available. Either method will indicate the clinically effective dosage range for the particular type of patient included in the trial.

Of particular importance is the introduction of chemical and biological methods of potency assay where results can be used to grade senna preparations in terms of their likely effect on the constipated bowel in humans.

We would emphasize the agreement between the various forms of assessment, laboratory and clinical, in indicating gross disparities between similar doses of apparently identical standard *B.P.* syrups. The laboratory tests confirm earlier suggestions of the serious deterioration which may take place in such aqueous preparations. Again, average doses of the two *B.P.* syrups tested clinically gave no better results than inert syrups. On the other hand, the dry granular preparation tested (senokot) proved to be chemically stable and to have the potent clinical effect which had been predicted from the results of both chemical and biological assay.

Summary and Conclusions

The design and conduct of controlled clinical trials of the therapeutic effect of different senna preparations are described. The results obtained in constipated patients of different clinical types have been compared with the potencies estimated from chemical assay of sennoside content and biological assay based on the laxative action in mice. It was concluded that: (1) Laxatives could be effectively graded by simple clinical trials in both short-stay hospital patients and the more chronically constipated elderly sick. (2) Clinical response rates are in general agreement with the results of both types of laboratory assay methods. Not only do apparently identical *B.P.* preparations of syrup of senna differ widely in their therapeutic effect, but, at average doses, the *B.P.* syrups tested were no better than inert controls. Chemical assay confirmed previous indications of deterioration in aqueous *B.P.* preparations. (3) A dry granular preparation of senna pod (senokot), used in dosages usually prescribed, proved to be chemically stable and to have a potent laxative effect.

We should like to thank the sisters in charge of the wards concerned, Sisters Anderson, Ronaldson, Cawthorn, and East, for their conduct of this trial, and we are indebted to Westminster Laboratories Ltd. for supplies of senokot and the specially prepared inert granules.

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Speaking at the Royal Institution in London on February 15, Dr. MARGARET MEAD discussed factors in social evolution. Borrowing, either of isolated traits or of whole patterns of behaviour, was one of the essential mechanisms of human evolution, she said. In 1928–9 she had carried out an anthropological study of a Melanesian village in the Admiralty Islands, and had repeated the study 25 years later. In this time the villagers had established a small "distinctive imitation of Western democratic Christian society," with ideas drawn from Christianity, British administration, and the American expeditionary forces. Contact in childhood with adults who were perceived as being of the same order as the children—in this case, their own parents—and dissatisfaction among the adults with the state of their culture, seemed to have been two preconditions of this change. This state of affairs could be contrasted with treating children as lower or imperfect human beings, rearing them with the help of another class such as nurses or teachers, or letting older children or grandparents bring them up.

STANDARDIZED SENNA AS A LAXATIVE IN THE PUERPERIUM

A CLINICAL ASSESSMENT

BY

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For many years senna has been regarded as a safe laxative for pregnant and puerperal women. Variability in efficacy from case to case led to diminished use of the drug until in recent years a standardized preparation became available. For this preparation, marketed under the name "senokot," stability and consistency of potency are claimed (Ryan, 1951). A number of favourable reports have now been published (*British Encyclopaedia of Medical Practice*, 1956) and a preliminary trial suggested that senokot might be suitable for use as a routine laxative for puerperal women (Duncan, 1953). In this further clinical trial the laxative effect of cascara and senokot are compared.

Spontaneous Bowel Movement.—As a preliminary step 100 consecutive puerperal women (32 primiparae and 68 multiparae) were observed with regard to spontaneous bowel movement. No laxative was given. The findings are shown in Table I.

TABLE I.—*Bowel Movement After Delivery in* 100 *Cases*

	No. of Patients
First spontaneous action on 2nd day	4
" " " " 3rd "	22
" " " " 4th "	30
" " " " 5th "	15
" " " " 6th "	4
" " " " 7th "	1
" " " " 8th "	1
Enema required	23

Design of the Trial

All patients in puerperal ward A were given, as a routine laxative, tab. extract cascara *B.P.*, 6 gr. (0.4 g.), on the morning of the third puerperal day. No further laxative or enema was given for 48 hours.

In puerperal ward B exactly the same routine was followed except that the laxative used was "senokot" granules, 2 teaspoonfuls (equivalent to 11 gr. (0.7 g.) of senna pod). Patients who had been delivered by the abdominal route and 12 patients whose bowels moved spontaneously before the third morning were excluded from the trial. No other exceptions were made.

The interval between administration and bowel movement, and the nature of the first motion, were recorded. The patients whose bowels moved within 24 hours of the dose were regarded as having shown a positive response, and in these the number of bowel movements within the period was noted. These objective observations were made by senior members of the nursing staff. Subjective impressions, such as the severity of colic, were more difficult to assess.

Comparison of the Two Groups

The fact that the two groups are comparable in respect of parity, nature of delivery, and previous history in relation to aperients is shown by Table II.

TABLE II

	Cascara Series		Senokot Series	
	Multip.	Primip.	Multip.	Primip.
Spontaneous delivery without tear	78	14	74	21
Episiotomy, forceps, or tear	21	29	22	31
Total	99	43	96	52

Of the cascara series 37 patients had been in the habit of taking aperients before pregnancy, and a total of 58 had taken aperients during the pregnancy. Of the senokot series 29 patients had been in the habit of taking aperients before pregnancy and a total of 56 had taken aperients during the pregnancy.

Results

The results of the trial are summarized in Tables III–V.

TABLE III.—*Response to the Laxative*

	No. of Patients	
	Cascara Series	Senokot Series
Bowels open within 4 hours	6	20
„ first open between 4 and 12 hours	39	87
„ „ „ 12 „ 24 „	35	21
Total positive response within 24 hours	80 (56·3%)*	128 (86·5%)*
No response within 24 hours	61	19
Time of response not recorded	1	1
Total No. in trial	142	148

* $P<0.01$.

TABLE IV.—*Nature of Motions in Patients Showing a Positive Response Within 24 Hours*

Nature of First Motion	No. of Patients	
	Cascara Series	Senokot Series
Normal	29 (36·25%)	60 (46·9%)
Loose	23 (28·75%)	39 (30·5%)
Watery	3 (3·75%)	16 (12·5%)
Constipated	23 (28·75%)	10 (7·8%)
Not recorded	2	3
Total (positive response) ..	80	128

TABLE V.—*Number of Motions Within 24 Hours of Taking the Laxative*

	Cascara Series	Senokot Series
Patients having 1 motion	67	86
„ „ 2 motions	9	23
„ „ 3 „	2	9
„ „ 4 or more motions ..	2	10
Total (positive response) ..	80	128

Resumption of Normal Bowel Habit.—After initial bowel movement 52 of the cascara series and 32 of the senokot series required further aperients or an enema during the puerperium. This is not regarded as significant, because 37 of the cascara series and 29 of the senokot series had been in the habit of taking laxatives regularly even before pregnancy.

Incidence of Gripes.—Of patients who had a positive response within 24 hours, 10 (12.5%) in the cascara series and 22 (17.2%) in the senokot series experienced gripes.

Lactation.—No difference in lactation performance was observed between the two groups. There was no evidence that either laxative had an adverse effect on lactation. Illingworth (1953) suggested that babies may develop diarrhoea when receiving milk from mothers taking senna or cascara. Experimental evidence (Tyson *et al.*, 1937; Friebel and Walkowiat, 1951) shows that senna glycosides do not appear in maternal milk. Certainly in this small series there was no instance of diarrhoea amongst the babies.

Previous History in Relation to Laxatives

For the purpose of comparison of the two groups in the trial a detailed history of the previous use of laxatives was taken. The results of this inquiry are presented as they give an indication of the habits in relation to laxatives in a small sample of married women.

Of the 95 primigravidae, 23 took laxatives regularly before they became pregnant. The drugs used were liquid paraffin in 5 cases, cascara in 5, salts in 4, doctor's prescription in 2, and various (1 each) in 7. During pregnancy a total of 39 primigravidae took laxatives regularly.

Of the 195 multiparae, 43 took laxatives regularly before the present pregnancy. The drugs used were liquid paraffin in 12, cascara in 9, "agarol" in 7, various in 15. During pregnancy 75 of the multiparae took laxatives regularly.

In view of the evidence that liquid paraffin prevents absorption of fat-soluble vitamins it is interesting to note that 43 of the 290 women studied took liquid paraffin regularly during the pregnancies.

Discussion

In the preliminary study it was found that 56 out of 100 patients had spontaneous bowel movements by the end of the fourth puerperal day. The positive-response rate in the cascara series (56.3%) shows no improvement on this. In the senokot series the positive-response rate was 86.5%, and this difference is statistically significant. In these positive-response groups a higher proportion of the senokot series had normal motions (46.9% compared with 36.25%), but also a higher proportion had loose or watery motions (43% compared with 32.5%). On these findings it is clear that with the dosage used senokot was a more effective laxative than cascara. The question arises whether this greater effect was merely a matter of size of dose. The pharmacopoeial dose of tab. extract cascara *B.P.* is 2–8 gr. (0.13–0.5 g.) (the dose used was 6 gr. (0.4 g.), which is three-quarters of the maximum *B.P.* dose) and of senna pod *B.P.* is 10–30 gr. (0.65–2 g.) (the dose used was equivalent to 11 gr. (0.7 g.), which is one-third of the maximum *B.P.* dose). The laxative effect should therefore have been greater rather than less in the cascara series. The reason for this discrepancy appears to lie in the fact that tab. extract cascara *B.P.* is unstandardized and contains only part of the original activity of the bark (Fairbairn and Mahran, 1953), whereas senokot is standardized and contains 100% activity of senna pod (Fairbairn and Michaels, 1950). A further point of practical importance is that for a fully active preparation such as senokot the upper limit of dosage for senna pod *B.P.* (30 gr.—2 g.) may be too high.

No untoward side-effects of the laxatives were noticed apart from gripes. The fact that a higher proportion of the senokot series had gripes is thought to be due to overdosage, because for the purpose of the trial it was necessary to give the same dose to all patients. Further experience with senokot has shown that an occasional patient experiences severe gripes in spite of smaller dosage, but this has been so infrequent that it has not detracted from the advantages of the drug. The majority of patients expressed the opinion that they preferred senokot to other laxatives which they had used in the past. This might be attributed to the novel form of the preparation in chocolate-flavoured granules. Senokot is also available, however, in tablet form, and a further series of 138 patients was studied under the same trial conditions with the exception that granules were replaced by tablets. The results of this further trial are so similar to those reported above that they are not given in detail. More than half of these patients said that they preferred senna to other laxatives they had used.

The continued use of senokot since the trial was completed has confirmed that it is a very satisfactory laxative for puerperal women. Its value during pregnancy is much more difficult to subject to a clinical trial, but it seems very satisfactory for this purpose. A few patients complaining of severe morning sickness have improved dramatically following regular administration of senokot. The question whether senna is more effective in this respect than other laxatives will require further study.

Summary

In a series of 100 puerperal women who were given no laxative in the puerperium only 26 had spontaneous bowel movements by the end of the third day, but 71 had had spontaneous motions by the end of the fifth puerperal day.

In a clinical trial, extract of cascara in a dose of 6 gr. (0.4 g.) (three-quarters of the pharmacopoeial maximum) was compared with a standardized preparation of senna in a dose of 11 gr. (0.7 g.) (one-third of the pharmacopoeial maximum). With the dosages used the senna (" senokot ") was shown to be a more effective laxative.

In the course of the trial it was noted that, of 290 women, 66 had been taking laxatives regularly before they became pregnant and that 43 had taken liquid paraffin regularly during their pregnancy.

I thank Miss G. C. Cruickshank, of the Maternity Department, Western General Hospital, Edinburgh, for her careful supervision of this trial, and Dr. D. H. McVie for his help with the earlier stages. I am indebted to Westminster Laboratories Ltd. for supplies of senokot.

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TREATMENT OF HYPOPITUITARISM

BY

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Before cortisone became available patients with pituitary insufficiency presented a difficult therapeutic problem, and many died as a result of adrenal crises or hypopituitary coma. All this has now been altered, and the major complications endangering life can readily be prevented by the addition of cortisone to existing methods of therapy. We have shown that patients with Addison's disease can be maintained in good health on cortisone as the sole method of treatment (Beck and Montgomery, 1956), and it is now generally recognized that, provided adrenal gland replacement is carried out, the therapeutic control of patients with pituitary insufficiency is usually satisfactory.

There is still diversity of opinion over what additional treatment, if any, is necessary in the latter. Sheehan and Summers (1954) report on the excellent response obtained in four cases treated with cortisone alone. On the other hand, Perkins and Rynearson (1952), Hart (1953), Querido *et al.* (1954), Whittaker and Whitehead (1954), and others advocate a wider range of substitution therapy and include deoxycortone acetate (D.C.A.), testosterone, and thyroid in addition to cortisone.

With the object of determining the simplest and most effective method of treatment for hypopituitarism, four patients suffering from post-partum pituitary insufficiency were studied as out-patients, and their response to traditional methods of therapy, supplemented with cortisone, was compared with their behaviour when treatment was continued on cortisone alone.

Method

The four patients were treated for periods ranging from 8 to 20 months on combined therapy consisting of D.C.A., sodium chloride, methyltestosterone, stilboestrol, thyroid, and cortisone (combined therapy), and subsequently for periods of 7 to 11 months on cortisone alone. Each patient was carefully assessed at three stages: before treatment started; when D.C.A., salt, testosterone, stilboestrol, and thyroid were withdrawn; and, finally, at the end of the trial period on cortisone. As a safeguard, each patient was interviewed monthly or more often as necessary, and the blood pressure and weight were recorded. At the three major examinations special attention was paid to the following points: energy and capacity for work and recreation; emotional tone, sense of well-being, and mental state; libido; menstruation; incidence and severity of infections and crises; tolerance of cold; weight and blood pressure; condition of hair and skin; and certain laboratory investigations. The decision to start the trial with combined therapy first, followed by cortisone alone, was made partly because we felt that the withdrawal of a drug providing a measure of relief of symptoms would be more readily noticed by the patients. An additional reason was that several patients were already on a modified form of combined treatment, so it was decided to extend and proceed with this aspect first.

Clinical details of the four patients together with details of treatment given are recorded in Table I.

Results of Treatment

Energy and Capacity for Work.—Profound weakness and lack of energy were characteristic of each case before the clinical trial started. A remarkable recovery was evident with combined treatment, and this improvement was maintained without any deterioration in three cases on cortisone alone. One patient felt well enough to resume her work as a weaver in addition to household duties. Another housewife was able to nurse an invalid relative living at some distance from her home. In the fourth case there was reappearance of asthenia and intolerance to cold, and thyroid had to be restarted seven weeks after its withdrawal.

Emotional Tone, Sense of Well-being, and Mental State.—The patients were depressed and low in spirits before treatment began, and mentally dull or sluggish. All returned apparently to normal on combined therapy, and no change was noticed by the patients, relatives, or physicians when therapy was continued on cortisone alone, except in Case 2, where mental sluggishness, depression, and misery were quickly apparent despite additional cortisone dosage. These symptoms were attributed to lack of thyroid, and they quickly regressed when this was restarted.

Libido.—This was lost in all subjects, and in two there was no improvement throughout the trial with either therapy, but libido had always been weak in these two women. However, one patient noticed some improvement in libido and sexual response with combined treatment, an improvement little altered with cortisone alone. Another patient reported almost immediate improvement in libido and return of orgasm on combined therapy. This was fully maintained with cortisone.

Menstruation.—All had complete amenorrhoea from the onset of their illness until three reported a three to four-day menstrual staining or bleeding during the periods of cyclical stilboestrol withdrawal. One patient (Case 4) did not take stilboestrol very regularly and did not menstruate. There was complete amenorrhoea again when stilboestrol was withheld.

Incidence and Severity of Infections and Crises.—One patient was initially admitted to hospital in coma. The other three had no history of frequent infections or crises before treatment. Since the start of treatment all have remained well and no difference has been apparent between the two forms of therapy.