CHAPTER 31

Indications for Research: III

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The striking feature of this collection of papers is the range of different theories about enuresis put forward, and the lack of evidence to decide between them. So far we just do not know what is the aetiology of this most common and troublesome of childish disorders. In the heat of dispute there is a danger of coming to premature conclusions. We must instead have a long cool consideration of the evidence, which we need to help us to arbitrate between the conflicting claims.

There are a plethora of studies needing to be done, and I will make no attempt to be comprehensive in my discussion of research needs. What I have to say reflects my own interests and is no more than a collection of my random thoughts, but it may serve to provoke others into taking up some of the threads still dangling.

The first general point to make is that there is no shortage of hypotheses which deserve testing. There should be an end to large scale 'fishing expeditions', using a host of heterogeneous variables in the hope that something will emerge. There is no point in collecting a lot of data without hypotheses, and hoping that the computer will produce something useful. At this stage what are needed are well planned investigations to critically examine and evaluate the precise hypotheses which are already available.

The second general point concerns classification. It is most unlikely that enuresis will turn out to be a unitary condition with a single cause. Accordingly, all investigations should differentiate certain sub-groups which appear to have some validity. In all the studies which I shall mention, I suggest that, as a bare minimum, the following groups should be compared: primary and acquired enuresis; nocturnal and diurnal enuresis; enuresis with and without accompanying psychiatric disorder; boys and girls; and probably also nocturnal enuresis with and without accompanying diurnal frequency of micturition.

Genetic Factors

Bakwin's twin studies (see this volume, Chapter 9) have clearly shown that there is an important genetic component in nocturnal enuresis. But serious questions remain. For example, his findings suggest a sex difference in the extent to which inherited variables contribute to the genesis of nocturnal enuresis. In boys, the monozygotic: dizygotic concordance ratio was 2·3, but in girls it was only 1·5. This suggests that environmental factors may be more influential in the causation of enuresis in girls. Our own data suggest that in girls enuresis is more often associated with psychiatric disorder. Is this type of nocturnal enuresis genetically different? The sex difference found by Bakwin needs confirmation in further studies, but his observation emphasises the need to compare sub-groups when carrying out genetic studies.

That concern leads us to ask what it is that is inherited. Is it variation in the rate of maturation of certain parts of the brain, in bladder capacity, in emotional disorder? Is it a 'disease' of nocturnal enuresis, or is it food allergy—as Gerrard and his colleagues (Esperanca and Gerrard 1969*b*, Zaleski *et al.* 1973) suggest may sometimes be the case? Twin studies are needed in order to look at these separately, and then by partialling out the separate effects of each variable it might be possible to determine which, if any, of these various factors account for monozygotic-dizygotic differences in diurnal and in nocturnal enuresis.

There is then the question of how *large* a part genetic factors play in nocturnal enuresis. The basic point in this connection is that there can *never* be a single figure for this. The reason is that genetic effects are not independent of the environment. There is an interaction between the two, so that the importance of genetic factors depends on the amount of variation in the environment. If the environment is identical for everyone, *all* differences between people must be genetically based. Conversely, if certain individuals are genetically identical (as are pairs of monozygotic twins*), then all differences between them must be due to environmental influences.

These observations have implications for the conclusions which may be drawn from twin studies. Because the environment is so similar for twins reared together, twin studies tend to exaggerate the influence of inherited factors with respect to the variation between people in the population at large. Twins reared apart provide one method of coping with this difficulty, but such cases are quite rare. Studies of adoptees provide another (and possibly better) alternative. These have been used with great effect in the Scandinavian studies of schizophrenia (see the various reports in Rosenthal and Kety 1968), and the method could usefully be applied to enuresis. Simply, all that is required is to take children adopted in infancy who later show enuresis. The rate of enuresis in the biological parents is then compared with that in the adoptive parents. Genetic influences will be shown by a high rate of enuresis in the true parents whereas environmental influences will be shown by a high rate in the adoptive parents. This technique provides a neat way of looking at genetic factors in a situation which allows greater environmental variation.

Electroencephalography

The investigations of Salmon *et al.* (this volume Chapter 11) suggest that the electroencephalographic (EEG) patterns of nocturnally enuretic children may differ from those of other children. But the studies have not been adequately controlled, and the EEGs have not been rated 'blindly'. So the first requirement is a controlled study of an epidemiologically based sample of nocturnally enuretic children, in which the EEGs are rated *without* knowledge of which children were enuretic, or in which there is a computer analysis of the EEG records. In this connection it is, of course, important to determine whether there are 'immaturities' in the EEG record (*i.e.* whether the EEG is appropriate for a younger child), or whether there are also 'abnormalities'

*Modern research shows that monozygotic twins are not completely identical genetically, but they approximate to that situation.

(*i.e.* features which are abnormal at any age). Again it would be necessary to differentiate children with primary and secondary nocturnal enuresis, and also the other subgroups already mentioned.

If it can be established that enuresis (of any type) is indeed associated with particular EEG features, the next question is 'what mechanisms are involved?' Two investigations might shed light on this issue. The first would be a longitudinal study of enuretics in which EEG changes would be related to changes in wetting. In short, can we predict on the basis of the early EEG what is going to happen later in the development of bladder control? When the child becomes dry, is this preceded, accompanied or followed by EEG changes, or are the two quite unrelated?

The second type of study requires the recording of EEGs in a group of children with a high risk of enuresis, but still below the age at which bladder control normally develops. This would enable one to determine whether the EEG findings could predict which children would gain bladder control at night at the usual time, and which would continue to be nocturnally enuretic into middle or later childhood. Either the younger sibs of enuretic children, or the offspring of adults who had been enuretic as children, would constitute suitable samples for this purpose.

Sleep Patterns

The need for further studies into the depth of sleep and enuresis has already been emphasised by Graham (this volume Chapter 10). Recent advances in techniques of measuring different aspects of sleep should make it possible to check claims that children have characteristic patterns of wetting related to the phases of sleep. In view of the uncertainties about how drugs and the bell-and-pad lead to bladder control, it would be worthwhile studying the efficacy of these in terms of effects on sleep patterns.

Mac Keith (this volume Chapter 32) also indicates the need for a longitudinal study to confirm or refute Duché's suggestion (this volume Chapter 2) that whether or not infants wake to wet may predict the later failure or success in acquiring bladder control by the age of five.

Bladder Capacity

Gerrard and others have shown a quite strong and reasonably consistent association between bladder capacity and enuresis (Esperanca and Gerrard 1969*a*). This is an important observation, but there is great uncertainty as to what it means. Following Muellner (1960), Gerrard and his colleagues (Esperanca and Gerrard 1969*a*, Zaleski *et al.* this volume Chapter 12) have put forward the view that in many cases a small bladder capacity is the cause of nocturnal enuresis. This is certainly possible, but there are two findings which indicate that it is probably an insufficient explanation. First, there is considerable overlap between night-time enuretics and non-enuretics in bladder capacity. For example, according to Gerrard's own figures, nocturnal enuretics of eight years have a larger bladder capacity than non-enuretics of four years. Why is it that the four-year-olds do not wet at night? Secondly, once nocturnal continence is established, having a lot to drink in the evening, so that the production

of urine during the night exceeds the maximum bladder capacity, leads to waking, and not usually to wetting.

What hypotheses can be suggested to account for the findings? At least three come immediately to mind. First, the apparently small bladder capacity of nocturnal enuretics could be just a methodological artefact. The first voiding of urine in the morning is usually taken as a measure of maximum bladder capacity, because in normal subjects this corresponds well with the results of a water load test. But does it in enuretics? If a child wets during the night, the first voiding in the morning is bound to be of smaller volume than if he did not wet, simply because there has been a shorter filling time. In other words, the finding may be purely tautological. It should be added that the same mechanism will affect mean bladder capacity, because the average voiding volume in enuretics will be reduced by the smaller early morning specimen. To exclude this artefact, mean bladder capacity should be based on day-time specimens *excluding* the first voiding, and maximum bladder capacity should only be assessed on a water load test.

Second, the small bladder capacity of enuretics (if confirmed) could merely reflect a compensatory response, the bladder remaining small because it is not stretched by nocturnal dilatation. To examine this possibility, different treatment methods might be compared. As far as is known, the bell-and-pad does not directly influence bladder capacity. Therefore, it is important to know what happens to bladder capacity in children who become continent with this method of treatment. Does the bladder capacity increase prior to continence developing, as it develops, after it is established, or is there no temporal connection between the acquisition of bladder control and increasing bladder capacity? Conversely, what happens to *nocturnal* enuresis if day-time training is used to increase the time between voidings and so increase mean bladder capacity? Some studies have suggested that this leads to a lessening of wetting at night (Hägglund 1965, Starfield and Mellits 1968), but systematic controlled investigations are needed to confirm or refute this suggestion.

Third, it may be that, as Gerrard suggests, the small bladder capacity can be a cause of nocturnal enuresis. As with the EEG, a predictive study (of the sibs or offspring of enuretics) might settle this question. If bladder capacity is measured in young children before control is normally acquired, does bladder size predict which children will remain enuretic? Do the children who continue enuretic have smaller bladders at an age when all children are wet? The answers should be 'yes' if small bladder size does actually lead to enuresis.

Diurnal and Nocturnal Enuresis

This brings us to the vexed question of whether diurnal and nocturnal enuresis are both part of the same disorder. This problem has been raised several times throughout this volume, and various views have been expressed as to whether similar or different mechanisms are involved. At present, there is not adequate evidence to decide on this issue, but we could find out. If the same mechanism were involved in both varieties of enuresis, there should be a high correlation between the time of acquisition of bladder control by day and bladder control by night. Furthermore, this

high correlation should apply both in the general population (which it almost certainly does), and in a population of enuretic children (where it may not).

Alternatively, the question could be approached by looking to see what happens to nocturnal enuresis when treatment methods are used which specifically focus on day-time wetting. For example, operant techniques applied only to the control of diurnal enuresis would be very suitable for this purpose. If diurnal wetting is brought under control by this means, what happens to the nocturnal wetting?

Diet

Gerrard and his colleagues have suggested that some cases of enuresis are due to a food allergy (Esperanca and Gerrard, 1969*b*, Zaleski *et al.* 1973). There are two bits of evidence which point to this conclusion. First, there are the single cases mentioned by Esperanca and Gerrard (1969*b*) in which, apparently, nocturnal enuresis can be switched on and off according to dietary changes. If that result can be replicated, it will be convincing evidence for the importance of diet in that individual child. However, the finding will need confirmation by means of a controlled study comparing the effects of withdrawing or adding foods associated with enuresis in that individual and the effects of withdrawing or adding *other* foods. In other words, how repeatable are the findings in an individual child? It should be noted that the work of Gerrard and his colleagues suggests that this association only applies to a small minority of cases. His therapeutic trial showed no over-all effect when dietary changes preceded the administration of imipramine (Esperanca and Gerrard 1969*b*).

The second piece of evidence is the association found between enuresis and the allergic diathesis in a hospital study (Zaleski *et al.* 1973). This would be more convincing if it could be replicated using a general population sample. One of the drawbacks of this type of hospital study is that when associations are examined between disorders in which only a proportion of those affected get referred to hospital (as in the case with both enuresis and allergic conditions), associations of an artefactual kind are very likely to occur for statistical reasons alone (Berkson 1946). This statistical artefact could explain the finding of Zaleski *et al.* Whether in fact it does can only be determined by similar studies of the general population.

Drugs

In this volume we have been told of various therapeutic studies that need to be carried out. Here, I want to confine my attention to studies using drugs as a tool to investigate mechanisms. It has been well established that imipramine is an effective agent in controlling enuresis while the drug is given (although the relapse rate is high when the drug is stopped). The question arises as to *how* it works. It is a drug with many actions (anticholinergic, antidepressive, sedative, alpha-blocking, local anaesthetic, and also an effect on nocturnal arousal), and it is uncertain which of these actions controls the enuresis. It is often argued that an anticholinergic effect is the most important, but against this view is the fact that one large controlled trial failed to show any benefit from propantheline—an anticholinergic agent (Wallace and Forsythe 1969). Blackwell and Currah suggest that imipramine may work best in

girls, and Kolvin *et al.* have found it to work best with secondary enuresis (see Chapters 25 and 26 in this volume). Both these findings suggest that an antidepressant effect may be operative. Salmon's evidence on the efficacy of chlordiazepoxide ('Librium') (this volume Chapter 22) also suggests that, in some children, something other than an anticholinergic effect may control enuresis.

Three approaches may be used to investigate which pharmacological effect is the mediating mechanism. First, the effects of imipramine can be studied in relation to the children's psychiatric state. If the drug proved to be more effective in a psychiatrically abnormal group of enuretics, an antidepressant or sedative effect would seem most likely.

Second, the benefits of imipramine with respect to nocturnal and diurnal enuresis could be correlated with measured individual pharmacological effects. For example, the anticholinergic effect could be assessed by the use of salivary pads. It could then be determined whether the control of enuresis did or did not relate to the degree of anticholinergic action. By following a similar strategy with other pharmacological actions, it should be possible to determine which action is most closely associated with the control of enuresis.

Third, different drugs may be used for the same purpose. For example, an anticholinergic drug without an antidepressant effect could be compared with an antidepressant without an anticholinergic effect. The same procedure would be used to compare and control imipramine's other pharmacological effects. By finding other drugs, each of which has one of imipramine's actions but not the others, the action which controls enuresis could be isolated.

Bell-and-Pad (Buzzer Alarm)

The same questions arise with the bell-and-pad method of treating nocturnal enuresis. Clearly this works with many children, but *how* does it work? It is supposed to have a conditioning effect (although there is vigorous dispute as to what type of conditioning is thought to be involved), but it might work simply by altering sleep patterns. Turner *et al.* (1970) found that waking the child was as effective in controlling enuresis over a four week period as the bell-and-pad mechanism. Baker (1969) found the same, but also showed that the bell-and-pad was more effective over a ten-week period. This finding needs replication. Perhaps the best way of controlling for the placebo effect of 'gadgetry', as well as for the effect of waking-up, would be to wire up the bell-and-pad apparatus to wake children randomly through the night (or during the phase of sleep when the child usually wets), and to compare the results with those obtained with the usual apparatus, in which the alarm going off is contingent with the child's wetting.

Association with Psychiatric Disorder

There is a definite association between enuresis and psychiatric disorder (see the chapters by Shaffer and by Rutter *et al.* in this volume, pages 118 and 137), but the association only occurs in a minority of cases. A similar association exists between

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