Drug Treatment of Disease

SEDATIVES FOR CHILDREN

BY

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Vast sums of money are spent on the new tranquillizing drugs, but the evidence that the great majority of them achieve anything more than the simple, inexpensive, time-honoured drugs chloral, phenobarbitone, and aspirin is either extremely tenuous or non-existent. In any case it must always be remembered that these drugs do not cure the underlying disease, for they can only relieve symptoms. In all cases mentioned below the first essential is to treat the causative disease or emotional problem. It is interesting to note that at the Children's Hospital, Sheffield, with approximately 6,000 admissions and 8,500 new out-patients a year, the total spent in 1959 on the new tranquillizing drugs was £8, most of which was spent on meprobamate for the treatment of epilepsy (without much success), rather than for its purely sedative action. It may be argued, of course, that we should have used these drugs a great deal more.

There is very little occasion for using sedative drugs for long periods. In general they should be used in adequate dosage for short periods, and not for chronic cases. It should also be remembered that the child's symptoms can sometimes be relieved more successfully by giving a sedative drug to the mother rather than to the child.

Below I have listed the commoner conditions in children for which sedative drugs can often be profitably prescribed.

Cerebral Irritability in the Newborn Baby

Chloral in a dose of $\frac{1}{2}$ to 1 gr. (30–60 mg.) may be given by mouth at intervals of two to four hours. An alternative is a subcutaneous injection of sodium phenobarbitone $\frac{1}{2}$ gr. (8 mg.).

Evening Colic in the First Three Months

Having satisfied oneself that the diagnosis is correct, that the baby is not howling because he is hungry and that he is not crying merely because he wants to be picked up and played with (i.e., he continues to cry even when picked up), one should give dicyclomine hydrochloride syrup ("merbentyl"), in a dose of $\frac{1}{2}$ to 1 teaspoonful (5–10 mg.) 20 minutes before the evening feed which has been found to precede the pain.

It should not be forgotten that infants grow out of the colic by the age of 2 to 3 months, so the medicine should by then have been discontinued. The cost is about 1d. per dose. Suffering parents would think that that was cheap even if they had to pay for it out of their own pockets.

Sleeplessness in Infants and Toddlers

The first essential is to deal with the management of the bad habits which have been allowed to develop. These consist chiefly of picking the baby up from his cot as soon as he whimpers, taking him downstairs as soon as he cries, sitting and playing with the child

because he will not otherwise go to sleep, repeatedly going in to see the child to see if he is still breathing (so that he gets to expect a visit from his mother and stays awake till she comes), taking the child into the parents' bed when he cries, and allowing him to sleep in the parents' room after night feeds have been dropped (usually between 2 and 3 months of age). When one of these bad habits has been allowed to continue for long, it is very difficult to break it, and the first few days of proper management can be helped by the use of a sedative drug. I know of nothing better than chloral for the purpose. I tell mothers to begin with 5 gr. (350 mg.), and if that does not work to give $7\frac{1}{2}$ gr. (0.5 g.) on the next evening, and if necessary 10 gr. (0.7 g.) on the next evening. The medicine is given about 20 minutes before the child goes to bed. Chloral is a safe drug. The hypnotic action is thought to be due to reduction of trichlorethyl alcohol, which is a cerebral depressant.

The taste is unpleasant, but it does not usually present much difficulty in a baby. The disadvantage of the chloral elixir for infants in the *B.N.F.* is the fact that 60 minims contain only 1 gr. of chloral.

It is quite useless to combine the chloral with potassium bromide, for there is no synergistic action between the two, and bromides have no effect until a certain serum-bromide level is reached after very large doses, or several days' administration.

Surprisingly enough the *B.N.F.* still contains a prescription for chloral with potassium bromide, after mentioning the fact that the sedative action of the mixture is entirely due to the chloral.

The chloral should be given for a few days only. There is no excuse at all for giving hypnotic drugs to children night after night.

Phenobarbitone for the purpose is useless. There is no evidence that the more recently introduced drug thalidomide ("distaval") possesses any advantage over chloral apart from its better taste, and it costs about 40 times more. It may be useful for infants who refuse to take chloral.

Teething

Much of the crying which is commonly ascribed to teething is due not to teething but to the formation of bad habits in connexion with sleep, as mentioned above.

If the baby really has discomfort from teething, aspirin is the drug of choice, in a dose of $2\frac{1}{2}$ to 5 gr. (0.15 to 0.3 g.) at night not repeated until the next night.

Convulsions

Space will not permit a discussion of the treatment of epilepsy.* When a child is seen in a convulsion, the best immediate treatment, if it does not terminate spontaneously, is an intramuscular injection of

*This was the subject of an article in this series by Dr. Denis Williams, *Brit. med. J.*, 1958, 2, 1155.

paraldehyde into the middle of the outer aspect of the thigh, in the following dosage :

Under 3 months		$\frac{1}{2}$ ml.
3-6 months		1 ml.
6-12 months		1.5 ml.
1-2 years		2 ml.
2-5 years		3-4 ml.

An alternative treatment is sodium phenobarbitone by intramuscular injection in the following dosage :

3 months		$\frac{1}{2}$ gr. (16 mg.)
3 to 12 months		$\frac{1}{2}$ gr. (32 mg.)
2 years		$\frac{1}{2}$ -1 gr. (32-65 mg.)

It is vital that the cause must always be sought, and in all cases hospital investigation should be carried out. In the case of suspected febrile convulsions a lumbar puncture should always be performed to exclude meningitis.

A convulsion due to acute nephritis necessitates immediate hospital treatment. The child is likely to be given 1-2 oz. (28-57 ml.) of 50% magnesium sulphate per rectum, or (preferably) a ganglion-blocking agent.

A convulsion due to tetany likewise calls for hospital treatment, because the cause must be determined. The child is likely to be given 3 to 10 ml. of 10% calcium gluconate intravenously.

Nervousness, Nervous Habit, Tics, School Phobia

I am constantly impressed by the number of children who have been given sedatives for these conditions, and especially for tics. In my opinion there is only rarely a place for barbiturates or other sedatives here. Tics, in particular, are totally unaffected by them. I have tried tranquillizing drugs as an adjuvant in the treatment of school phobia without any success.

Most of the drugs used have a potentially harmful effect. It is not sufficiently realized that phenobarbitone may have the opposite of the effect desired, aggravating chronic anxiety and worsening irritability and bad behaviour. There is probably no place for bromides here; they are cumulative in action, and may cause annoying rashes, depression, and other untoward symptoms. Tranquillizing drugs are of very doubtful and certainly unproved value in these conditions, and may have serious toxic actions.

The treatment of all these conditions depends not on medicine but on a thorough review of the child's environment and management. In the first place, much of children's nervousness of which parents complain is entirely normal for the age, and calls for no treatment at all. In other cases, in which nervousness is excessive, the child takes after his parents in that respect, and medicine will not alter it. As for tics, the essential thing is for the parents to ignore them. If they are getting on top of the parents, the parents may themselves be given a sedative, but not the child. School phobia is best dealt with by thoroughly investigating the home and school environment, remembering that in the great majority of cases the trouble lies in the parental attitudes, rather than in the school.

Hyperkinesia

In the great majority of cases mothers' complaints of overactivity of their child are allayed by reassurance that he is entirely normal, and that normal small children (especially around the 6-year-old period) do not sit still. In my opinion it should be most exceptional to give any medical treatment for a hyperkinetic child of normal

intelligence. If the hyperkinesia is seriously interfering with school work, which must be very exceptional, I would try, for a short period only, one of these drugs: dexamphetamine, meprobamate, or chlorpromazine. There have been many reports about the effectiveness of dexamphetamine for the purpose, though one would have expected it to have the opposite effect. I have tried it on a few children myself, without success.

The aimless overactivity of mentally defective children is very distressing to parents. Many have found that dexamphetamine in a dose of 10 to 20 mg. per day is useful for the purpose, but I have not been impressed by it in cases which I have treated myself. Tranquillizing drugs may well be tried, and in severe cases even prolonged administration may be justified. I have tried meprobamate in doses of 200 to 800 mg. four times a day at the age of 5 to 12 years, but found it of value in one or two only. The toxic actions include insomnia, vomiting, urticaria, anaphylactoid reactions, bronchospasm, oedema, and arthralgia, with tremors and anxiety on withdrawal. In solution it is very unpleasant to take. Chlorpromazine in a dose of 1 mg. per kg. per day (usually 30-150 mg. per day at the age of 5 to 12 years) may be worth trying. Untoward symptoms include tremors, hepatitis, rash, oculogyric crises and other Parkinsonian symptoms, agranulocytosis, nasal congestion, and unexplained fever.

Acute Psychotic Anxiety

If phenobarbitone fails, I would try meprobamate or chlorpromazine.

Chorea

In conjunction with such specific treatment as may be indicated (such as steroids with salicylates if there is an active rheumatic process with carditis) one would give phenobarbitone by mouth in a dose of $\frac{1}{2}$ gr. (32 mg. twice a day) at the age of 5 years.

Premedication

There is a difference of opinion on whether premedication before anaesthesia is desirable for children or not. Some feel that proper explanation of what is going to happen, with kind and wise management by all concerned with the child, is of greater value than any medicine. Others advocate that all children, or at least those liable to show anxiety about operative procedures, perhaps because of a previous unfortunate experience, should be given a sedative prior to anaesthesia.

For a baby prior to operation for pyloric stenosis under local anaesthesia, chloral by mouth in a dose of 1 gr. per lb. (140 mg. per kg.) (usually 6 to 10 gr. or 400 to 650 mg.) is satisfactory. For older children quinalbarbitone ("seconal") may be given in the following dosage :

1-2 years		$\frac{1}{4}$ to $\frac{1}{2}$ gr. (32 to 97 mg.)
2-6 years		$\frac{1}{4}$ to $\frac{3}{4}$ gr. (97 to 190 mg.)
6-12 years		$\frac{3}{4}$ to 7 gr. (190 to 450 mg.)

The maximum safe dosage is 0.1 gr. (6.5 mg.) per lb. (13 mg. per kg.). A dose of $\frac{1}{4}$ gr. costs approximately a farthing.

The old combination of morphine and atropine remains a satisfactory mixture for premedication. It seems that methylpentynol is not of value for premedication, and it is unpleasant to take.

Sedation Before Minor Surgical and Other Procedures

For minor procedures, such as the careful examination of an optic disk, or an encephalogram, rectal thiopentone is recommended. An enema is given if there is constipation. No food is given for at least three hours before the thiopentone. A hypodermic injection of atropine 1/150 or 1/100 gr. (0.43 or 0.65 mg.) is given half an hour before the thiopentone. The thiopentone is dissolved in 20 to 40 ml. of warm tap-water and injected slowly into the rectum by a rubber catheter. The buttocks are then held together to prevent the drug being returned. The dosage is as follows:

Dosage Schedule of Thiopentone for Children Weighing up to 52½ lb. (23.8 kg.)

Weight of Child lb.	kg.	Dose of Thiopentone
7.5-12.5	(3.4- 5.7)	0.2 g.
12.6-17.5	(5.7- 7.9)	0.3 g.
17.6-22.5	(8.0-10.2)	0.4 g.
22.6-27.5	(10.3-12.5)	0.5 g.
27.6-32.5	(12.5-14.7)	0.6 g.
32.6-37.5	(14.8-17.0)	0.7 g.
37.6-42.5	(17.1-19.3)	0.8 g.
42.6-47.5	(19.3-21.6)	0.9 g.
47.6-52.5	(21.6-23.8)	1.0 g.

Post-operative Treatment

For the relief of pain, tinct. opii B.P. in a dose of 1 minim (0.06 ml.) per year of age (sometimes with 2 additional minims for older children) is very effective.

Pethidine in a dose of 50 to 75 mg. by mouth is effective, but perhaps not quite so effective as tinct. opii B.P. It is slightly more expensive if given by mouth, but about 10 times more expensive than nepenthe if given by injection.

Cough

In my opinion there is very little need to give sedative cough medicines to children. Most coughs in children are productive, so that cough suppressants, such as codeine or pholcodine, are definitely contraindicated. A cough on going to bed is commonly due to a postnasal discharge, and neither suppressants nor expectorants are helpful. There is probably nothing better than the simple linctus for infants B.P.C., or opiate linctus of squill for infants—each in a dose of 60 minims (3.5 ml.). For a dry, irritating, unproductive cough, the codeine mixture for infants B.P.C. is adequate.

The first essential in the treatment of cough in children is to treat the cause. This may involve giving the appropriate antibiotic or bronchodilator drug, the treatment of an antrum infection, or the removal of adenoids.

Migraine

For the treatment of an attack of migraine, the most useful drugs are aspirin, tab. codein. co., "cafergot," and "migril." The difficulty with all these drugs is the fact that they may not be retained on account of vomiting. Aspirin and tab. codein. co. are each effective in most cases. Cafergot contains 100 mg. of caffeine and 1 mg. of ergotamine tartrate, and migril contains ergotamine tartrate 2 mg., caffeine (alkaloid) 100 mg., and cyclizine hydrochloride 50 mg. in each tablet. One tablet of cafergot may be given at the age of 5 years.

Frequent administration of the ergotamine drugs should be avoided because of the theoretical risk of ergot poisoning.

Migril is twice as expensive as cafergot and more than 50 times as expensive as aspirin, so that aspirin, being very effective and the cheapest, should be used first. Tab. codein. co. might be tried second if aspirin does not prove satisfactory.

Itching

As an adjuvant for the treatment of eczema, phenobarbitone or an antihistamine drug such as mepyramine maleate ("anthisan") may be used. A dose of 30 minims (1.8 ml.) of the elixir containing 12.5 mg. may be given to an infant under 1 year. At the age of 2 to 3 years the equivalent of 25 to 50 mg. may be given. The taste is unpleasant. Promethazine hydrochloride may also be used, though it is more expensive than mepyramine. At the age of 2 to 5 years 5 to 15 mg. may be given as a dose.

CELL PHYSIOLOGY IN CANCER

[FROM A SPECIAL CORRESPONDENT]

The 14th annual symposium on fundamental cancer research was held at Houston (Texas) on February 25-27 under the title of "Cell Physiology and Neoplasia." There were about 450 participants, mostly from the United States.

Several papers dealt with the properties of malignant cells. Dr. A. B. NOVIKOFF (New York) described how far staining methods for detecting enzyme activity have progressed in the past few years, particularly on the intracellular level. Biochemical, cytochemical, and electron-microscope studies now combined to give information of the highest value. He described differences between normal liver and three rat hepatomas revealed by the combined approach he was advocating, and he had high hopes that by studying tumours with graded malignancy and growth rate in such a manner we should come nearer to detailing the cell's transformation to malignancy as distinct from a phase of rapid division. Dr. S. KIT (Houston) compared various fractions of nucleic acids from normal and malignant tissues. He presented extensive data on spontaneous primary and transplanted lymphomas and normal spleen, stressing the technical requirements necessary to reveal differences in base sequence along polynucleotide claims. Dr. W. S. BECK (Boston) discussed the biochemistry of ribonucleic acid (R.N.A.), and its precursors in relation to malignancy. He commented on the significance of differences between the R.N.A. metabolism of normal and neoplastic cells, of which advantage could be taken in chemotherapy. Dr. C. LEUCHTENBERGER (Boston) demonstrated by spectrophotometric methods variation of deoxyribonucleic acid (D.N.A.) in tumours, both human and experimental. In normal tissues the D.N.A. pattern was constant and orderly, in benign lesions and malignant tissue the D.N.A. content of cells was increased and showed a much larger variation from cell to cell.

Chromosome Studies

Professor P. C. KOLLER (London, England) reviewed chromosome studies of tumours. He illustrated that in cells of experimental tumours deviation from normal was frequent, though such abnormalities were probably secondary phenomena. He had found no evidence to show that grossly visible chromosome changes were the