58 mm. At 3.15 p.m. 40 grains of raspberry extract (Ext. 49a) were administered by mouth. At 3.45 p.m. the blood pressure showed a reading of 106/58. The effect of fragarine upon the uterine contractions was to inhibit them. At first the contractions became less frequent, and finally they ceased altogether (see Fig. 1). No toxic effects of the extract were evident.

The effect of fragarine upon uterine contractions initiated by the administration of pituitary extract is shown in Case 2.

Case 2.—A 7-para. Eighth day of puerperium. Uterus involuted to size of twelve weeks' gestation and retroverted. The cervix admitted one finger, and the intra-uterine bag was inserted at 5.30 p.m. The blood pressure registered 120/70. Five units of pituitrin were administered at 5.35 p.m. At 5.45 p.m. the blood pressure was 126/72, and 20 grains of extract (49a) were administered. At 6 p.m. the blood pressure registered 112/70, and a second dose of pituitrin (5 units) was given. The effect of fragarine upon the uterine contractions was to

muscle. Contractions are diminished in force and frequency, secondary contractions are eliminated, and such contractions as occur are evenly spaced. The effect of fragarine upon the blood pressure is less pronounced in the human species in such concentrations and doses as have been applied. It is true that a very slight fall in the systolic pressure is noticeable, but there is no subsequent "conspicuous rise" as noted by Burn in the spinal cat.

It is obvious that further work remains to be done both from the pharmacological and from the clinical aspect, but apparently in fragarine we have available an active principle that may have a useful clinical application in the treatment of irregular routine action during labour and menstruation. In the absence, as yet, of any more elegant preparation, crude raspberry-leaf tea is being used in one of the Worcestershire maternity hospitals, and the nursing staff report favourably upon its effect in "making things easier."

In concluding this preliminary report of work still in progress my thanks are due not only to Mr. Bennison, Mr. Withell, and Prof. Burn for their active co-operation, but also to Prof. Gilding of the Department of Physiology, University of Birmingham, Prof. Chassar Moir, Oxford, and my registrar, Miss Terry, for valuable help in completing the clinical investigations.

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