in the air collected on June 27 was surprising, and, taken in conjunction with the low general bacterial count, may represent some other factor such as the effect of differences in light or ventilation which we have not recognized.

Finally, the measures taken to disinfect the male ward appear to have been successful in that for a time they eliminated staphylococci and reduced the incidence of infection. From the information available, it is not possible to tell if the epidemic strain of *Staph. pyogenes* was brought back to the ward by a member of the staff from some other part of the hospital, or was brought in by a patient, or came from some unsuspected hiding-place which had escaped disinfection. This staphylococcus had been isolated from time to time in other parts of the hospital.

Summary

During a period of nine weeks, 24 of 83 patients undergoing clean operations in one surgical unit developed wound sepsis and seven developed other staphylococcal infections. All but one of the staphylococci tested from the wounds and other lesions belonged to one phage type.

In many cases wound sepsis seemed to follow infection acquired in the operating theatre, and there was strong evidence implicating one of the members of the surgical team in these infections.

Some cases of wound infection and most of the other infections seemed to have been acquired in the ward. It is suggested that one patient, who had a staphylococcal lung abscess, may have been responsible for widespread dissemination. The epidemic type was found in large numbers in the air and on bedclothes, curtains, etc.; it was carried by only one member of the nursing staff.

We are greatly indebted to Dr. Radmila Skalova, of the Medical Faculty of the University of Zagreb, Yugoslavia, who, while working with a British Council bursary at the Central Public Health Laboratory, gave much assistance with the bacteriological air sampling.

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The latest *Life Tables* volume of the Registrar-General's *Decennial Supplement for England and Wales, 1951* (H.M.S.O., 3s.), is based on the 1951 census populations and on the mortality experience in England and Wales as a whole during the three years 1950–2. It shows that the expectation of life of a boy at birth has increased by nearly 15 years in the past 40 years; for a girl the increase is more than 16 years. These increases are largely the result of the immense improvement in infant mortality. In 1910–12 120 of every 1,000 boys born and 98 of every 1,000 girls born died before reaching their first birthday; the corresponding figures for 1950–2 were 33 boys and 25 girls. Women have fared better than men in the improvement of longevity. While for women there has been a continued substantial lightening of mortality even beyond the age of 80, for men the improvement has been much less. For men aged 60 the expectation on 1950–2 mortality is about 14¾ years, an increase of only three-eighths of a year on the figure 20 years earlier, whereas for women of that age it is 18 years, an increase of 1½ years. Persons living in England have a higher expectation of life than those living in Scotland or Wales. The rural districts show mortality lighter than the national average. Alone of all the major conurbations Greater London experienced lighter mortality than England and Wales as a whole.

CLINICAL AND LABORATORY ASSESSMENTS OF SENNA PREPARATIONS

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The use of standard British pharmacopoeial preparations of senna implicitly assumes that all such preparations will have, for the same dosage, similar laxative effects, and that, subject to individual variation, like effects will be consistently produced by the same dose of the same preparation at different times.

Work directed by one of us (J. W. F.) led to the development of a reliable bioassay procedure, using mice as the test animal (Lou, 1949); and the indications of laxative potency given by this method agree closely with those derived from a physico-chemical method of assay which determines the amount of the glycosides, sennosides A and B, present in different senna preparations (Fairbairn and Michaels, 1950). When applied to standard preparations of senna both these laboratory assay methods strongly suggest that senna pods and different samples of the *B.P.* liquid extract vary widely in potency: indeed, some of the extracts appear to be virtually inert. Further, *B.P.* liquid extract of senna appears to lose potency when kept over a period of time (Fairbairn and Saleh, 1953).

These indications, however, are based on laboratory techniques and need not necessarily apply in clinical practice. Although American workers (Miller and Alexander, 1949) have shown that bioassay results agree with laxative effects in humans, their subjects were normal (unconstipated) individuals. We here describe controlled clinical trials designed to measure the relative laxative potency of various *B.P.* senna preparations in constipated patients in hospital practice and to compare clinical results with the findings of chemical and biological assay. At the same time we have included in the trial a new granular type of senna preparation ("senokot"), for which total retention of the activity of the crude drug, consistency, and stability of potency are claimed (Ryan, 1951). Its laxative efficiency has been favourably assessed by several workers (*Brit. Ency. med. Pract.*, 1956), but no rigorously controlled observations have been reported.

Trial Design

Stage I

In the first stage of the trial, doses of the various senna preparations within the usually prescribed range were given to two groups of patients complaining of constipation; one group comprised expectant mothers in the obstetric wards of a general hospital—that is, "short-stay" patients—the other consisted of patients of both sexes in wards containing some elderly chronic sick—that is, "long-stay" patients. Four preparations were used at two dosage levels. The first levels, representing the average of the *B.P.* dosage range for the syrups and its approximate equivalent for senokot, were:

*1. Syrup of senna *B.P.* (A) 5 ml. (made from 1.25 g. senna pod)
*2. Syrup of senna *B.P.* (B) 5 ml. („ „ „ „ „)
3. Senokot granules .. 6 g. („ „ 0.9† g. „ „)
4. Blank syrup (taste and appearance similar to the *B.P.* syrup of senna).

One dose of each preparation was measured into glass containers. These were numbered in random order and used as required, in that order, in the wards. Any one patient received only one dose. The patient, the physician, and the sister-in-charge did not know the chemical or biochemical activity of the preparations which had been administered. A time limit of 24 hours was given for a bowel action to result. If none was produced, another type of laxative was given. The results of the administration of the senna preparations under trial were recorded on standard forms according to the time, type (full, scanty, or fluid), and frequency of motions.

The second dosage levels for the two syrups were increased by 40% above the first to 7 ml.—that is, approximately the maximum *B.P.* doses. To avoid drastic purging the dose of senokot was increased by only 25% to 7.5 g.

In the trials at these higher levels the trial procedure was repeated, but the inactive control preparation used was a chocolate granule containing no senna but otherwise indistinguishable from senokot.

Stage II

In the second stage of these trials the design was rather different. To minimize the effect of individual differences in response to laxatives, and to balance the effects of order of administration, each of the four preparations was administered in turn to elderly patients suffering from severe chronic constipation. A latin square type of design ensured that, within each set of four patients, each type of preparation was given once to each patient and once in each order from first to fourth (Table I).

TABLE I.—*Order of Administration of Preparations*

Patient	1st	2nd	3rd	4th
1	Syrup A	Syrup B	Senokot	Inert granules
2	„ B	Inert granules	Syrup A	Senokot
3	Senokot	Syrup A	Inert granules	Syrup B
4	Inert granules	Senokot	Syrup B	„ A

Half the patients were given doses at the average levels already indicated, half were given the higher dosages. Inert granules were used as controls throughout this stage. Otherwise the procedure was as before. If, however, no bowel action resulted after at least 24 hours, another type of aperient (not one of those under trial) was given and the trial resumed when the patient next complained of constipation.

To ensure that the dosage of the preparations being clinically assessed had a consistent sennoside content throughout the trials, the same samples of the three preparations were reassayed chemically before the second stage began. The results seen in Table II show the changes in sennoside content which had taken place. The apparent loss in potency by one-third noted in one of the *B.P.* syrups was then compensated for by increasing the average dose from 5 ml. to 7 ml., and the maximum dose from 7 ml. to 9.5 ml. The small sennoside content of the other *B.P.* syrups had virtually disappeared and no such compensation was practicable. Since the chemical content of senokot showed no loss, the dosage was left unchanged.

*The strongest and the weakest (on the basis of chemical and animal assay) of a number of different commercial samples of *B.P.* syrup of senna examined for this investigation.

†Reduced from 1.25 g for the syrups owing to the anticipated higher laxative potency of senokot.

TABLE II.—*Chemical Reassays of Senna Preparations*

Preparation	Mg. Sennoside Content/Aliquot		
	1953	1955	Loss %
Syrup of senna B ..	0·3	Traces	100
„ „ „ A ..	2·8	1·9	33
Senokot	4·7	5·0	0

Summary of Results

In a preliminary analysis of the results two criteria of clinical potency were used: (1) The percentage of "satisfactory" results—that is, one or more full motions produced within the time limit. Motions described as scanty or otherwise unsatisfactory by the patient were ignored. (2) The total number of motions produced within the time limit without regard to the patient's subjective report.

TABLE III.—*Response to Control Preparations*

Type of Control	Type of Patient								
	Short-stay			Long-stay			Total		
	No. of Cases	Criteria 1	Criteria 2	No. of Cases	Criteria 1	Criteria 2	No. of Cases	Criteria 1	Criteria 2
Syrup ..	19	42%	1·3	13	23%	0·8	32	33%	1·1
Granules	16	63%	0·9	15	53%	0·6	31	58%	0·8
Mean	35	53%	1·1	28	38%	0·7	63	46%	1·0

Criterion 1: Satisfactory. Criterion 2: Number of motions per patient in 24 hours.

In Table III are compared the results, using each criterion, of the effects of the control substances during stage I in the two groups of patients. The difference in response rates between the two types of clinical case is in line with expectation. The large subjective element in the first criterion is evident in the increase in response achieved simply by substituting the more elegant and novel but inert granular preparation for the syrup type of control. On the other hand, the second criterion shows a satisfactory consistency between the two inert preparations. Partly for this reason and partly because the bioassay method on mice depends on counting the number of extra or fluid motions produced, this second criterion has been used throughout. To match the bioassay technique more closely and to minimize any differences between wards, the final result is expressed as a percentage increase in the number of motions produced by a particular senna preparation over the number produced in the same trial group by the inert control.

Table IV shows the results obtained in the first stage of the trial. As already seen, the response rate is greater among the short-stay patients, but the general trend of the results is similar in the two groups: in total, only the higher doses of one of the *B.P.* syrups and both doses of senokot produce a laxative effect which is appreciably better than the corresponding inert controls.

In the alternative trial design the individual variation is minimal, but the chronically constipated patient gives a less marked response to laxatives. Table V shows that in these circumstances again only the high doses of one syrup (syrup A) and both dosages of senokot effect any marked rise above the control level. An analysis of variance showed that these results were unlikely to be fortuitous ($P<0.01$).

It is clear that there are appreciable differences in laxative potency between the various preparations used; it

remains to decide whether these clinical indices agree with the results of chemical and biological assay. Table VI sets out the laboratory and clinical assay results for each preparation arranged in order of the potency as estimated by bioassay. The close correlation between chemical and biological assay methods is obvious. More striking, however, is the relationship seen in Figs. 1 and 2 between chemical assay results and clinical response rates where preparations are tested both separately on different patients and serially on the same patient. In the type of patient included in this trial no perceptible rise in clinical response above the control level of 100% occurs consistently with sennoside contents below about 15 mg. per dose.

TABLE IV.—*Clinical Response to Different Senna Preparations in Different Patients (Mean Number of Motions in 24 Hours)*

Preparation	Short Stay			Long Stay			Total
	No.*	Mean†	Control	No.*	Mean†	Control	Unweighted Mean Control
Average Dosage							
Syr. control	19	1·3	100%	13	0·8	100%	100%
,, senna B	14	0·7	54%	16	0·7	88%	71%
,, ,, A	17	0·6	46%	16	1·2	150%	98%
Senokot ..	14	1·8	138%	16	1·6	200%	169%
Maximum Dosage							
Granule control ..	16	0·9	100%	15	0·6	100%	100%
Syr. senna B	17	0·5	56%	15	0·7	117%	87%
,, ,, A	17	1·6	178%	14	0·9	150%	164%
Senokot ..	13	2·2	244%	14	1·1	183%	214%

* Number of patients. † Mean number of motions per patient.

TABLE V.—*Clinical Response to Different Preparations in Same Patients (Mean Number of Motions in 24 Hours)**

Preparation	Average Dosage		Maximum Dosage	
	Mean No.	Control	Mean No.	Control
Granule control	0·7	100%	0·4	100%
Syr. senna B	0·7	100%	0·6	150%
,, ,, A	0·6	86%	0·8	200%
Senokot	1·4	200%	1·2	300%

* 16 patients in each dosage group.

TABLE VI.—*Correlation of Chemical, Biological, and Clinical Assay Results*

Preparations	Mg. Sennosides Dose		Control Response	
	Chemical Assay	Bio-assay*	Different Patients	Same Patients
Syr. senna B (av. dose) ..	1·3	2·0	71%	100%
,, ,, B (max. ,,) ..	1·8	2·8	87%	150%
,, ,, A (av. ,,) ..	13·8	22·1	98%	86%
,, ,, A (max. ,,) ..	17·5	30·9	164%	200%
Senokot (av. dose)	29·0	51·0	169%	200%
,, (max. ,,)	36·0	65·0	214%	300%

* The bioassay figure is always higher than the chemical assay figure, since the sennoside A and B content represents only about two-thirds of the total biological activity (Fairbairn and Saleh, 1951).

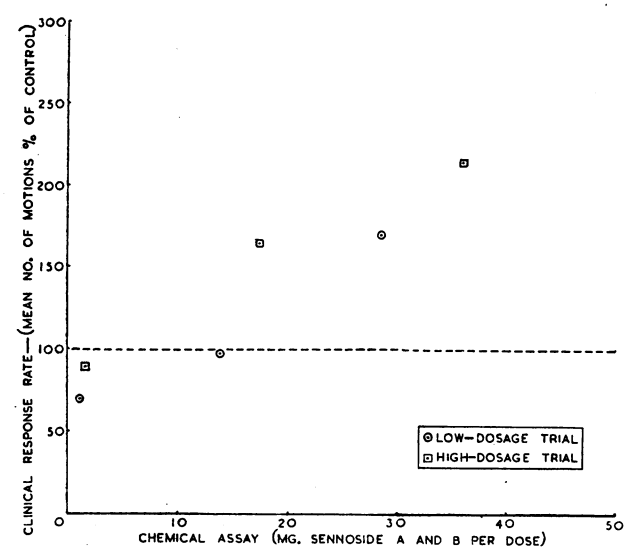

FIG. 1.—Stage I. Clinical and chemical assay results (in different patients).

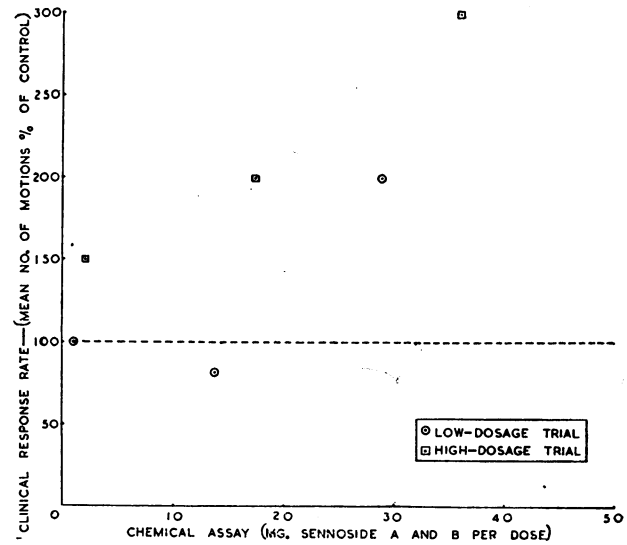

FIG. 2.—Stage II. Clinical and chemical assay results (in same patient).

Discussion

These clinical trials show how, by careful design and conduct, results of practical value can be simply attained with the use of crude criteria in a relatively minor but important ailment. The nature of the control preparation may be crucial when more subjective patient responses are involved. Changing the inert preparations from syrup to granules can produce a rise in the proportion of "satisfactory" responses from 33 to 58%. It seems better to minimize these psychological influences by using simple objective criteria such as the number of stools produced within 24 hours. For the group of short-stay hospital patients comparisons of preparations allocated separately and at random to different patients will give essentially the same indications as trials where individual variation in response is minimized by serial administration of drugs, in a balanced and randomized design, to the chronically ill.

The analysis of variance set out in Table VII suggests that while order of presentation is unimportant compared with the random variability in response of the same patient

TABLE VII.—*Analysis of Variance of Response Rates in Trials on Same Patients (Maximum Dose)*

Sources of Variation	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio
Difference due to treatments	4·92	3	1·64	4·56*
Personal differences ..	18·23	15	1·22	3·39*
Order of presentation ..	1·17	3	0·39	1·08
Random within-person variability	15·16	42	0·36	
Total ..	39·48	63		

* $P < 0.01$.

at different times, personal differences in responsiveness are of some account in trial design. This implies that the serial type of trial which minimizes these personal differences is, for this type of patient at least, the more effective test procedure. On the other hand, the greater responsiveness of the younger "short-stay" patient makes such cases more sensitive indicators of differing laxative potencies. Choice of method in clinical trials of laxatives can thus be decided simply on the basis of the number and type of clinical cases

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