THE ACTIVE CONSTITUENTS OF RASPBERRY LEAVES

A Preliminary Investigation

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Parts of the raspberry plant (*Rubus idæus* Linn., Family *Rosaceæ*) have been used medicinally for centuries—certainly as early as the sixth century A.D. Dioscorides[1] devoted a monograph to certain *Rubus* species. Raspberry leaf "tea" is a herbal medicine in Britain, but is apparently little used in the U.S.A.[2] In herbals, it is stated that parturition becomes easier and speedier if the warm "tea" is taken freely before and during confinement. It is claimed to be an efficient substitute for ergot,[3] and has also been employed empirically in cases of severe dysmenorrhœa.

Despite the traditional uses and claims for its pharmacological activity, nothing appears to have been published concerning the pharmacological or clinical evaluation of the drug until 1941, when two preliminary reports, by Burn and Withell,[4] and by Whitehouse,[5] appeared. The former prepared infusions of the dried leaves, and concentrated them by evaporation under reduced pressure subsequent to various treatments with ethanol, basic lead subacetate, or charcoal. The resultant extracts were tested upon isolated uteri of the cat, dog, rabbit and guinea-pig, and upon cat and rabbit uteri *in situ*. The actions on intestine, spleen, heart and blood-vessels were also investigated.

It was concluded that a principle was present which relaxed the smooth muscle of the cat uterus and intestine *in situ*, although the effect on the uterus was variable. Relaxation was also produced in isolated preparations of cat uterus and intestine. The same principle, or another, caused contraction of the rabbit uterus *in situ* and of the isolated cat, rabbit and guinea-pig uteri when these were not in tone.

The principle causing relaxation was concluded to be the probable basis of the traditional use of the "tea" for making uterine activity less painful. Whitehouse[5] concluded that the human puerperal uterus, like that of the non-pregnant cat, showed relaxation in response to extracts.

A further note[6] from the Oxford Medicinal Plants Scheme reported a continuation of the work of Burn and Withell. Confirmation of the effects of extracts upon cat uterus *in situ* was obtained. Work in the U.S.A.[2] has established that leaves from the black raspberry were more active than those from the common red raspberry. All American workers used leaves collected from wild plants.

EXPERIMENTAL

The material used throughout this present work consisted of the dried leaves from a cultivated crop of *Rubus idæus* (commercial variety *Malling Promise*) grown in Kent in 1951. Prior to further comminution, it consisted of the chopped leaves, including rachis; the proportion of cane present was negligible. The material was collected after fruiting, and was dried by means of warm air at a temperature not exceeding 60° C.

Preliminary work.

Various methods of extracting the active principles were investigated; several points arising are summarised below:—(1) Extraction with organic solvents yielded inactive extracts. Infusion with water followed by evaporation under reduced pressure gave products which stimulated smooth muscle. (2) Strong solution of lead subacetate, B.P. 1948 proved an effective reagent for removing tannins present in appreciable amounts in the aqueous extracts. Excess of lead was removed by (*a*) precipitation with hydrogen sulphide; the products exhibited a spasmolytic action on smooth muscle; or (*b*) adjustment of the *p*H to 3 with 0·5N sulphuric acid[7]; this reagent was effective in simultaneously removing calcium which is always present in the extracts. The products gave an overall effect of stimulation of smooth muscle, but the presence of a "spasmolytic" could be demonstrated. (3) Evaporation of the extracts to dryness under reduced pressure, after removal of tannins as in 2 (*b*) above, yielded a light yellow viscous mass exhibiting pharmacological activity, and containing reducing sugars.

When a solution of this extract, possessing stimulant properties, was passed through a column of the cation exchange resin Amberlite IRC.50 (H), the aqueous eluate exhibited a stimulant action 10 to 20 times as powerful as the original solution. Further elution of the column with 0·005N hydrochloric acid yielded a solution having powerful spasmolytic properties. Similar qualitative results were obtained after employing Amberlite IR.120.(H) cationic exchanger, when aqueous eluates were obtained which were almost 30 times as powerful in stimulating the isolated guinea-pig uterus as the solution admitted to the column. Qualitative separation of the "spasmolytic" and stimulant activities was also achieved by the use of a column of activated charcoal.

These qualitative results confirm the view that previous workers[4,5] had been working with extracts containing a number of active principles. As a result, the various pharmacological effects tended to mask one another. Some extracts examined in the course of this investigation were apparently inactive when tested on isolated tissues, but powerful spasmolytic and powerful stimulant effects could separately be demonstrated upon subsequent separation of the pharmacologically active constituents. The general extraction process and ion exchange procedures described below are based on the above observations. The results of some experiments indicated that the drug may not have been completely exhausted, but active material of sufficiently constant composition was obtained to yield consistent results.

General Extraction Process

1 kg. of leaves in approximately No. 10 powder was infused for 45 minutes with 10 l. of boiling distilled water, and the infusion was strained off through muslin, the marc being well pressed. The marc, after infusing with a further 10 l. of boiling distilled water, was again strained and pressed thoroughly (*p*H approx. 5·3). Strong solution of lead subacetate was then added over a period of 1 hour, until no further precipitate was obtained, constant mechanical stirring being maintained the whole time. (Between 900 and 1000 ml. of the reagent were usually required.) The suspension was stirred for several hours, and filtered (*p*H between 6·1 and 6·5 at this stage). The filtrate was evaporated under reduced pressure at a temperature not exceeding 50° C. to approximately 500 ml., and titrated with 2N sulphuric acid to *p*H 2·8 (300 to 400 ml. required) to precipitate the calcium and excess of lead present. After filtration, the filtrate was adjusted to *p*H 5 to 6, and evaporated under reduced pressure at a temperature not exceeding 50° C. to approximately 100 ml. Ethanol (600 ml.) was added, and a precipitate of pharmacologically inert material filtered off. The filtrate was evaporated to low bulk under reduced pressure at a temperature not exceeding 30° C. to yield a yellow solution which was used for pharmacological tests and for subsequent experiments involving ion exchange resins. Evaporation to dryness gave a yellow viscous mass containing reducing sugars and constituting 6 to 7 per cent. of the original dried leaf powder.

Ion Exchange and Pharmacological Results

The "purified" extract (200 ml. $\equiv$ 100 g. of powdered leaf), *p*H adjusted to between 5 and 6, was added to a column (100 $\times$ 2·2 cm.) of the cationic exchange resin Amberlite IR.120 in the acid form. Water (5400 ml.) was then passed through the column at the rate of 30 ml. per hour. The first 2250 ml. of eluate was collected in 15 ml. fractions and the remainder in 120 ml. fractions. A solution of N sulphuric acid was used next as eluant (1000 ml. collected in 100 ml. fractions). Finally, ethanolic sulphuric acid (50 ml. of concentrated sulphuric acid, 50 ml. of water and 900 ml. of ethanol) was used; this eluate (1000 ml.) was collected in 100 ml. fractions. In general, aliquots were prepared for pharmacological examination by adjustment to *p*H 6, and removal of ethanol, when present, under reduced pressure. All the early pharmacological work on these fractions was carried out on isolated tissues alone, for purposes of economy. The uterus and ileum of virgin guinea-pigs were found most suitable, and were used throughout suspended in oxygenated Tyrode's fluid at 34° to 37° C. The results obtained are outlined in Table I.

In subsequent work, the rate of flow was increased and the aqueous eluates were collected in larger fractions; this caused no alteration to the general pattern reported in Table I. Elution of the column in some experiments with 2N ammonia solution, after elution of the stimulant fractions, yielded dark yellow coloured solutions possessing little activity. When the "spasmolytic" only was required for a more detailed pharmacological investigation, the "purified" extract was adjusted to between

TABLE I

Eluant	Fraction	Volume collected, ml.	*p*H of eluate	Pharmacological action on isolated tissue
Water		200	5 to 6	None.
		60	1 to 2	None.
	α 1 to 8	120	1	Smooth muscle stimulation (A) which disappears and is replaced by an atropine-like spasmolytic action upon making the solutions alkaline with sodium bicarbonate.
	α 9 to 10	30	2	Smooth muscle stimulation (A).
	α 11 to 18	120	3 to 4	Smooth muscle stimulation—isolated uterine muscle more susceptible than other smooth muscle. Not all the stimulant activity disappears upon standing after the addition of sodium bicarbonate.
	α 19 to 35	255	4 to 5	Smooth muscle stimulation (B) which is unchanged after a few minutes boiling with sodium bicarbonate solution. No stimulation of type (A) detectable.
	α 36 to 90	825	5 to 6	Smooth muscle stimulation (B), all the fractions tested having about the same level of activity.
	α 91 to 130	600	5 to 6	Smooth muscle stimulation (B) becoming progressively weaker in the fractions.
	α 135 to 160	3,120	5 to 6	None.
N sulphuric acid	β 1 to 10	1,000		Slight "spasmolytic" action (C).
Ethanolic sulphuric acid	γ 1 to 6	600		Strong "spasmolytic" action (C), fraction γ 2 giving the most powerful effect.

Fractions 1, 2; α1, 2, 3, 5, 10, 11, 12, 13, 14, 15, 18, 19, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160; all β and γ series were tested.

*p*H 5 and 6 with calcium carbonate before addition to the column. The column was first eluted with water to remove the stimulant fractions, then with ethanol, and finally with ethanolic sulphuric acid—the latter eluted the "spasmolytic." Water, followed by calcium carbonate, was added to these acidic eluates to adjust the *p*H to between 5 and 6. Precipitated calcium sulphate was removed and the ethanol was distilled off under reduced pressure. The final solutions were almost colourless.

Smooth Muscle Stimulation A

Eluates exhibiting this effect on isolated tissues behaved as stimulants of the central nervous system and cardiovascular toxins (extreme cyanosis and widely dilated hearts) when injected intraperitoneally into mice, and caused death in convulsions when given intravenously to chicks, in doses equivalent to 0·1 g. of leaf. These 3 actions faded in parallel when the solutions were left standing for several weeks, and disappeared rapidly when the solutions were made alkaline with sodium bicarbonate. Reduction in stimulant action toward smooth muscle was attended by the appearance of non-specific spasmolytic action which was almost equally antihistaminic and parasympatholytic when measured on isolated guinea-pig tissues. This spasmolytic action washed out only very slowly from the tissues. None of these activities have been further examined.

Fractions α 11 *to* 18.

These apparently contain a mixture of active principles—possibly those responsible for stimulant actions A and B in addition to other materials. In some experiments the eluates obtained in this region gave a much greater stimulation of isolated uterus than of other smooth muscle.

Smooth Muscle Stimulation B

Action upon guinea-pig uterus.

After a latent period of about 90 seconds, the uterus went into spontaneous activity. The tissue had to be washed out for about 5 minutes, even after the use of only small doses, before the action was lost. The action was unchanged upon boiling the solutions for a few minutes with sodium bicarbonate solution and failed to potentiate the action of acetylcholine but was blocked by a dose of atropine which was only just enough to block the action of acetylcholine.

Action upon guinea-pig ileum.

The ratio of effective doses, ileum/uterus was 1 to 2. The effect of acetylcholine, but not that of histamine, was markedly potentiated (see Fig. 1). The stimulant action was not blocked by a dose of nicotine sufficient to paralyse the gut's response to nicotine, but was blocked by a dose of atropine just sufficient to abolish the action of acetylcholine without producing more than a very slight depression of the histamine effect.

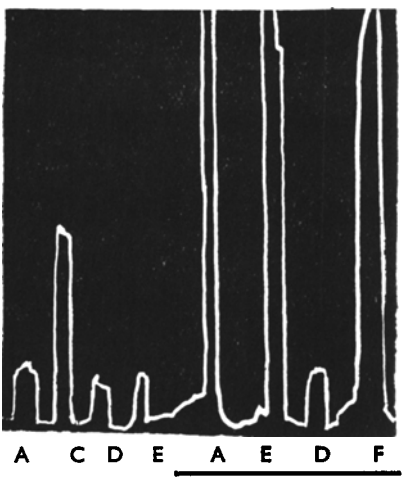


Fig. 1. The action of Stimulant B on guinea-pig ileum. Responses of the ileum, suspended in a 20-ml. bath of oxygenated Tyrode's fluid at 32°., are shown to the following drugs:—A, 0·2 μg. and C, 0·3 μg. acetylcholine; D, 3 μg. histamine; E, 20 μg. nicotine; F, 1·0 ml. of a solution of stimulant B. During the period indicated by a black line, the bath fluid contained 0·1 ml. of the stimulant B solution per 20 ml.

Action upon frog rectus.

The continued use of doses of solutions exhibiting stimulation B activity did not produce contraction of the rectus but gradually and reversibly potentiated the effect of acetylcholine. This effect, like that of eserinisation, took about 15 minutes to become obvious and then disappeared slowly upon washing the tissue (see Fig. 2).

The above results indicated the presence of an anticholinesterase which was more powerful as an inhibitor of the pseudo- than of the true cholinesterases. Confirmation

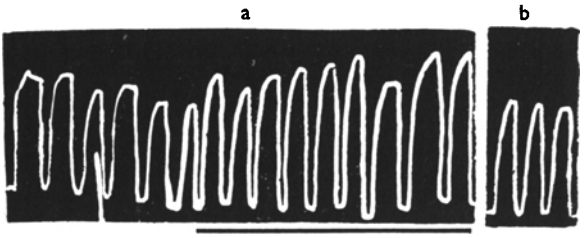
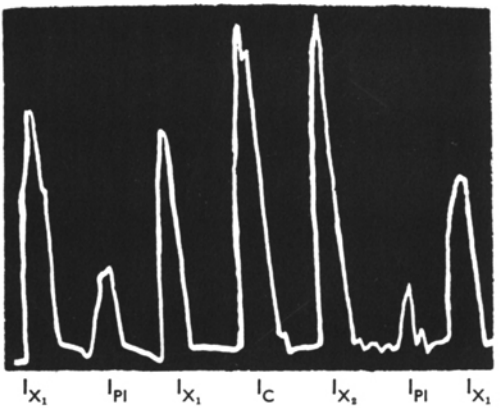


FIG. 2. Potentiation of the effect of acetylcholine on the frog rectus abdominis by stimulant B solution. The tracing shows the responses of the frog rectus, suspended in a 5-ml. bath of oxygenated frog Ringer's solution, at room temperature, to 1 μg. of acetylcholine added to the bath every 5 minutes for a 1 minute contact time. Ringer's solution containing 0·1 ml. of stimulant B solution per 5 ml. was used during the period marked by a black line. Trace b starts 10 minutes after a return to normal frog ringer.



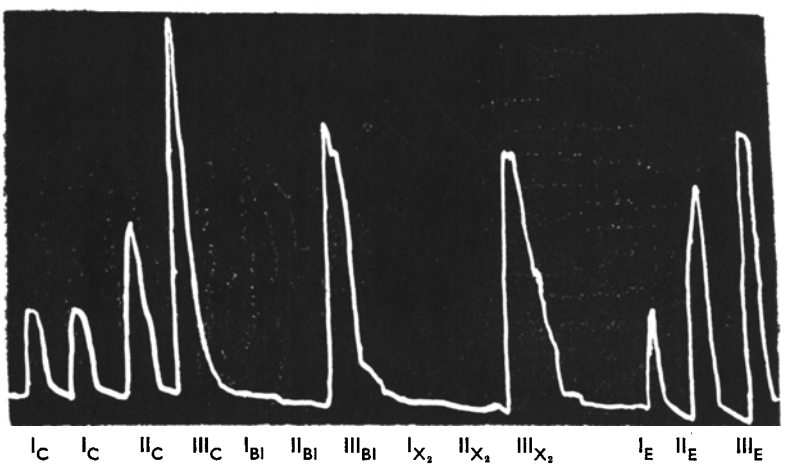


FIG. 3. The records demonstrate effective protection of acetylcholine against plasma esterase, but not of amechol or of acetylcholine against red cell esterase, by solutions of stimulant B. Drugs were tested at 2 minute intervals for a contact time of 30 seconds on guinea-pig ileum suspended in 15 ml. of oxygenated Tyrode's fluid at 38° C. I, acetylcholine, 1·5 μg.; II, amechol, 3 μg.; III, carbachol, 4 μg. Pretreatment of these solutions is denoted by suffix; c = control, standing untreated; Pl = subjected to 15 minute contact with 0·03 ml. fresh human plasma; Bl = similar contact with 0·03 ml. washed, packed, human red cells. Suffix X_1, X_2, and E denote pretreatment with plasma (upper record) or blood (lower trace) in the presence of 0·1 ml. (X_1) or 0·2 ml. (X_2) of stimulant B solution, or of 10 μg. eserine.

was obtained when these solutions failed to protect acetylcholine from the true esterase of red blood cells, but effectively protected acetylcholine from destruction by the plasma pseudo-esterases (see Fig. 3). The weak action of this component as an inhibitor of the true esterase was also demonstrated on the rat nerve diaphragm preparation; although it slightly potentiated the maximum twitch, it had little action as an antagonist of curare block.

"Spasmolytic" Action C

On isolated tissues, in preliminary screening tests, the most obvious effect of these eluates was that of non-specific spasmolytic action. These

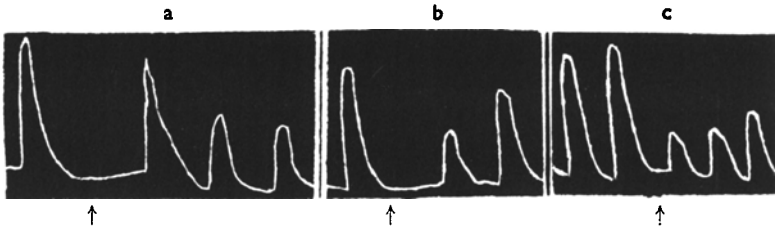


Fig. 4. The action of "spasmolytic" C on guinea-pig ileum. The ileum, suspended in a 20-ml. bath of oxygenated Tyrode's fluid at 34° C., contracted at 2 minute intervals in response to 30 second contact with the stimulant drugs:—(*a*) nicotine 20 μg., (*b*) acetylcholine 2 μg., (*c*) histamine 1 μg. At each arrow, 0·1 ml. of solution of the "spasmolytic" C was added to the bath, 30 seconds before the addition of activating drug.

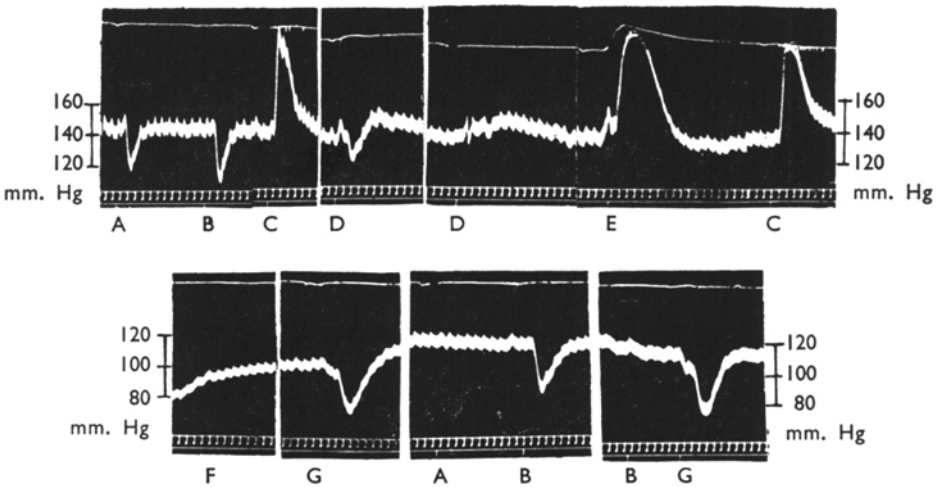


Fig. 5. The multiple actions of "spasmolytic" C on the mean arterial blood pressure. Simultaneous tracings were taken from a nictitating membrane (above) and of arterial pressure (below) in a cat (wt. 2·5 kg.) under chloralose anæsthesia. Solutions of drugs in 0·9 per cent. sodium chloride were injected intravenously:—A, 0·1 μg. acetylcholine; B, 0·5 μg. histamine; C, 400 μg., and F, 800 μg. of nicotine acid tartrate; D, 1·0 ml., and G, 2·0 ml. of a solution of "spasmolytic" C; E, 20 μg. adrenaline. The following were injected between records:—at X, 2 mg. atropine sulphate; at Y, 5 mg. hexamethonium bromide; at Z, 5 mg. mepyramine maleate. Time trace, 10 seconds.

eluates antagonised histamine, parasympathomimetic and sympathomimetic drugs nearly equally wherever these drugs act as smooth muscle stimulants (see Fig. 4). They also antagonised smooth muscle stimulant

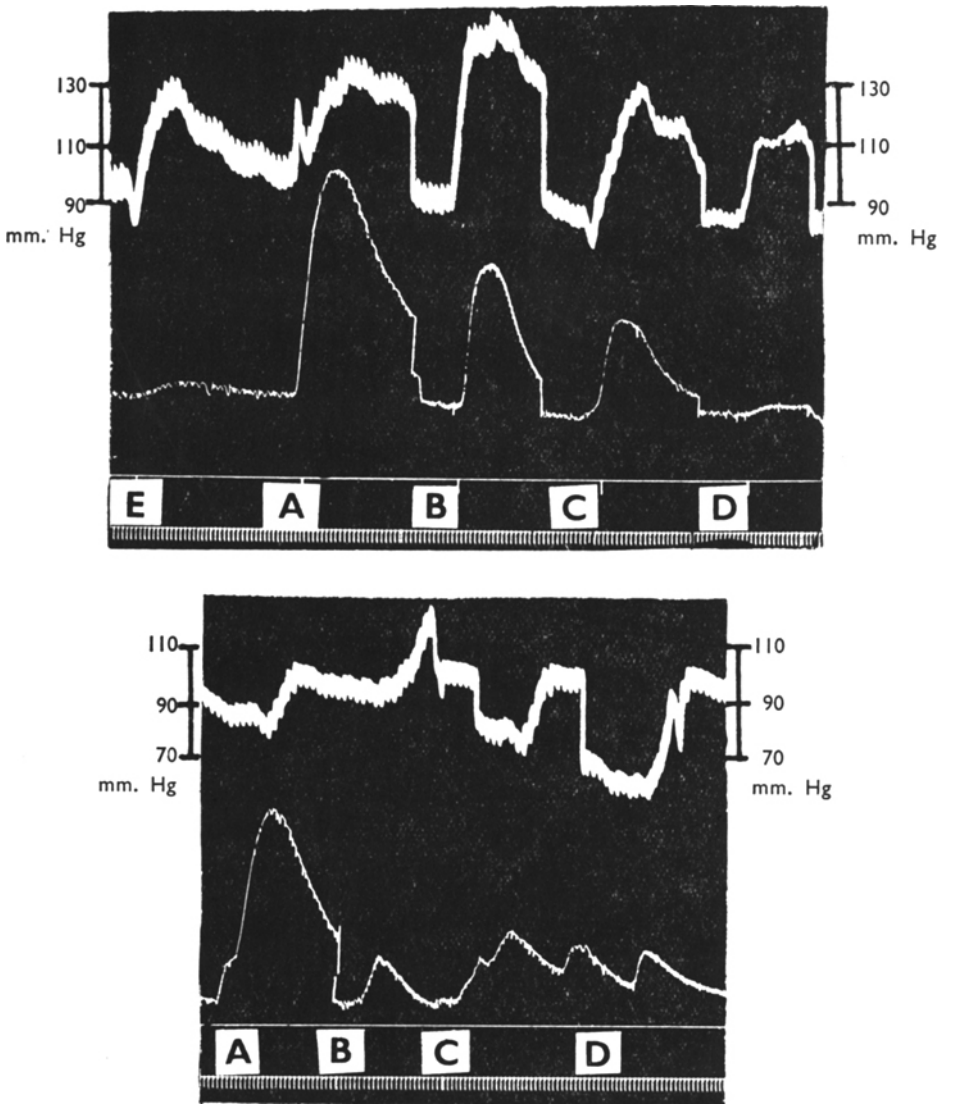


FIG. 6. The effect of adrenalectomy on the responses of the mean arterial pressure (above) and nictitating membrane (below) to the nicotine-like action of "spasmolytic" C. The records were taken from a cat (wt. 1·5 kg.) under chloralose anæsthesia, after the intravenous injection of 1·5 mg. of atropine sulphate, which had abolished the muscarine-like actions of 5 μg. of acetylcholine. Drugs, in 0·9 per cent. sodium chloride were injected intravenously:—A, 5 μg. adrenaline; E, 2 ml. and C, 3 ml. of "spasmolytic"; B, 375 μg. and D, 250 μg. nicotine acid tartrate. Upper record before, lower record after, acute adrenalectomy. Time trace, 5 seconds.

actions A and B from raspberry leaves. Sufficient spasmolytic activity was obtained from 0·01 g. of raspberry leaf powder to antagonise the effect of 100 μg. of acetylcholine upon isolated tissues. Only when separation of the raspberry leaf constituents exhibiting different pharmacological activities had been achieved, were the latter more fully examined pharmacologically. Hence this fraction was named "spasmolytic" although such action occurs in the whole animal only in doses far in excess of those which produce nicotine-like, and muscarine-like effects.

In chloralosed cats, the "spasmolytic," administered intravenously (in a dose only 10 times larger than that which must be added to isolated tissue in a 20-ml. bath to produce atropine-like action) has both muscarine- and nicotine-like action (see Fig. 5). The muscarine-like action was shown by a fall in blood pressure and bradycardia; both effects were abolished by atropine. Addition of atropine revealed the strong nicotine-like action of the "spasmolytic," as evidenced by contraction of the nictitating membrane, rise in blood pressure, tachycardia, and increased respiration (see Fig. 6). Hexamethonium bromide completely abolished these nicotine-like actions, revealing a vasodepressor action unaffected by atropine and antihistamines. The nicotine-like action of these eluates was also demonstrated by their ability to cause contraction of the frog rectus, which was antagonised by hexamethonium ions. Still larger doses of these eluates produced, in the whole animal, a short-lived depression of conduction through the superior cervical ganglion; this depression followed initial ganglionic stimulation.

A white solid has been obtained from these "spasmolytic" solutions and attempts to isolate the pure active material are in progress.

Discussion and Conclusions

It has been shown that aqueous extracts of raspberry leaves (*Malling Promise* variety) contain a number of active constituents, including

A. *A smooth muscle stimulant* which behaves as a central nervous stimulant and cardiovascular toxin upon injection into mice. It is unstable in the presence of sodium bicarbonate, the reduction in stimulant action being attended by the appearance of a non-specific spasmolytic action.

B. *An anticholinesterase* which is a more powerful inhibitor of the pseudo- than of the true cholinesterases. This constituent is much more stable to sodium bicarbonate than constituent A.

C. *A "spasmolytic"* which, in the doses used in our preliminary screening, relaxed isolated tissues, and has both muscarine- and nicotine-like actions in the whole animal in doses far lower than are required to produce blocking effects. This "spasmolytic" differs pharmacologically from that appearing upon breakdown of the constituent A.

The active constituent C antagonises the stimulant actions A and B. Consequently partially purified extracts from raspberry leaves can exhibit "stimulant" or "spasmolytic" actions upon isolated tissues depending upon the purification procedures adopted. It is probable that previous workers have been dealing with complicated variable mixtures and have

reported mean pharmacological actions; the present preliminary investigation emphasises the difficulty of the interpretation of such results. The mean effect of crude raspberry leaf extracts obtained in this investigation is stimulation of isolated tissues despite the presence of a powerful "spasmolytic."

In our early experiments in which the "spasmolytic" C was separated from the stimulant fractions, the mixed latter fractions were considerably more potent as stimulators of uterine than of other smooth muscle. It is possible that there is another stimulant present which exhibits this more selective action and there are indications that it is eluted from the column in the mixed fractions between the complete elution of stimulant A and the anticholinesterase.

It is rather difficult to assess the value of the traditional use of raspberry leaf infusions to give easy and speedy parturition in terms of the various active constituents exhibiting mutually antagonistic actions which are reported in this preliminary investigation, especially when the infusions have to be taken *before* and during confinement. At present it is impossible to predict what the overall clinical effect could be. Further work towards complete isolation of the various active constituents is in progress and may help to clarify the basis for the claims made for the beneficial effects of raspberry leaf extracts.

SUMMARY

1. A method for the preparation of active extracts from raspberry leaves is described.

2. Aqueous extracts have been shown to contain a number of active constituents including a smooth muscle stimulant, an anticholinesterase, and a "spasmolytic."

3. The method of separation of the active constituents is described; their pharmacological actions are reported.

We wish to thank Messrs. Potter and Clarke, Ltd., for supplies of raspberry leaves, and for generous financial help towards the cost of the pharmacological work. We are also indebted to Dr. J. M. Rowson for his interest.

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DISCUSSION

The paper was presented by MR. K. R. FELL.

DR. J. W. FAIRBAIRN (London) said he understood that raspberry leaf extracts relaxed uterine smooth muscle when in tone and contracted

the uterus when not in tone. Was this now confirmed? The leaves had been collected after fruiting, but it was a general rule that plant drugs were more active before fruiting. It might be of interest to compare the activity of the leaves before the fruit had set.

DR. W. MITCHELL (London) asked what alkali was used to adjust the *p*H of the acid solution, in the general extraction process, to *p*H 5 to 6.

MR. T. D. WHITTET (London) said that Professor Nixon, of University College Hospital, had demonstrated that the uterus *post partum* acted to drugs very similarly to the uterus at term and he was able to test the various drugs on women without discomfort to the volunteer patient. If a sufficiently purified product could be provided, Professor Nixon would be willing to carry out experiments.

DR. J. M. ROWSON (London) said that earlier collection of the leaves might result in a smaller tannin content, which would help in one of the difficulties of their preliminary purification. Were the authors able to make any recommendation about the most suitable presentation for administration? Was there any indication of the relative activities in different parts of the leaf? The authors had taken entire leaf samples, but it might be that the rachis contained less activity. Was there any indication of loss of potency resulting from lead subacetate precipitation?

MR. A. R. G. CHAMINGS (Horsham) asked whether there was any qualitative relationship between the pharmacological action of raspberry leaves and that of ergot.

MR. F. FISH (Glasgow) asked the authors to indicate the nature of the various products. Were they water-soluble alkaloids or glycosides?

DR. G. E. FOSTER (Dartford) said that sometimes the presence of inorganic salts had a profound influence on the pharmacological properties of some active principles. Had the authors examined their extracts for inorganic materials?

DR. J. G. DARE (Leeds) remarked that the leaves were used by dog breeders. Could an indication of clinical activity be obtained by experiments with that species?

MR. K. R. FELL, in reply, quoted from the original text of Burn and Withell (*Lancet*, 1941, **241**, 1) on the difference in action on smooth muscle in tone and not in tone. "The fact that the use of raspberry leaf infusion has a traditional use to make uterine activity easier suggested that there might be a clinical application. It is difficult to understand how uterine relaxation could assist parturition. Rather, it would be thought to delay it by diminishing the forces available to bring about the birth of the child. Conceivably it might assist in dilatation of the os through being exerted chiefly on the lower uterine segment. But a drug which relaxed uterine muscle could be valuable in the relief of painful menstruation when due to spasmodic contraction of the uterus." A recommended dosage was 15 to 30 g. as a 5 per cent. infusion. He agreed that the leaves might be more active in the Spring than in July, when they were usually collected. It would be necessary to do much work on different species, and care

had been taken to point out that the work done had been on one well-known commercial variety only. All the *p*H measurements had been made by potentiometer and the adjustments generally had been effected by calcium carbonate. In the work they had encountered large amounts of tannins which might have adsorbed some of the active principles, and removal of the tannins was a difficult problem. In one instance they had removed lead as sulphide and they suspected that this had removed one of the active principles. The main constituent found so far in the yellow viscous substance was sugar. This was removed to some extent by an ion exchange technique. He did not know the chemical nature of the three active constituents. Calcium was the main inorganic constituent, being present in the form of oxalate. In crude extracts it did not appear to influence the general pharmacological picture. The final extracts used had, in fact, been calcium-free.

DR. A. H. BECKETT, in reply, said that they had extracted fractions with different pharmacological actions, but so far had not isolated the active principles. The question of inorganic materials had been thoroughly investigated. He thought it was too early to move to clinical trials.

DR. M. F. LOCKETT, in reply, said that once the extract had been put through an ion exchange column it did not have a multiple action on the same uterus. The extracts were not yet free from toxic compounds and they were not, therefore, in a position to submit them to clinical trials.

MR. J. A. STALLWORTHY (Senior Consultant Gynæcologist to the United Oxford Hospitals) said that he became interested in the clinical side of the question some years earlier, but could so far report only negative results. Raspberry leaf had been tested in some of the conditions mentioned in the discussion but with no success. One preparation, which they had been assured was safe for use intravenously, had been used on a volunteer, but he was seriously ill for a few days afterwards and raspberry leaf preparations had not been used intravenously since. For the last two years they had been carrying out clinical trials, with proper statistical control, on the effect of raspberry leaf tablets in labour, but these trials were not yet complete. The result of the authors' further work might be of the greatest value in clinical medicine. One of the greatest causes of difficulty in labour, and of prolonged labour, was not too much relaxation but not enough. A preparation which would give to the uterus a more normal rhythm of powerful contraction followed by profound relaxation would help in prolonged and difficult labour. Difficulty was often caused by the fact that the uterus would not relax completely between the contractions. The suggestion that raspberry leaf might have an ergot-like action was new to him.