Results

The results of this test were assessed by taking the total number of wet beds in the two groups in the two weeks before treatment (period 1), in the two weeks during which the tablets were given (period 2), and in the four weeks after treatment was stopped (period 3). These figures are shown in Table II.

TABLE II.—Results of Test

	Group A (Propantheline)			Group B (Placebo)		
	Dry Beds	Wet Beds	Ratio D/W	Dry Beds	Wet Beds	Ratio D/W
Period 1 ..	118	344	0.343	132	316	0.418
.. 2 ..	152	310	0.490	105	342	0.308
.. 3 ..	269	655	0.410	213	683	0.311

I am indebted to Dr. Louis Griffiths for the following statement on the statistical significance of these figures: "During period 1 there is no significant difference between the treatment and placebo group ($\chi^2=1.8$, $P>0.1$). In period 2 the diminution in the number of wet beds is highly significant ($\chi^2=17.6$, $P<0.01$). The increased number of wet beds due to the placebo is also probably significant ($\chi^2=4.07$, $P>0.02$). In period 3, the post-treatment period, neither group of figures shows significant differences."

It would therefore seem safe to conclude that propantheline bromide, used in this way, has a small (5%) but definite effect in diminishing the number of wet beds in nocturnal enuresis, an effect which disappears (as statistically significant) in the post-treatment period. If individually severe cases only are selected for study—that is, those children showing in period 1 a D/W ratio of less than 0.25—we get

TABLE III.—Results in Severe Cases Only

	Group A (Propantheline) (17)			Group B (Placebo) (16)		
	Dry Beds	Wet Beds	Ratio D/W	Dry Beds	Wet Beds	Ratio D/W
Period 1 ..	12	212	0.057	16	208	0.078
.. 2 ..	31	193	0.139	19	205	0.092
.. 3 ..	36	418	0.086	26	422	0.062

the results shown in Table III. Dr. Griffiths comments: "In period 1 there is no significant difference between the two groups. In period 2 the difference due to treatment is highly significant ($\chi^2=9.1$, P almost reaching the 0.001 level). The differences in period 3 are not significant."

The effect of the propantheline bromide in this group is more emphatic, but it shows no persistence into the post-treatment period. No child was cured; but cures were, of course, hardly to be expected, since the drug was used for quite a short time and the dosage used was empirical. In using amphetamine in the treatment of enuresis it is customary to give the maximum dosage—for example, up to 20 mg. a day for four to eight weeks—before concluding that the drug is of no value; thus there should be relative optimism concerning results to be expected when propantheline bromide is used in rather larger doses and for longer periods.

There is no sex bias in the incidence of enuresis, but in the present series there was a rather large preponderance of boys, owing to the fact that all the "deprived" children came from boys' homes. There is, however, no significant difference in the results of treatment when the sexes are compared.

Pharmacology

Propantheline is 2'-diisopropylaminoethyl xanthen-9-carboxylate methobromide. It is described as an "autonomic blocking agent" (acetylcholine inhibitor) or, in other words, as an anticholinergic drug. Its potency, in various forms of trial, is two to three times greater than that of atropine. Its essential effects are those of atropine—decreasing salivary and gastric excretion, and (in sufficiently large dosage)

causing acceleration of the pulse, constipation, blurring of vision, and retention of urine. In therapeutic dosage such effects are quite exceptional, and none of the children in this trial were reported to have been upset or to have shown any toxic symptoms at all. In extreme overdosage in animals, a curare-like action is apparent; a lethal dose in rats (LD50) is about 1,000 mg. per kg. One-tenth of the minimal lethal dose was given to rats daily for some months without any observed effects except in slowing the rate of growth.

Summary

A controlled trial of propantheline in the treatment of 65 enuretic children is described.

The drug was found to have a limited but definite action in reducing the number of wet beds in enuresis, and as an adjuvant to the full consideration of the individual child suffering from this complex condition to have a definite place in treatment.

My thanks are due to Messrs. Searle and Co. for supplies of "pro-banthine" and for their full co-operation during the trial; to Miss Elizabeth Harvie, children's officer for the County of Kent, for her help in obtaining the co-operation of superintendents of children's homes; and especially to Miss Kathleen Minchin, secretary to the Children's Department, Farnborough Hospital, who undertook most of the tedious work of collecting and abstracting the reports.

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A CONTROLLED TRIAL OF PROPANTHELINE IN BED-WETTING*

BY

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It is the purpose of this paper to report the result of a small controlled trial of propantheline ("pro-banthine") in the treatment of simple nocturnal enuresis.

The literature on bed-wetting reveals many different therapeutic regimes based on many different theories of aetiology, and many empirical routines based on no particular theory but justified by the results obtained. It is a disappointing feature of most of the papers that little attempt is made to control the various factors that may influence the results of treatment. The critical reader is left with an uneasy feeling that the doctor's confidence in his treatment has played an important part, and that perhaps indirect psychotherapy by suggestion is responsible for the successful cases. This dearth of controlled experiment is the more disappointing because the results of treatment are so easily seen: there can be little observer error about a wet bed or a dry one.

For many years atropine preparations have been thought to be of value in relieving frequency and urgency of micturition and have been in vogue for a long time in the treatment of enuretic children. Recently methantheline ("banthine") and propantheline have been widely used in urinogenital surgery. The pharmacological activity of these substances (an anticholinergic effect) upon the normal and neurogenic bladder has been demonstrated (Keizur and Hodges, 1953). By producing

*A summary of this paper was communicated to the East Anglian Paediatric Club on October 1, 1955.

a partial block of the parasympathetic innervation of the bladder methantheline has a powerful depressant action upon the detrusor muscle. The potential value of such a drug in the treatment of enuresis is obvious, and favourable results have been reported (O'Malley and Owens, 1953). Propantheline, being equally or possibly more effective in its action on the bladder and producing fewer side-effects, would seem to be particularly promising in the treatment of simple enuresis; dramatic benefit has been reported (Gordon, 1954), and scepticism regarding the part played by propantheline has been expressed (Dimson, 1954).

Case Material

The material of the experiment reported here consisted of the cases of simple bed-wetting referred to an ordinary paediatric out-patient clinic. This material may be to some extent selected, since the family doctors may have referred obviously emotionally disturbed children to a children's psychiatrist and may have sought surgical advice in those cases in which urinary tract abnormality seemed likely.

The medical history, physical examination, and laboratory testing of casual urine sample were the routine initial investigations. During the period of this study no case was seen in which organic disease seemed likely and no child was seen in whom major juvenile psychoneurosis seemed probable. These children all received the routine treatment of this particular clinic, with, in addition, "special pink tablets, a new American treatment, which seems very promising"—the pink tablets being either 15-mg. tablets of propantheline or identical-seeming but inert blank tablets specially prepared by the manufacturers for the purpose of this study.

Routine Treatment.—This may be briefly described as an explanation to the parents and child that bed-wetting is a simple babyhood habit which has lasted rather longer than usual—an assurance that it is not a symptom of serious kidney, bladder, or mental disease. They are told with emphasis that since the wetting occurs in sleep the child cannot be blamed for it. They are asked to ignore wet beds but to count only the dry nights, to regard each dry bed as an occasion for congratulation and breakfast-table celebration and even as meriting some small and consistent reward. The child makes a special mark on the kitchen calendar to show the record of dry nights to the doctor at the next visit. No medicines are used in this routine treatment but the child is asked to co-operate in a severe restriction of drinking during the second half of the day: nothing to drink between midday dinner and breakfast the following morning. It is doubtful if fluid restriction is of any direct benefit, though what might have been a soaking bed may become a damp one. But there may be some indirect advantages: as many enuretic children drink a great deal, this habit is restricted; any latent desire to punish in the minds of the parents may be diverted; and any feeling of guilt in the mind of the child may be expiated by the thought that the imposed thirst represents a distinct contribution on his part.

The Experiment

Apart from considerations that may have influenced the family doctors in referring the cases, the experimental material was quite unselected. All cases attending the children's out-patient clinic were accepted for this study. To secure alternate case control they were divided at random into two groups (odds and evens) by the simple expedient of using the last digit of the hospital record number: a less arbitrary method of random sampling might have provided a better-balanced pair of groups, but considerations of simplicity prevailed. Table I shows differences between the groups that might have been important had a different result been obtained.

TABLE I.—*Comparison of the Two Groups of Patients*

	Treatment	Control Group
Number	9	6
Boys	6	6
"Old" patients	2	2
Age { Range	3 to 11 years	5 to 15 years
Average	6.2 years	9.4 years

The majority of cases were new, but a few "old" cases which had been receiving the routine treatment were also incorporated. Most of the children were asked to keep the score for a preliminary period during which little attempt was made to apply the routine treatment: this was to supply a datum line from which subsequent progress might be measured. The few exceptions to this rule represent those whose performance might have been influenced inadvertently by waiting-room conversation; these were admitted at once to the first experimental period.

There were three experimental periods, each of four weeks. In the first each child was given one tablet at bedtime; in the second period the dose was doubled; at the beginning of the third period the phrase, "Let us just try one more month on two tablets," was used to substitute the tablet given previously for an apparently identical but pharmacologically different tablet. This change, being unknown to the patient and parents, constitutes the second of the two controls used in this study; for each patient contributed results "on treatment" and "on inert placebo." Finally, a fourth period of follow-up observation was recorded to count the number of dry nights without tablets.

It is readily agreed that in therapeutic trials of this sort the active and blank tablets should look alike and the change be unknown to the patient. It is not always appreciated that the nature of the tablets should also be unknown to the experimenter. In this case the hospital pharmacist dispensed active tablets or blanks according to the "odd" or "even" grouping (by case-record number) of the patients and made the tablet substitution after four weeks on two tablets every night; he divulged the key only after the results had been collected and tabulated. To maintain this control inviolate it seemed important that the experimenter should avoid specific inquiries about possible side-effects lest he inadvertently discover the key, and then become unconsciously influenced by this knowledge in applying the suggestion therapy that is the basis of the routine treatment. In fact, the parents of three children volunteered a complaint of dryness of the mouth whilst in the two-tablet period: it transpired that two of these children were receiving propantheline and one the blank tablets at that time.

Results

Tables II and III record the results obtained in the treatment group and the control group respectively. The whole numbers indicate the number of dry nights in successive four-weeks periods (28 days). A fraction records a result of a lesser period: the numerator being the dry nights, the denominator the number of nights of observation. Refusal to take tablets is recorded where it occurred, and the subsequent score of dry nights—that is, without tablets—is recorded in the follow-up columns.

In three cases the experiment was abandoned because of failure to respond to treatment. My somewhat arbitrary approach to the problem of enuresis carries with it a slight but definite risk that serious organic or psychological causes for bed-wetting may be overlooked: it is my practice, therefore, to reconsider and reinvestigate each case that fails to respond favourably to the simple routine treatment.

Scrutiny of the individual case results (Tables II and III) shows a tendency to improve from month to month and suggests that the improvement is unaffected by the abrupt change from two active tablets to two inert tablets (Table II), or vice versa (Table III). The follow-up period without tablets shows that the improvement can be maintained without them.

The records of all the patients completing the experiment are available for testing the provisional conclusion (drawn from Tables II and III) that propantheline has failed to influence the result of the routine treatment. Table IV shows that there is no significant difference between the number of dry and wet nights during each child's month on either two tablets of propantheline (30 mg.) or two tablets of the placebo.

TABLE II.—*Treatment Group. Number of Dry Nights in Consecutive Four-weeks Periods*

Case	Tabs. 0	Propantheline		Placebo Tabs. ii	Follow-up
		Tabs. i	Tabs. ii		
B	14	27	26	28	28
D	10/21	8	19	22	27
F	16	14	20	22	9*
H	—	22	†	—	20/21
J	23	20	23	23	24
L	14	16	6 6†	—	18/21 28/28
N	14	11	9	±	—
P	—	13	14	23	17
R	0	0	0	±	—

A fraction indicates less than four weeks' observation: 10/21 = 10 dry out of 21 nights.

* Postal follow-up, family moved from district.

† Patient refused tablets.

‡ Failure of treatment, case eliminated from series.

TABLE III.—*Control Group. Number of Dry Nights in Consecutive Four-weeks Periods*

Case	Tabs. 0	Placebo		Propan- theline Tabs. ii	Follow-up
		Tabs. i	Tabs. ii		
A	9	14	24	22	27
C	24	19	19	†	22
E	—	25	19	25	28
G	3	2†	±	—	—
I	3	18	14	16	18
K	5	15	14	11	15

†† As Table II.

TABLE IV.—*Comparison of Performance on Propantheline, 30 mg., and Placebo of all Cases Completing Course*

		Treatment (Propantheline Tabs. ii each night)	Control (Placebo Tabs. ii each night)
Dry nights		176	189
Wet ..		76	63

Discussion

Though these results show no advantage of propantheline over an inert tablet of similar appearance it does not necessarily follow that propantheline is of no benefit in the treatment of enuresis. Some effect might have been demonstrated, for example, if a larger dose had been used. Dr. Kenneth Holt (personal communication) has found that larger doses can be given to enuretic children without producing side-effects. If the dose used were suboptimal the younger children in this series, receiving higher body-weight dosage, might show benefit. This is not apparent: there were only three children under the age of 6; they scored a total of 60 and 66 dry nights on two 15-mg. tablets of propantheline and two blank tablets respectively.

It will be appreciated that had the result been less definite this relatively crude experiment could only have served as a pilot study. Had the results suggested any slight advantage of propantheline over the control treatment the significance of this advantage would need to be established by a larger series of patients or a more sensitive experimental plan.

There are two conclusions to be drawn from this experiment. That the observed improvement is due to some other factor than propantheline; and that the routine treatment, with its confident emphasis on the child's ability to be dry at night, achieves its purpose.

Perhaps one may also venture a personal opinion. It seems possible that propantheline has had an indirect

influence upon these results by its effect upon the manner in which the routine treatment was presented. So tedious does the ever-present problem of enuresis become to those who conduct paediatric out-patient clinics that anything that rekindles a waning interest in the problem has a marked stimulating effect upon the interest with which cases are welcomed, and so it may enhance the value of the simple psychotherapy-by-suggestion that is the basis of the routine treatment. Every critical appraisal of new treatments for enuresis must take account of this possible effect.

Summary

Treatment of a small series of cases of simple nocturnal enuresis in children is described. The effect of propantheline, 15 and 30 mg. every night, is compared under controlled conditions with an apparently similar but pharmacologically inert preparation. The improvement observed in the majority of cases seems to be independent of propantheline treatment; that is to say, no significant effect ascribable to the drug has been demonstrated.

Grateful acknowledgment is made to Messrs. G. D. Searle and Co., Chicago, manufacturers of pro-banthine, for the supply of both the active and the specially prepared inert tablets; to Mr. F. Marshall, hospital pharmacist, for his help with the records; and to Miss B. J. Bird, secretary, for tabulating the results.

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CASE OF UNIUMBILICAL-DIBRACHIDICEPHALIC MONSTER

BY

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Obstetricians and others have always been interested in anomalies of foetal development, and consequently the literature on human malformations and monsters is quite extensive. However, the incidence of dicephalic monsters is low and the statistics of their occurrence are not particularly accurate. For these reasons the following case is reported.

Clinical History

The mother was a healthy Hainanese woman aged 44, and this was her third pregnancy. The previous two had been normal and had ended in the live births of two male children, 20 years and 5 years ago respectively. She had not received any antenatal care, and was admitted to the Kangang Kerbau Hospital on August 24, 1955, in labour. Two days previously she had had a small painless vaginal haemorrhage. The last menstrual period was stated to be November 26, 1954, making the estimated date of delivery September 2, 1955.

On examination she was established in labour. The size of the abdomen corresponded to the period of amenorrhoea, though there was some degree of hydramnios. The breech was presenting and a foetal heart was heard and regarded as normal. Labour progressed quickly, and four hours after admission the breech was distending the vulva. Spontaneous delivery of the breech with flexed legs followed quickly, but