CHAPTER 25

The Psychopharmacology of Nocturnal Enuresis

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Psychopharmacology is one science where the child has not proved father to the man. Neglect in the area of pediatric drug research has been due both to reluctance to give medication to children (particularly on an experimental basis) and to methodological problems. The dominance of a psychoanalytic viewpoint in child psychiatry has led to drugs being regarded as an alibi for the parents, an evasion for the therapist, and a punishment for the child (van Praag 1969). Methodological problems, which begin in a diagnostic quagmire, are confounded by the difficulties of assessing change in a maturing organism, which, though unwilling or unable to complain, is acutely sensitive to outside influences (Fish 1968*a*).

The proceedings of the first conference on research in child psychopharmacology were published in 1959 (Fisher 1959), but, out of a total of 159 studies written in English before then, only 33 showed even the basic elements of experimental design (Fish 1968*a*)

Apart from the excursions into folklore catalogued by Glicklich (1951), the study of drugs in enuresis made an equally slow start; in an extensive review of the literature before 1959, Kim (1959) reported that almost all studies of drugs for this condition were uncontrolled, and that favorable and unfavorable results were equally common for any particular drug treatment.

Research in the general area of pediatric psychopharmacology has continued at a snail's pace. A recent textbook on *Principles and Problems in Establishing the Efficacy of Psychotropic Agents* (Levine *et al.* 1971), sponsored jointly by the Psychopharmacology Research Branch at NIMH and the American College of Neuropsychopharmacology, contains a review (DiMascio 1971), which remarks that whereas tens of thousands of articles on adult psychopharmacology have been published in the last fifteen years, less than 500 have been devoted to the use of psychotropic drugs in children, and the majority of these 'show a marked lack of application of sophisticated research techniques'.

It is, therefore, surprising to discover that at least a fifth of these recent papers have been devoted to the study of drugs in enuresis, and that a reasonable proportion are well-controlled double-blind studies. A literature search of the Index Medicus since 1962, supplemented by a bibliography compiled by the International Reference Center on Psychotropic Drugs, revealed a total of almost 100 publications on the topic. The reason why enuresis has been so favored may have something to do with the fact that a wet bed provides both a tangible criterion measure and a source of unified complaint from parent and child. For once, the experimenter and subject can agree precisely on what they wish to improve and why they need to do so. In addition, bedwetting is a very common problem; the prevalence figures are well-known (Yates

1970), and it is amusing to note that when Bindelglas *et al.* (1968) placed an advertisement for volunteers in the local newspaper they achieved a sample size of 100 by noon on the day in which it first appeared.

As a science, psychopharmacology is concerned with discovering whether drugs alter behavior and, if so, by what mechanism. To find an answer to the first question, it is necessary to know what factors in the patient, the treatment, or its evaluation qualify any general conclusions about whether or not a drug works. A good beginning can be made by examining the literature, to determine what general conclusions have been arrived at concerning the efficacy of drug treatment for enuresis.

Efficacy of Drugs Used to Treat Enuresis

Table I shows the recent drug studies reported in enuresis, and the extent of the experimental control applied. While the drugs cover the whole spectrum of psychopharmacology, more than four fifths of the research has been devoted to the tricyclic antidepressants, and the majority of this to the prototype drug, imipramine. It is pleasing to note that about half of the studies have been double-blind, a reflection of the recent upsurge of interest and awareness in experimental design.

TABLE I
Recent drug studies in enuresis

Drug	*Type of Study*	*Authors*
Imipramine	Double-blind	Abrams (1963), Agarwala and Heycock (1968), Alderton (1970), Bindelglas *et al.* (1968), Blackman *et al.* (1964), de Jonge (1969), Dorison and Blackman (1962), Drew (1966, 1967), Fisher *et al.* (1963), Forsythe and Merrett (1969), Friday and Feldman (1966), Harrison and Albino (1970), Hicks and Barnes (1964), Ice *et al.* (1966), Kardash *et al.* (1968), Kolvin *et al.* (1972; and this volume Chapter 26), Kurokawa and Ohtaguro (1963), Laybourne *et al.* (1968), Manhas and Sharma (1967), Mariuz and Walters (1963), McConaghy (1969), Miller *et al.* (1968), Milner and Hills (1968), Noack (1964), Poussaint and Ditman (1965*b*), Ritvo *et al.* (1969), Robson (1969), Schjetne and Uri (1970), Shaffer *et al.* (1968), Thomsen *et al.* (1967), Treffert (1964), Ulf (1964), Valentine and Maxwell (1968), Yodfat (1966).
Imipramine	Single-blind	Meijer (1965), Ritvo *et al.* (1967).
Imipramine	Uncontrolled	Bauersfeld (1969), Cerny (1963), Epstein and Guilfoyle (1965), Franczak *et al.* (1966), General Practitioner Research Group (1970), Hagglund and Parkkulaninen (1965), Ingle and Panase (1968), Jaremko *et al.* (1968), Kumar and Gopal (1968), MacLean (1960), Munster *et al.* (1961), Nikclic and Kapamadzija (1964), Philpott and Flasher (1970), Rosenthal and Richmond (1969), Rydzyński and Weychert (1966), Salgado and Kerdel-Vegas (1963), Stolze (1965), Strauss (1966), Wiesner (1967), Woodhead *et al.* (1967).
Imipramine	Case Reports	Cahill (1967), Destounis (1963), Epstein and Quevedo (1964), Margolis (1962), Tec (1963).
Amitriptyline	Double-blind	Drew (1967), Lines (1968), Poussaint *et al.* (1966), Ulf (1964).
Amitriptyline	Uncontrolled	Kurokawa and Ohtaguro (1963), Porot and Girard (1970).
Amitriptyline	Case Report	Finkelstein (1965).
Protriptyline	Uncontrolled	Poussaint and Ditman (1965*a*).
Protriptyline	Case Report	Ayres (1966).
Trimipramine	Double-blind	Forsythe (1971), Rett (1968).
Desipramine	Double-blind	Liederman *et al.* (1969), Milner and Hills (1968).
Nortriptyline	Double-blind	Forsythe and Merrett (1969), Lake (1968), Milner and Hills (1968), Smith and Gonzalez (1967).

With the exception of the tricyclic antidepressants, which are discussed below, there is little substantial evidence for the efficacy of any other type of agent.

Stimulants

Despite its historical prominence as a drug for bedwetting, there is no controlled support for the utility of amphetamine. The one double-blind study (McConaghy 1969) found it markedly inferior to both imipramine and the bell-and-pad apparatus, and no better than placebo. One non-blind study (Pooley and Shersby 1963) at the Ilford Enuretic Clinic showed that dexamphetamine (10 mg) and a sustained release preparation (5 mg) were effective in 64 per cent and 75 per cent respectively of the enuretics treated, most of whom were deep sleepers; however, there was no control group. Two studies have been made of the use of amphetamines as adjuncts to conditioning with the bell-and-pad, but neither was blind, and while one reported success (Young and Turner 1965), the other showed total failure (Kennedy and Sloop 1968).

Of the other stimulants used, ephedrine (15 to 45 mg) was shown by the General Practitioner Research Group (1970) in a controlled study to be effective in producing

TABLE I (contd.)

Drug	*Type of Study*	*Authors*
M.A.O. Inhibitors	Uncontrolled	Naldi (1961), Prodi and Betolotti (1963).
M.A.O. Inhibitors	Case Reports	Gates (1965).
Amphetamine	Double-blind	McConaghy (1969).
Amphetamine	Uncontrolled	Kennedy and Sloop (1968), Pooley and Shersby (1963), Young and Turner (1965).
Ephedrine	Double-blind	General Practitioner Research Group (1969).
Phenmetrazine/ Methylphenidate	Double-blind	Breger (1962), Harrington (1960).
Trichlofos	Double-blind	General Practitioner Research Group (1969)
Meprobamate	Double-blind	Breger (1961).
Hydroxyzine	Double-blind	Breger (1962).
Chlordiazepoxide	Double-blind	Ingle and Panase (1968).
Chlordiazepoxide	Uncontrolled	Guttin (1964).
Chlordiazepoxide	Case Reports	Harrer (1968), Roy *et al.* (1963).
Reserpine	Uncontrolled	Lambros (1955).
Trifluoperazine	Case Reports	Freed (1961).
Thioridazine	Case Reports	Majdecka (1965).
Anticonvulsants	Case Reports	Guttiérrez (1964).
Anticholinergics	Double-blind	Jones and Tibbetts (1959), Leys (1956), Mayon-White (1956), Wallace and Forsythe (1969), Whitehead (1967), Wilkin-Jensen (1959).
Anticholinergics	Case Reports	Holt (1956).
Diuretics	Case Reports	Dobson (1968), Drug and Therapeutics Bulletin (1970).
Pituitary Snuff	Double-blind	Jones and Tibbetts (1959).
Pituitary Snuff	Case Reports	Holt (1956).
Amitriptyline & Chlordiazepoxide	Double-blind	Forsythe (1971).

a significant reduction in wet nights, but it was concluded that the benefits were 'small in nature' compared with the results with tricyclic antidepressants reported earlier by the same group. The results reported with methylphenidate (Breger 1962) of success in 43 per cent (cured or greatly improved) are curious, since the drug response in this study was no better than the placebo response reported by the same author for an identical population and similar experimental design the previous year (Breger 1961). Finally, phenmetrazine was claimed by Harrington (1960) to be effective in controlling enuresis, but analysis of the data shows no significant drug-placebo differences.

Monoamine Oxidase Inhibitors

Of three reports on these drugs, one is anecdotal (Gates 1965); the second, an uncontrolled study of nialamide (25 to 50 mg), reported a small benefit in 18 mentally retarded children (Prodi and Betolotti 1963), while the third claimed less benefit in such children than in normal enuretics (Naldi 1961).

Sedative-Hypnotics

In a double-blind study, Breger (1961) found that meprobamate (600-1000 mg) did not differ from placebo. In the same author's study of methylphenidate referred to above (Breger 1962), hydroxyzine (20 to 40 mg) produced equal benefit, but again did not differ from the placebo response reported in the study with meprobamate (Breger 1961). Ingle and Panase (1968), in their study of 25 children, compared the effect of the tranquillisers meprobamate (400 mg) and hydroxyzine (1 mg/kg) with that of imipramine, and found a better response to the antidepressant. Trichlofos (0·5 to 1·5 g) was also used in the General Practitioner Research Group's (1970) study, and produced results similar to those obtained with ephedrine, *i.e.* though moderately beneficial the drug was inferior to tricyclic antidepressants.

Harrer (1968) suggested that chlordiazepoxide could suppress the response of the bladder musculature to emotional stimuli, but other workers have suggested that the drug may provoke enuresis in some patients (Roy *et al.* 1963). In clinical trials, Guttin (1964) reported improvement in 45 out of 50 children given chlordiazepoxide (10 mg), but the study was uncontrolled.

Major Tranquillisers

Majdecka (1965) reported an improvement in two out of four children given thioridazine (less than 25 mg), but the accounts are sketchy. Lambros (1955) gave reserpine (0·75 mg) to seventeen chronic enuretic children, and found that sixteen became dry within three nights. However, ten subsequently relapsed on drug withdrawal, and the results could not be repeated when medication was re-instituted. Freed (1961) reported beneficial results in a few children given trifluoperazine.

Anticonvulsants

In a letter to the *Lancet*, one worker (Guttiérrez 1964) claimed beneficial results with anticonvulsant medication in enuretics with abnormal electroencephalograms (EEGs). The benefit could well have been secondary or non-specific.

Diuretics

Dobson (1968) reported that three children became dry during treatment with frusemide (20 mg, twice daily). This uncontrolled observation later formed the basis of an advertising claim for the product that was castigated by the *Drug and Therapeutics Bulletin* (1970).

Anticholinergics

On clinical grounds, Holt (1956) and Bakwin (1961) suggested that anticholinergic drugs were effective in controlling enuresis, but this has not been confirmed in several double-blind studies that have been carried out with propantheline (Leys 1956, Mayon-White 1956, Jones and Tibbetts 1959, Wilkin-Jensen 1959). In a large study with 300 severely enuretic children, Wallace and Forsythe (1969) failed to show that propantheline, either alone (45 mg) or in combination with phenobarbital (45 mg), was any more effective than a placebo over a four-month period. It is of interest, however, that a smaller study with geriatric subjects using larger doses (75 mg) did report benefit (Whitehead 1967).

Pituitary Snuff

Pituitary snuff has been reported beneficial in cases of enuresis because of its anti-diuretic effects (Holt 1956), but Jones and Tibbetts (1959) did not confirm this in a controlled study.

Tricyclic Antidepressants

Acting on the suggestion of his senior psychologist, the Australian psychiatrist MacLean (1960) made a short claim in the December 1960 issue of the *American Journal of Psychiatry* that imipramine had benefitted enuretic children, possibly as a result of its anticholinergic side effects.

Events then followed a classical sequence; the earliest corroborative studies provided enthusiastic support, but were uncontrolled (Munster *et al.* 1961, Margolis 1962, Salgado and Kerdel-Vegas 1963). The first double-blind study (Dorison and Blackman 1962) reported negatively, and was followed by two further negative reports (Blackman *et al.* 1964, Hicks and Barnes 1964). The fact that these early controlled studies were amongst the few unfavorable comparisons of the drug has probably contributed significantly to prolonging the controversy over whether or not the effects seen with imipramine are due to suggestion or are specific. What is worse, these studies were not appropriate refutations of MacLean's hypothesis, since they were all three conducted on adult hard-core enuretic army or navy recruits on the verge of obtaining their discharge from the service. As might be anticipated in such a population, the largest and most completely documented of these studies (Blackman *et al.* 1964) failed to report any significant improvement in the enuresis with either drug or placebo.

The situation since these beginnings is tabulated in Table II for all the tricyclic drugs that have been reported on.

It will be seen that the overwhelming majority of studies of imipramine in children have reported favorable and statistically significant results compared with a placebo.

TABLE II
Double-blind studies with tricyclic antidepressants

Authors	*Drug*	*Type of Patient*	*Number of subjects analyzed*	*Duration on drug*	*Cured* per cent*	*Significant difference from placebo*
Abrams (1963)	Imipramine	Institutionalized behavior disorder	13	4 weeks	N.S.	None
Agarwala and Heycock (1968)	Imipramine	Out-patients (children)	29	2 weeks	21	$P < 0{\cdot}006$
Alderton (1970)	Imipramine	Institutionalized behavior disorder	9	4 weeks	N.S.	$P < 0.025$
Bindelglas *et al.* (1968)	Imipramine	Volunteers (children)	63	4 weeks	20	$P < 0{\cdot}01$
Blackman *et al.* (1964)	Imipramine	Army recruits	35	2 weeks	55	None
de Jonge (1969)	Imipramine	Out-patients (children)	26	4 weeks	N.S.	Significant: P not given
Dorison and Blackman (1962)	Imipramine	Army recruits	30	2 weeks	N.S.	None
Drew (1966)	Imipramine	Institutionalized children	28	8 weeks	N.S.	$P < 0{\cdot}01$
Drew (1967)	Imipramine	Adult subnormal in-patients	28	4 weeks	None	None
Drew (1967)	Amitriptyline	Adult subnormal in-patients	28	4 weeks	N.S.	None
Fisher *et al.* (1963)	Imipramine	Institutionalized subnormals (children and adult)	34	4 weeks	12	None
Forsythe (1971)	Trimipramine	Out-patients	186	8 weeks	0	None
Forsythe and Merrett (1969)	Imipramine	Out-patients (children)	76	8 weeks	1	$P < 0{\cdot}001$
Forsythe and Merrett (1969)	Nortriptyline	Out-patients (children)	86	8 weeks	0	$P < 0{\cdot}05$
Friday and Feldman (1966)	Imipramine	Out-patients (children)	51	2 weeks	N.S.	$P < 0{\cdot}05$
Harrison and Albino (1970)	Imipramine	Orphanage children	62	3 weeks	N.S.	$P < 0{\cdot}02$
Hicks and Barnes (1964)	Imipramine	Navy recruits	100	10 days	8	None
Ice *et al.* (1966)	Imipramine	Institutionalized delinquent and dependent adolescents	19	6 weeks	N.S.	Degree of significance not given
Kardash *et al.* (1968)	Imipramine	Out-patients (children)	45	4 weeks	46·5	$P < 0{\cdot}001$
Kolvin *et al.* (1972)	Imipramine	Volunteers (children)	62	2 months	N.S.	$P < 0{\cdot}025$
Lake (1968)	Nortriptyline	Out-patients (children)	54	2 weeks	N.S.	$P < 0{\cdot}001$
Laybourne *et al.* (1968)	Imipramine	Out-patients (children)	24	2 weeks	N.S.	$P < 0{\cdot}05$
Liederman *et al.* (1969)	Desipramine	Out-patients (children)	100	8 weeks	17	$P < 0{\cdot}05$

Lines (1968)	Amitriptyline	Out-patients (children)	36	3 months	16	$P < 0{\cdot}001$
Manhas and Sharma (1967)	Imipramine	Paediatric out-patient and in-patient clinics	72	4 weeks	60	$P < 0{\cdot}001$
Mariuz and Walters (1963)	Imipramine	Institutionalized behavior disorder	23	20 days	N.S.	$P < 0{\cdot}001$
McConaghy (1969)	Imipramine	School children	60	12 weeks	54	$P < 0{\cdot}05$
Miller *et al.* (1968)	Imipramine	Volunteers (children)	107	20 weeks	< 24	$P < 0{\cdot}01$
Milner and Hills (1968)	Imipramine	Adult in-patients, schiz., subnormals	212	2 weeks	< 10	$P < 0{\cdot}001$ to $0{\cdot}20$ (depending on popul.)
Milner and Hills (1968)	Desipramine	Adult in-patients, schiz., subnormals	212	2 weeks	< 10	$P < 0{\cdot}03$—N.S.
Milner and Hills (1968)	Nortriptyline	Adult in-patients, schiz., subnormals	212	2 weeks	N.S.	$P < 0{\cdot}004$—N.S.
Noack (1964)	Imipramine	Out-patients (children)	16	Sequential	N.S.	80% certainty
Poussaint and Ditman (1965*b*)	Imipramine	Out-patients (children)	47	4-8 weeks	60	$P < 0{\cdot}0005$
Poussaint *et al.* (1966)	Amitriptyline	Out-patients (children)	32	4-8 weeks	10	$P < 0.0005$
Rett (1968)	Trimipramine	Children in-patients, subnormals and organics	12	N.S.	N.S.	N.S.
Ritvo *et al.* (1969)	Imipramine	Children (EEG study)	7	1 week	0	Significant alteration in sleep stages
Robson (1969)	Imipramine	Geriatric in-patients	36	3 weeks	None	None
Schjetne and Uri (1970)	Imipramine	Out-patients (children)	28	4 weeks	N.S.	$P < 0{\cdot}012$
Shaffer *et al.* (1968)	Imipramine	Out-patients (children)	59	12 weeks	36	$P < 0{\cdot}0005$
Smith and Gonzalez (1967)	Nortriptyline	Subnormal children in-patients	34	20 days	N.S.	$P < 0{\cdot}01$
Thomsen *et al.* (1967)	Imipramine	Institutionalized behavior disorder	19	4 weeks	N.S.	$P < 0{\cdot}001$
Treffert (1964)	Imipramine	Child and adolescent psychiatric in-patients	9	4 weeks	N.S.	$P < 0{\cdot}01$
Ulf (1964)	Imipramine, amitriptyline, and Preparyl	Institutionalized psychiatrically disturbed children of low intelligence	33	10 days	N.S.	No significant difference from placebo using Tofranil and Preparyl
Valentine and Maxwell (1968)	Imipramine	Institutionalized severely subnormal children	16	3 weeks	None	None
Yodfat (1966)	Imipramine	Out-patients (children)	35	10 days	100	$P < 0{\cdot}001$

*N.S. = Either not stated or method of analysis is unsuitable (*e.g.* group analysis, reduction in mean scores).

There are three exceptions. The first is Abrams' (1963) study of thirteen institutionalized children with severe neurotic disturbances, in which the results are confusingly presented without statistics. The other two (Fisher *et al.* 1963, Valentine and Maxwell 1968) reported on subnormals.

With the exception of one study using trimipramine (Forsythe 1971), all the double-blind studies conducted on children using other tricyclic drugs have also reported favorable results compared with a placebo. Forsythe and Merrett (1969) showed imipramine and nortriptyline to be equally effective, whilst another large comparative study (Milner and Hills 1968), using nortriptyline, imipramine and desipramine in a heterogeneous group of adult patients, showed that the most marked changes occurred in response to nortriptyline, but the drugs were not compared statistically. Ulf (1964) carried out a double-blind trial comparing imipramine and amitriptyline, and found the latter to be significantly superior in a group of disturbed children of low intelligence.

The general conclusion to be reached from an overview of the drug treatment of enuresis is that only the tricyclic antidepressants have been convincingly shown to be better than placebo, but that evidence is still lacking as to whether individual drugs within this category differ significantly from one another.

The Degree, Rapidity, and Persistance of Response to Tricyclic Antidepressants

It is necessary to ask not only whether these drugs differ from placebo in their effect, but to what degree, how rapidly they work, and for how long the effects persist.

Degree of Response

In considering this factor, it is pertinent to note Forsythe and Merrett's (1969) observation that 'parents are not the slightest bit interested in a "significant reduction in the number of wet nights". They are looking for a cure, a permanent cure, and they want to know what are the chances of the tablets curing their child.'

The clinically important fact in any study is, therefore, not the p value, but the number of children who are completely relieved of their symptoms. In this instance, the dictates of common sense and some confusion in the data combine to serve a common purpose. Because different authors have used a variety of methods of quantifying change (*e.g.* reduction in base-lines, percentage improvements, mean incidence of enuresis per unit time—ranging from one to four weeks), the only method of comparing outcome in different studies is to compare the proportion of cases of total remission of the symptom. Fortunately, this figure is also the most meaningful clinically.

Total remission figures are obtainable in fifteen of the double-blind studies which have shown a statistically significant difference between treatment with tricyclic antidepressants and placebo treatment. In these studies, the proportion of total remissions ranges from zero to 100 per cent, but the most extreme values can readily be accounted for by experimental factors. For example, in Forsythe and Merrett's (1969) study, which provides the two poorest responses, the children were selected on the basis of their wetting the bed at least six nights a week for a year, and were clearly a hard-core group. The enthusiastic report of Yodfat (1966) of total remission in all

children is based on a study which claims to be double-blind, but in which all the children were treated with the placebo first and the drug second. In nine of the fifteen studies for which figures are available, the percentage of total remissions ranges from 10 to 50 per cent. It is therefore reasonable to conclude that in studies lasting from two to twenty weeks the incidence of total remission is almost invariably below 50 per cent, and is often in the region of 10 to 20 per cent.

Rapidity of Response

Six of the seven reports which make specific comment on the rapidity of response to imipramine state that when there is an effect it occurs within the first week (Destounis 1963, Salgado and Kerdel-Vegas 1963, Epstein and Guilfoyle 1965, Drew 1966, Woodhead *et al.* 1967, Bauersfeld 1969). Several insist that the effect often takes place after the initial dose of the drug.

The only apparent exception is the paper by Forsythe and Merrett (1969), which states that the response is gradual over the first five weeks, but these authors appear to have mis-interpreted their own data. Their Table VII showing weekly changes in average frequency does not contain any base-line data. When base-line data are included, by taking their admission criteria of six wet nights per week, it can be calculated that 80 per cent of the maximum reduction in frequency of enuresis took place in the first week of treatment.

Thus all studies, including two double-blind studies, are unanimous in suggesting that maximum effects occur within the first week of treatment, and possibly much earlier.

The Duration of Response

The longevity of a response, if it occurs, may be considered both in terms of its persistance immediately following withdrawal and at longer-term follow-up.

(*a*) *Immediate Relapses.* It is noteworthy that MacLean's first report on the effects of imipramine on enuresis contains the cautious statement that 'no conditioning to dryness, such as frequently follows treatment with clinical awakening, has been noted, for children relapse as soon as the drug is withdrawn' (MacLean 1960). Subsequent studies have provided general support for this statement. Eleven authors comment specifically on this point. Only two claim sustained effects in more than half of responders, and both are uncontrolled observations (Epstein and Guilfoyle 1965, Kumar and Gopal 1968). Five double-blind and one single-blind study (Mariuz and Walters 1963, Meijer 1965, Drew 1966, Yodfat 1966, Miller *et al.* 1968, Forsythe and Merrett 1969) confirm that cessation of medication often results in rapid relapse. In the study of Miller *et al.* (1968), only 10 per cent of those whose enuresis responded to imipramine remained dry immediately following withdrawal of the drug. The lowest relapse rate is reported by Yodfat (1966), with 30 per cent of those who became dry remaining dry. As noted before, this study is of doubtful double-blind integrity.

(*b*) *Long-Term Results.* There are eight studies that have reported a long-term follow-up, but generally the observations have been of poor quality and anecdotally reported. A major problem in interpreting the information is that two factors are

TABLE III

Long-term follow-up after drug withdrawal

Authors	*Duration of follow-up after stopping drug*	*Number and percentage of original population still dry*
Bindelglas *et al.* (1968)	16 months	12/30 (40%)
General Practitioner Research Group (1969)	6 months	13/32 (40%)
Kardash *et al.* (1968)	4 months	13/35 (29%)
McConaghy (1969)	1 year	2/11 (18%)
Poussaint and Ditman (1965b)	1-3 months	11/47 (24%)
Poussaint *et al.* (1966)	4-6 months	5/50 (10%)
Shaffer *et al.* (1968)	3-14 months	3/56 (5%)
Yodfat (1966)	3-5 months	12/35 (35%)

often confused: (*a*) the percentage of the original enuretic population dry at follow-up; and (*b*) the percentage of those enuretics who became dry during drug treatment who are still dry at follow-up. Table III shows the results in terms of the first criterion. It appears that anywhere between 5 and 40 per cent of the original study populations may be dry at intervals of one to sixteen months after cessation of drug therapy. These are not startlingly successful figures in view of the maturational factors operating in their favor (*i.e.* natural remission), and they compare unfavorably with the 53 to 100 per cent recovery rates after six to sixty-three months follow-up reported for bell-and-pad therapy (Yates 1970).

Several of the studies mentioned in Table III also give information concerning the fate of children who became dry during treatment. Thus, Shaffer *et al.* (1968) state that only three out of twenty children remained dry at follow-up. Bindelglas *et al.* (1968) give a more encouraging report that, of those who were dry at the end of six months and received no further medication, 85 per cent were still dry sixteen months later.

Perhaps it is asking too much to expect the data to present a clear-cut picture when one is dealing with a maturational defect in which the study populations often include children of varying ages. The point is best illustrated by the variety of responses noted by Poussaint *et al.* (1966) four to six months after the end of their double-blind therapy, 8 per cent had improved and relapsed when the drug was withdrawn, and 10 per cent had become dry with treatment and remained dry without further drug therapy, 8 per cent had improved and relapsed when drug was withdrawn, and 10 per cent had improved but not become dry while on the drug, and then continued to go on to become dry despite drug cessation.

To summarize, it seems that a minority of patients treated with imipramine become totally dry within a matter of weeks, and that response, when it is due to the drug, usually occurs within the first week. If the drug is stopped after only a few weeks, relapse is quite likely to occur. If the patient remains dry immediately following this withdrawal, the long-term follow-up results seem still to be in doubt, and have not yet been subject to properly controlled investigation.

Factors in Experimental Design and Evaluation

Both in interpreting existing data and planning future studies, it is pertinent to investigate the ways in which experimental design and methods of evaluation can color the results of research and their meaning.

The Placebo Response

In view of the earlier controversies surrounding this topic, it may seem provocative to question whether a placebo response really does play a part in the drug treatment of enuresis. With a maturational defect, what is taken to be a placebo response may, if treatment is persisted with for long enough, simply be a case of spontaneous remission. The difficulty of deciding whether remission of the symptom is spontaneous or due to a placebo response certainly accounts for some of the popularity of bedwetting panaceas in the past, and also for some of the present problems in interpreting follow-up data.

In drug trials, however, the issue is whether immediate benefits follow drug administration that are not due to a specific pharmacological effect. This review of the literature suggests that a large part of what has previously been mislabelled 'placebo effect' may have been due to an experimental artifact. The point has been well put by Poussaint and Ditman (1965*b*), who suggest that the early response to the placebo in their study may have been due to the fact that parents exaggerated the initial frequency in order to have their children included in the study. This point was elegantly proven by Shaffer *et al.* (1968) in their double-blind study. When they looked at their first month of base-line records, they discovered that 60 out of 75 children were not wetting as often as the mother had reported. In a recent study, de Jonge (1971) found that eleven out of twenty-eight children 'improved' by at least 25 per cent during a four-week base-line period without treatment, and two became dry. The implications of this observation for research design are obvious. Drug effects should only be studied in enuresis when a base-line has been objectively recorded, and parents' reports of frequency cannot safely be regarded as an alternative.

It is particularly interesting to note that all seven studies in which a base-line was obtained reported an absent or negligible placebo response (Mariuz and Walters 1963, Meijer 1965, Drew 1966, Smith and Gonzalez 1967, Thomsen *et al.* 1967, Lake 1968, Milner and Hills 1968).

By contrast, a failure to establish base-line records has resulted in very variable 'placebo' responses being reported, even when identical research designs have been used by the same investigator (*e.g.* Breger 1961, 1962). In future studies, it might be advisable and kindly to abandon the placebo as a control agent, and to replace it with imipramine or some of the older remedies for which adequate controlled studies have still not been carried out. Even more important is the implication that control substances might be abandoned altogether, provided that a proper base-line is established, and that use could then be made of the doubled sample size to study the other potential determinants of outcome discussed below.

Crossover Design

A majority of double-blind studies on tricyclic drugs have utilized a crossover

design, and it is worth noting the premises on which this is based and the penalties which have been incurred. The clear-cut advantages are a reduction in the necessary sample size and the homogeneity of the data when each subject serves as his own control. The method is valid, however, only if spontaneous remission is unlikely, and if the drug action is rapid in onset and quick to disappear. The first two conditions appear to be satisfied by the data already examined, but there is doubt over the third. Several studies have demonstrated a significant order effect, in which drug action has apparently persisted into a subsequent placebo period. This effect has been clearly shown in seven double-blind studies (Smith and Gonzalez 1967, Thomsen *et al.* 1967, Agarwala and Heycock 1968, Kardash *et al.* 1968, Lake 1968, Shaffer *et al.* 1968, Harrison and Albino 1970), but has seldom been corrected for, with the result that drug-placebo differences may have been diminished. In future research designs, this effect should either be taken into account statistically, or controlled for by placing a no-treatment interval between episodes on active medication.

Methods of Rating

One undoubted source of variation in the data reviewed has been the method by which information about wet beds has been collected. Some investigators appear to have been satisfied with verbal reports, whereas others have used meticulous recording sheets (Milner and Hills 1968), calendar cards (Lake 1968), or colorful and attractive diaries which also help to maintain the child's interest (Pooley and Shersby 1963). This should also be considered as a potential explanation for differences between the results obtained in out-patient studies and those obtained in institutional settings where an objective check can be made of sheets and mattresses (Hicks and Barnes 1964).

Treatment Variables

A number of direct and indirect variables in the treatment may influence the outcome of a trial, or interpretation of the data.

Dosage and Regimen

Timidity in dosage, and the accompanying view that children are 'small adults', are at least partly responsible for the restricted and inflexible dosage schedules used both for treatment and research in enuresis. In addition, MacLean's (1960) original statement concerning dosage of imipramine has led to almost all studies being conducted with imipramine in doses of 25 or 50 mg at bedtime, the smaller dose being arbitrarily used in children under twelve years old. With only a few exceptions, all double-blind studies have adhered to this regimen. This not only makes assumptions concerning the immediacy of drug action, but violates the hard-learned lessons of adult psychopharmacology concerning individual variability in response to psychotropic drugs.

Among those who have experimented with dose levels, Shaffer *et al.* (1968) calculated dosage on the basis of surface area, and used both high and low doses in a multiple crossover design. The actual amounts given were within the 15 to 75 mg range, and the results showed no differences in outcome related to dose level.

Liederman *et al.* (1969) used 50 or 75 mg of desipramine depending on age, but though they noted individual variability in response this was not consistantly related to dose level. Similarly, Poussaint *et al.* (1966) failed to show any increased benefit when children who failed to respond to lower doses of amitriptyline were given up to 75 mg.

In contrast to these three negative reports, there have been six studies in which an alteration in dosage or regimen has been found to effect increased benefit. In a double-blind study, Drew (1966) reported that increasing the dose of imipramine from 50 to 100 mg improved results slightly (but not significantly). In another double-blind study, Agarwala and Heycock (1968) found significant differences from placebo with 50 mg of imipramine, but not with 25 mg, in a group of children who were all below twelve years old. In their double-blind study, Kardash *et al.* (1968) found that five children who had failed to respond to 50 mg did respond when the dose was later increased to 75 mg. Tec (1963) presented three case reports of children aged nine to thirteen years, who, after initial 'uncertain' results, showed 'remarkable' responses when the dose was later increased to 50 mg.

Epstein and Quevedo (1964) reported the case of a fourteen-year-old boy whose enuresis ended completely when he was switched from 50 mg of imipramine at night to a 25 mg thrice daily schedule. A more detailed and sophisticated experiment concerning the importance of timing of medication was Alderton's (1970) double-blind study, comparing the effects of giving medication at night (8.00 p.m.), mid-afternoon (3.15 p.m.), and at both times. An earlier study had shown that the mid-afternoon dose of 25 mg was more effective in controlling enuresis occurring before 1.00 a.m., while the evening dose was more effective in curbing bedwetting after this time. In the 1970 study, however, this difference was no longer significant, possibly due to use of a 50 mg dose, which produced higher and more sustained blood levels of imipramine. Cahill (1967) came to similar conclusions concerning the timing of drug administration in enuresis, on the basis of successful clinical experience.

The conclusions to be drawn from these experiments with the dosage and timing of medication are that the effect of imipramine may be an immediate one, related to time of administration, and that increased dosages may secure added improvement in individual cases. In future, flexible dosage regimens, such as have already been used by the General Practitioner Research Group (1969) and are common in adult psychopharmacology, might be worthy of further study.

Drug Compliance

A major factor in all drug studies is whether or not patients take the medication. This is especially important in children, who may have difficulty swallowing tablets. However, only two studies report excluding patients for this reason (Poussaint *et al.* 1966, Shaffer *et al.* 1968). Only Shaffer *et al.* (1968) seem to have gone to any lengths to check on compliance, by providing tablets in special packs which had to be returned. Since there is a simple and inexpensive urine test for the presence of imipramine (Forrest and Forrest 1960), it is surprising that this method of checking drug defectors has never been used in enuresis research.

Drug Combinations and Formulations

No controlled evidence exists as to whether drug combinations are of greater value than their individual constituents, although Stolze (1965) reported good results using a mixture of imipramine with atropine, and Noack (1964) claimed, on the basis of clinical experience, that tne addition of chlordiazepoxide sometimes enhances the effect of imipramine. Forsythe (1971) recently completed a double-blind study on 215 children in which significantly better results were obtained using a combination of amitriptyline (25 mg) and chlordiazepoxide (10 mg) than with a placebo.

Two studies have utilized liquid preparations of tricyclic drugs. Porot and Girard (1970) report good results with amitriptyline, while Philpott and Flasher (1970) obtained better results with imipramine syrup than with tablets in older boys. This might be due to better adherence to a liquid medication.

Combined Methods of Treatment

Surprisingly, there is only one report of the use of imipramine in conjunction with the bell-and-pad. Philpott and Flasher (1970) reported that the results of combined treatment was better than the bell-and-pad alone in 25 out of 33 patients, the improvement being most marked in boys. This study should certainly be repeated in a controlled manner.

Side Effects

DiMascio and Solty (1970) have recently reviewed the whole literature on the side effects of antidepressant drugs in children. In their incidence and severity these side effects, which include drowsiness, weight gain, and anticholinergic effects, appear to be similar to those reported in adults. In the particular field of enuresis, side-effects with imipramine are generally considered very rare (Abrams 1963, Noack 1964, Poussaint and Ditman 1965*b*, Drew 1966, Manhas and Sharma 1967, Agarwala and Heycock 1968, Miller *et al.* 1968, Milner and Hills 1968, G.P. Research Group 1969), and those that have occurred have not been serious enough to warrant stopping the drug (Poussaint and Ditman 1965*b*, Miller *et al.* 1968, Valentine and Maxwell 1968). Side effects noted with imipramine have included dizziness (Poussaint and Ditman 1965*b*), anorexia (Fisher *et al.* 1963, Poussaint and Ditman 1965*b*), and, in one case on 25 mg three times per day, an epileptic fit (Fisher *et al.* 1963). Shaffer *et al.* (1968) described three children who displayed an alteration in mental state, becoming restless and irritable, and experiencing difficulty in concentration associated with disturbance of sleep, nightmares and difficulty in getting to sleep; however, they noted that these children were all thought to be disturbed before treatment, and that the change seemed to represent an exacerbation of their normal behavior. One child in this study developed an acute peptic ulcer, but probably coincidentally. Sleep disturbances were noted in two cases by Noack (1964). Paralytic ileus has been reported in one case, the authors suggesting a need for careful supervision with a single high dose regime (Milner and Hills 1968).

Reports of side effects with amitriptyline are equally rare; those that have been described have been similar to those with imipramine, and have included occasional headache, decrease in appetite, stomach ache, and drowsiness. As with imipramine,

irritability has been described by parents in a few cases, particularly during the first two weeks of treatment (Poussaint and Ditman 1965*b*), but in none of these has the symptom been considered severe enough to warrant stopping treatment. Drowsiness is described more frequently with amitriptyline than with imipramine, and was sufficiently severe in one case in Kurokawa's group (Kurokawa and Ohtaguro 1963) to cause the drug to be discontinued.

On the other hand, the amphetamine group of drugs frequently give rise to side effects, particularly sleeplessness. McConaghy (1969), in his trial comparing imipramine, amphetamine, bell-and-pad conditioning and random awakening, noted that patients who were given amphetamine, both alone and in combination with the bell-and-pad treatment, showed more side effects than those on any of the other forms of treatment. None of the other treatments differed significantly from each other in the incidence of side effects.

Non-Drug Environmental Variables

Few studies mention whether parents were told what to do about such matters as fluid restriction, bladder emptying, and lifting; this is surprising since variables such as these can obviously have a profound effect on treatment outcome if they are not standardized in a manner similar to that described by Lake (1968).

Even when such instructions are given, parental attitudes can clearly influence the way in which these are implemented, altering the outcome of therapy either in obvious or subtle ways. According to Young (1965), a lack of parental co-operation is the commonest cause for failure of conditioning therapy in enuresis, and the same is certainly true of drug treatment, where parents may fear the child will be poisoned or become addicted (Ney 1969).

One further interesting non-drug variable reported in two studies has been the effect of changes in the weather. Drew (1966) noted that cold weather, because it tended to double the number of children who were enuretic, had a clear effect on the incidence of wet nights during his double-blind study, and that as a result drug-placebo differences were minimized. This finding was confirmed by Milner and Hills (1968), who showed in another double-blind experiment that schizophrenics and subnormal patients had significantly more dry nights when the weather was warm and dry.

Patient Variables

It is important when considering the effects of different forms of drug treatment to take into consideration individual differences in drug response. Such patient variables may bias the outcome of a study, especially if the sample groups studied are small, when random selection of patients may result in an uneven distribution of an unsuspected determinant of drug response. The only way of safeguarding against such an occurrence is to always compare the distribution of all such variables within the treatment groups.

There are a great many patient and illness variables with a putative influence on the outcome of drug therapy. Some of those which have been studied or commented on are discussed below.

Types of Patients and Methods of Selection

A striking feature of the literature on enuresis is the heterogeneity of patients studied and the varying ways in which the samples have been selected. Both factors place constraints on the generalizations that may be made from any particular study. Samples have been selected from institutions (from children's homes to mental hospitals), out-patient clinics (pediatric, psychiatric, or urologic), groups of service-men awaiting discharge (army or navy), volunteers obtained by sampling an entire school population (Miller *et al.* 1968, Kolvin *et al.* 1972), or even from volunteers recruited by advertising in the newspaper (Bindelglas *et al.* 1968). In attempting to clarify whether drugs have helped all types of enuretics it may be helpful to make the following arbitrary distinctions.

(*a*) *Children versus Adults.* As remarked earlier, results with adults have been less rewarding than with children. There are several possible reasons for this. Adult enuretics who have failed to yield to maturational factors may be a distinct aetiological group; in fact, the relationship between bedwetting and sleep patterns in adults appears to differ from that observed in children (Broughton 1968). Furthermore, adults may have already been exposed to a variety of drug treatments, and may be a selectively resistant population. Finally, their motivation for recovery may be suspect, especially since three of the negative studies in adults have been in recruits awaiting discharge from the service (Dorison and Blackman 1962, Blackman *et al.* 1964, Hicks and Barnes 1964).

(*b*) *Psychiatrically Adjusted versus Abnormals.* It is not clear from the interesting but conflicting reports in the literature how the response of enuretics to drug treatment is affected by the presence of various types of psychiatric disturbance. Out of five double-blind studies of imipramine using institutionalised maladjusted children, one (Abrams 1963) reported entirely negative results, while the other four reported varying degrees of success (Mariuz and Walters 1963, Ulf 1964, Thomsen *et al.* 1967, Alderton 1970). Although the patients in Thomsen *et al.*'s study showed significant improvement in response to the drug, this response was less marked than it was in the study of Mariuz and Walters. In discussing the discrepancy between the earlier study and their own, Thomsen *et al.* noted that their children were older, more severely disturbed, and less motivated.

Three studies have contrasted the psychiatric profiles of drug-responsive enuretics with those of non-responders. Meijer (1965) found that the responders had more neurotic traits and depressive elements (undefined) but better relationships with their families. A somewhat different conclusion was reached by Bindelglas *et al.* (1968), who compared the characteristics of their ten best responders with those of ten failures, at the end of a double-blind study of imipramine. They found no differences in IQ, reading level, organic disease, sexual identification, or self image in the children. They did, however, show some differences between the two groups in terms of parental attitudes and family dynamics, but without any consistent patterns that could explain differences in response to drugs. Ritvo *et al.* (1969), in a double-blind cross over study of imipramine in seven boys aged eight to ten years, made some interesting correlations between the EEG pattern, the type of enuresis, and the degree of psychiatric adjustment.

They found that enuresis occurring during EEG arousal was associated with increased neuroticism, while those who wet without EEG arousal had minimal evidence of maladjustment. The authors stress that their sample size was small and their conclusions tentative.

It has been recognized for many years (Anderson 1930) that institutionalized mentally subnormal children have a higher incidence of enuresis. Two double-blind studies have reported unfavorable results with imipramine in such children (Fisher *et al.* 1963, Valentine and Maxwell 1968). Drew (1967) also reported a negative response to imipramine in his study of adult subnormals, and Milner and Hills (1968) found that mentally subnormal adults were less likely to improve than schizophrenics. On the other hand, Smith and Gonzalez (1967) reported improvement in a group of 34 institutionalized boys, with an average IQ below 75, treated for 20 days with nortriptyline. Good responses in institutionalised children have also been reported in uncontrolled studies by Salgado and Kerdel-Vegas (1963) and Treffert (1964). Rett (1968) studied a heterogeneous group of organically brain-damaged children with an average IQ below 65, and reported benefit in a double-blind trial with imipramine, but also noted that more beneficial results were obtained in children with higher IQS.

From the available data, it seems that the effectiveness of imipramine may be somewhat inconsistently reduced by a number of psychiatric conditions which may co-exist with enuresis. It is impossible to tell whether a poor response in such cases simply reflects an inability or unwillingness to co-operate in taking medication and in following a regimen, or whether it has some more profound aetiological significance.

(c) *Age and Sex Differences.* It is well recognized that enuresis is a more common problem in boys at all ages than in girls. The sex and age composition of a research sample is, therefore, of considerable importance, since the presence of a larger number of girls, particularly in the older age groups, may suggest a more treatment-resistant or severely affected population. This possibility was shown by Philpott and Flasher (1970), who found that all the older girls (over nine years) were 'never dry', whilst only just over half the boys fell into this category. In general, however, they found no consistent differences in drug response related to age. A number of well-controlled studies comment on the lack of a relationship between age and drug response (Poussaint and Ditman 1965*b*, Poussaint *et al.* 1966, Bindelglas *et al.* 1968, Miller *et al.* 1968). On the other hand, Forsythe and Merrett (1969) found that children over the age of eight years responded statistically significantly better to both tricyclic drugs and to placebo. Exactly the reverse was found in Breger's (1961) study comparing meprobamate to placebo, for in both his treatment groups it was the younger children (ages not stated) who showed the best response. Liederman *et al.* (1969) also noted that their small group of older patients (19 to 22 years) did less well on desipramine than their younger subjects.

With regard to sex, a number of well-controlled studies have reported no differences (Miller *et al.* 1968, Forsythe and Merrett 1969, Philpott and Flasher 1970). However, it is interesting to note that all three studies reporting a sex difference show an increased response to drugs in females. Agarwala and Heycock (1968) reported a significant preference for imipramine over placebo by girls, but not boys (ages six

to twelve years), and Lake (1968) found that girls did better than boys with nortriptyline (ages five to twelve years). Finally, Milner and Hills (1968), in their adult psychiatric population, found that drugs were more often effective in females within most of their diagnostic categories.

These results in favor of enuretic females are particularly interesting because they contrast with the report by the Medical Research Council (1965) that when the same drugs are used to treat depression men respond more favorably than women.

(d) *Family History.* The presence of a family history of enuresis may clearly be an important aetiological factor and, therefore, a determinant of drug response. Again, the results are conflicting. Breger (1962) noted no relationship to outcome. In contrast, Rosenthal and Richmond (1969) found that ten out of fourteen adult recruits (71 per cent) who had a family history did well on imipramine, compared with 18 out of 42 (43 per cent) without a parental history. In their comparison of ten good-outcome with ten poor-outcome enuretics, Bindelglas *et al.* (1968) found that a good prognosis was linked to having a mother who had been enuretic, but that the reverse was true if the father had been a bedwetter. However, the numbers in each group were small.

(e) *Organic Features.* Many studies have scrupulously weeded-out children with organic conditions, so it is particularly interesting to note that their presence does not seem to impair the response to tricyclic antidepressants. Jaremko *et al.* (1968) studied the effects of imipramine in 83 children who had developmental lesions of the lumbo-sacral vertebral column, and found it just as effective in this group as in a control group of children with normal x-rays. Similarly, Epstein and Quevedo (1964) reported a case of a boy with congenital bladder-neck obstruction who responded well to imipramine (before surgery permanently relieved his condition).

Type and Severity of Enuresis

By no means all studies have differentiated between life-long and lapsed bedwetters, a variable which could have a profound influence on the results. In addition, the time of the bedwetting (early or late), its frequency (once or more nightly), and its severity (number of incidents in unit time) could all influence the outcome of therapy.

A number of well-controlled studies showing beneficial results have failed to comment on whether there was any difference in outcome between life-long and lapsed bed-wetters. Poussaint *et al.* (1966), whose sample contained 80 per cent life-long enuretics, Liederman *et al.* (1969), whose patients were equally divided, and Thomsen *et al.* (1967), who deliberately selected only life-long cases, all reported a significant benefit with imipramine, despite the differences in sample composition.

The relationship between the time of bedwetting and the outcome of drug treatment was studied by Bindelglas *et al.* (1968), who noted that only one out of ten successes wet early, compared to six out of ten failures. This finding may have been related to the fact that medication was given at bed-time rather than before, in which case it would tend to support Alderton's (1970) findings discussed earlier (see page 243). Cahill (1967) made a similar suggestion as to the importance of varying the time when medication is given, according to the time of bedwetting.

Some idea of the extent to which pre-treatment severity may influence results can be gauged by contrasting the inclusion criteria of Forsythe and Merrett (1969), who insisted on six or seven nights of bedwetting a week for at least a year, and the laxer criteria of Shaffer *et al.* (1968) who required only a history of twice-weekly wetting for an unspecified period. In fact, three double-blind studies have shown correlations between pre-treatment severity (number of incidents in unit time) and outcome. Liederman *et al.* (1969) noted better results with desipramine in high-frequency than in low-frequency bedwetters, and Miller *et al.* (1968) noted a similar difference. Lake (1968) showed that enuretics of medium severity (with an expectation between 38 per cent and 78 per cent wet nights) tended to do better on nortriptyline than either of the extreme groups (but the high-frequency group showed a greater reduction in the number of wet nights than the low group).

The influence that the number of times a patient wets during the night may have on outcome has been largely ignored, no doubt due to the difficulty of knowing for sure how many incidents have occurred. However, Bindelglas *et al.* (1968) did show that their group of failures contained more subjects (five out of ten) with a history of wetting several times a night than did their successes (none out of ten). In commenting on their results in adult enuretics, Milner and Hills (1968) speculated that larger drug effects might have been shown if they could have measured the frequency of bedwetting during each night.

The conclusion must be that there is some evidence that patients with severe enuresis may benefit most from treatment with tricyclic drugs, but that further attention to this factor is needed, particularly with regard to the difference between life-long and lapsed enuretics. The definition of what constitutes 'enuresis' varies markedly between studies, and must be taken into account when comparing outcomes.

Previous Drug Treatment

Since enuresis is a chronic condition, there is every likelihood that patients entering a drug study will previously have received some form of treatment elsewhere. There is a noticeable failure in the literature to record this important variable. Lines (1968) notes that patients were included in his study only if bedwetting had persisted after a regimen of clock training and lifting. Agarwala and Heycock (1968) included patients whether or not they had been treated with imipramine. It is noteworthy that both these double-blind studies still showed a significant drug-placebo difference, but it is not possible to be sure whether in some trials negative results have resulted from the inclusion of disproportionate numbers of drug-refractory individuals.

Mechanism of Action

Psychopharmacology is concerned not only with the detection of drug action, but also with its explanation. Broadly speaking, there have been three theories advanced to explain drug actions in enuresis, all of them reinforced by the recent discovery that tricyclic drugs are effective. These explanations have related to anti-depressant action, alterations in arousal and sleep mechanisms, and anticholinergic effects.

Antidepressant Activity

There is controversy over whether or not depression exists as an identifiable entity in children. Fish (1968*b*) comments that severe depressions are virtually non-existent under the age of eleven, when enuresis is most common. On the other hand, Frommer (1968) has reported extensively on the use of antidepressants and on the so-called 'depressive' syndromes in quite young children. It is probably true that the presence of depressive affect in childhood is rare, in which case we must question whether a symptom such as enuresis can legitimately be regarded as a 'depressive' equivalent. The theme of Sadoff's (1966) summary of the psychoanalytic literature on the topic is that bedwetting represents symbolic weeping at a stage when affective expression is underdeveloped. Several authors have discussed the possible antidepressant effect of imipramine with regard to enuresis (Hagglund and Parkkulaninen 1965, Poussaint and Ditman 1965*b*).

In connection with this controversy, it should be noted that just because enuresis responds to drugs known as 'antidepressants' in adults it does not follow that enuresis is a depressive equivalent. Unlike depression in adults, enuresis is much more common in males than females, and the drug response appears better in females than in males. Of more importance is the fact that the benefit, when it occurs, often does so very rapidly, in marked contrast to the antidepressant effect in adults, which often takes ten days or more to appear. This suggests that the mechanism of action is probably different and is not connected with the blockage of uptake of norepinephrine that is held responsible for the slow onset of an antidepressant effect.

Level of Sleep and Arousal

The theory that enuretics are deep sleepers and that drugs such as amphetamine act by lowering the threshold for arousal is difficult to sustain, in view of the relatively poor results obtained with stimulants, and the failure to show convincing differences between sedatives and stimulants, even when both differ significantly from placebo in the same study (Breger 1962, General Practitioner Research Unit 1970). The more recent discovery of the efficacy of the tricyclic antidepressants, many of which have marked sedative properties, adds to the difficulty of accepting this theory, particularly since compounds with markedly differing sedative properties, such as protriptyline and amitriptyline, seem to be effective. Nevertheless, Poussaint *et al.* (1966) did note that amitriptyline made some children irritable, though any speculation concerning a paradoxical arousal effect is weakened by noting that it occurred in seven children on the drug, but also in five on placebo. Philpott and Flasher (1970) commented on a boy who started waking to the alarm when 'bell-and-pad' treatment was supplemented with imipramine, and Ingle and Panase (1968) found that heavy sleepers became more alert when receiving imipramine.

A striking omission from most studies is any attempt to record the frequency of arising to pass urine, which should increase in children who respond to drug treatment, if the 'depth of sleep' hypothesis is to be accepted. Poussaint *et al.* (1966) noted that ten children on drug and six on placebo 'occasionally arose at night to urinate', but Mariuz and Walters (1963), who reported a highly significant drug effect, noted no increased frequency in arising to urinate.

Despite these unconvincing observations, interest in the possibility that drugs control enuresis by affecting the level of sleep has been perpetuated by the discovery of rapid eye movement (REM) sleep and the setting up of sleep research laboratories. At first the erroneous conclusion was drawn that bedwetting occurred during REM sleep, and that the beneficial effects of tricyclic antidepressants could be attributed to the fact that they suppressed the REM phase (Pierce *et al.* 1961, Khazan and Sulman 1968). This oversimplified view has been conclusively disproven by more recent sophisticated research (Broughton 1968, Kales and Kales 1970). To begin with, drugs which are highly effective at suppressing REM sleep, such as amphetamines and monoamine oxidase inhibitors, are of little value in enuresis. There is even the possibility that reserpine, which increases REM sleep, may benefit the condition (Lambros 1955). More damaging to the theory has been the unequivocal finding that enuresis does not occur during the REM phase. Wetting is commonest in the first third of the night when REM sleep is rarest and also takes place during arousal from deep Phase IV, but is not consistantly linked to any individual stages. Enuretics do not appear to differ significantly from normal controls in any sleep parameter linked to bedwetting (Broughton 1968). Finally, a study of sleep stage activity in enuretics treated with imipramine showed no consistant relationship between a beneficial effect of the drug and alteration in sleep stages (Kales and Kales 1970).

Anticholinergic Activity and Bladder Function

Interest in the theory that drugs which affect bladder function do so through their anticholinergic properties was naturally revived when imipramine was found to share anti-enuretic and anticholinergic properties. The evidence to support this theory is tenuous but more compelling than that for the sleep theories. It is suggested that anticholinergic drugs, by relaxing the detrusor muscle and increasing the tone of the vesicular outlet, permit an increase in bladder volume before the 'stretch reflex' causes bladder contraction and voiding.

Support for this hypothesis is provided by Hagglund and Parkkulaninen (1965), who compared the effects of imipramine on bedwetting and cystometrograms in 18 treated and 16 untreated enuretic children. They found a 34 per cent increase in bladder capacity in their treatment group, compared with a 9 per cent increase in the control group. They also showed that the desire to void occurred at a larger filling stage in 39 per cent of the treated subjects and in 11 per cent of the controls. Further evidence of an effect on the bladder is provided by Epstein and Quevedo's report (1964) on the effects of imipramine in a case of congenital bladder-neck obstruction.

In combined EEG and bladder tone recordings, it was shown that in comparison with normals enuretics had a greater number of spontaneous bladder contractions, which reached higher pressures. These contractions could be provoked by external stimuli (noise, *etc.*), but were unrelated to EEG changes. It seems possible, therefore, that tricyclic drugs may work at least as much, if not more, by a direct action on the bladder as on retarding the arousal from Stage IV that accompanies bedwetting (Broughton 1968).

Further indirect evidence that the anticholinergic activity may be the crucial one is provided by the time sequence of the drug effect. It has been noted above that

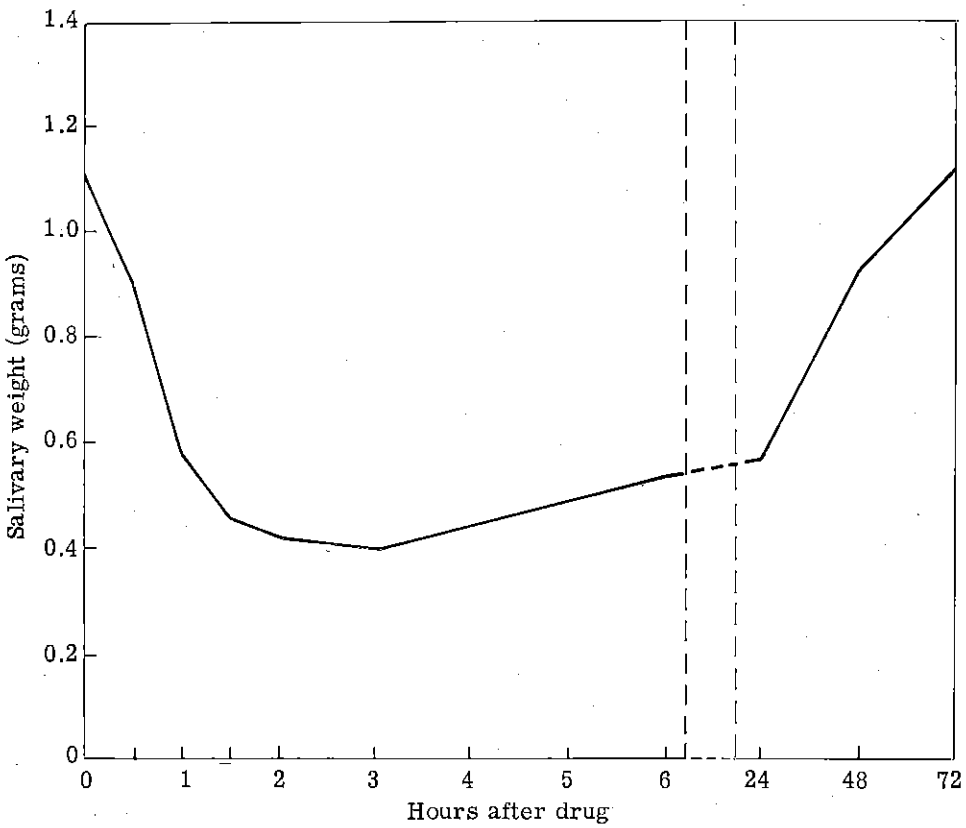

Fig. 1. Sequential effects of a single dose of imipramine (100 mg).

the results often appear after the first dose and usually within the first week, but that they may persist somewhat after drug withdrawal. Figure 1 shows the duration of anticholinergic activity, as measured by reduction in salivation, after a single 100 mg dose of imipramine (Blackwell *et al.* 1972). These experiments in adults have shown that maximum reduction in salivary flow occurs after three hours of a single large dose but persists for up to 72 hours. Furthermore, it is possible to show a clear-cut dose/response relationship. These observations offer some support to Alderton's (1970) experiments concerning the timing of medication in relation to acute anti-enuretic action, and add weight to the suggestion that experimentation with dosage and timing in children might lead to enhanced results.

No comparisons have been made between the effects of anticholinergic drugs and those of tricyclic antidepressants. Although the anticholinergic agents have been historically popular (Muellner 1961), the five double-blind studies have produced inconclusive results. Wallace and Forsythe (1969) showed no difference between propantheline (45 mg) and placebo in children who were particularly severe enuretics. By contrast, Whitehead (1967) obtained significant results in geriatric patients using somewhat larger doses (75 mg). This is an area where further research is necessary.

Summary and Conclusions

Enuresis has been the most extensively studied area in pediatric psychopharmacology. This is because it is a common, distressing condition in which it is easy to measure the effects of medication.

The tricyclic antidepressants are the only drugs shown to be superior to placebo in the treatment of enuresis. They appear to be effective irrespective of chemical subtype, but further studies are necessary to confirm this. The results are statistically significant in a large number of controlled double-blind studies. Differences from placebo might have been larger still, if studies had included an adequate pre-treatment base-line and crossover designs had been modified to account for carry-over effect.

The clinical value of the results is less marked. Benefit, when it occurs, usually commences within the first week of treatment, but total remission is seen in under half the patients. Relapse tends to occur immediately following withdrawal after short periods of treatment, and long-term follow-up studies suggest that total remission occurs in only a minority of patients. There is a suggestion of better responses in the more severely affected enuretics and in female patients. Less favorable responses may occur in adults, the poorly motivated, and mentally handicapped patients. Further research is necessary to define the characteristics of drug responders. Better results might be obtained in future by use of more flexible regimens and larger dosages.

In general, the results obtained with drug treatment are less promising than either the short- or long-term effects of the 'bell-and-pad'. However, the comparative convenience of drug treatment makes it a worthwhile first method of treatment. The use of tricyclic antidepressants as an adjunct to the bell-and-pad requires further study.

The mechanism of action of tricyclic antidepressants in enuresis is still incompletely understood. At present, the anticholinergic effects appear to be a more likely explanation than either an antidepressant effect or alterations to sleep and arousal mechanisms. Further research is needed, including careful comparisons between tricyclic antidepressants and other known anticholinergics, and between tricyclic antidepressants with different anticholinergic properties.

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