# Treatment—Drug and Dietary

# 4

## STIMULANTS

Jeff was transferred at the age of 6 from a regular first grade into a class which combined special education with intensive study of the effects of behavioral interventions. The program had been established as a joint project of the Urbana, Illinois school system and the Children's Research Center of the University of Illinois. The average class size was seven pupils, each class with two teachers, one experienced and trained in behavior modification and the other a student working for an advanced degree in special education. The program was devised by a research child psychiatrist, two professors of psychology, and a professor of social work, all of whom actively participated in implementing the program.

Jeff was moved into this class because of his inability to stay on-task for more than a few minutes. He spent much of his time aimlessly moving about the classroom making loud, inappropriate, and often derisive remarks; interrupted the other children by poking them, picking up possessions from their desks and dropping or throwing them; and despite normal intelligence he was learning little or nothing. His behavior seriously interfered with the learning of the other children, who openly showed their dislike of him. Although he enjoyed physical games, even in the gym he was unable to follow directions and rules and was sufficiently disruptive to spoil games for the other children.

During Jeff's first year in the special class there was little change. He made negligible progress either academicaly or socially.

An interesting comment made by one of his teachers was that even when she worked with him individually on reading, he was so distractible that she had to cover the pictures in the book in an effort to help him attend to the words.

At the beginning of his second year in the special class, Jeff was given a trial of methylphenidate (Ritalin) under double-blind, placebo-controlled conditions in a crossover design so that he acted as his own control. That is, part of the time he received active medication and part of the time placebo, the order being concealed from the teachers and other observers. On 10 mg of methylphenidate once a day in the morning, Jeff's behavior was strikingly altered. He became persistent and productive in his work, less impulsive and distractible, and was no longer easily frustrated. During the placebo period he was again belligerent, quarrelsome, inattentive, and restless. Accordingly, he was placed on 10 mg of methylphenidate once a day. Shortly after this regimen was begun his teacher wrote the following letter to Jeff's mother:

> Academically, Jeff is doing extremely well. He works very hard and very accurately by himself, as well as in a group. He will always begin the assignments as soon as they are given and he will work diligently for the period of time without disturbing anyone. He is making steady progress in reading and writing and phonics and he will begin level C in math tomorrow.
>
> Behaviorally, Jeff is also doing extremely well. He always finds a quiet activity to do during the 10 minutes free time period in the morning. He socializes cooperatively with the others. He shares and is helpful. On the playground Jeff is very much the same. He gets along well with the others, cooperates and plays fair.
>
> I am now working toward having Jeff return to his regular school for one period a day. If Jeff can handle this we will extend the time.

Jeff's return to the regular school was instituted gradually, and soon he was able to remain there all morning. His report was "very good" in reading, spelling, phonics, writing, math, and science. The daily reports contained only praise, and Jeff was very eager to attend the regular school all day and—as he put it in his own simple but revealing way—"be able to walk home with my brother." In 2 months he was attending full-time and his teacher wrote: "I am very pleased with Jeff's progress. He is very eager to learn and to complete his assigned work. He makes good contributions to our discussions and class meetings."

Jeff is now in the seventh grade, a strapping, poised boy of 12, successful in school, making even the difficult transition to junior

high with aplomb. He is a good student and athlete, popular with his peers, and his record is free of repeated grades, suspensions, and complaints from teacher to mother. He still needs, as shown by a placebo test every school year, 15 mg of methylphenidate once a day. There is no evidence of deleterious side effects and he has had a growth spurt during this year which has put him in a higher percentile for both height and weight than any that had been previously recorded for him.

Jeff's response to medication was, as any who have used methylphenidate know, the ideal—one all physicians would like to witness in their ADD patients but do so only occasionally. A less persistent and somewhat modified version of Jeff's responses is, however, not unusual.

Knowledge of the therapeutic effects of stimulant drugs on some children with the syndrome now called ADD or ADD-H is far from a recent acquisition. A descriptive statement, valid to this day, was published in 1971 by a so-called blue ribbon committee convened by the Office of Child Development of HEW[1] because

> of public concern about the increasing use of stimulant medications (such as dextroamphetamine and methylphenidate) in treating so-called hyperkinetic behavior disorders. The panelists were from the fields of education, psychoanalysis, basic and clinical pharmacology, internal medicine, drug abuse and social work. The panel's task was to review the evidence of research and experience and to prepare an advisory report for professionals and the public.
>
> The panel concluded: when the medication is effective, the child can modulate and organize his activities in the direction he wishes. The stimulant does not slow down or suppress the hyperkinetic child in the exercise of his initiative. Nor does it "pep him up," make him feel high, overstimulated, or out of touch with his environment. Much has been made of the "paradoxical sedative" effect of stimulants in such children. The term is inappropriate. Although their exact mechanism of action is not known, stimulants do not provide a chemical straitjacket. They do not act as a sedative. Rather, they appear to mobilize and to increase the child's abilities to focus on meaningful stimuli and to organize his bodily movements more purposefully.

The "purposeful organization" of bodily movements elicited by stimulant drugs is dramatically illustrated in Figure 4–1, showing a child's handwriting on medication and on placebo, the samples being obtained within 2 weeks of each other.[2] Similar remarkable effects on handwriting have been recorded by other investigators.[3]

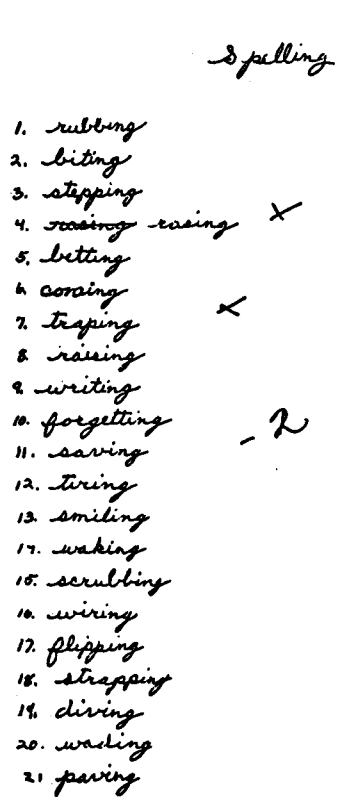



**Figure 4–1.** Handwriting samples made by a fourth-grade girl, an ADD research subject at the University of Illinois, who had been taking methylphenidate for several years. The sample on the left was done while she was still on medication; the one on the right, a few weeks later, was during her placebo trial. *(In Baxley GW, Ullmann RK: Psychoactive drug effects in a hyperactive child: A case study analysis of behavior change and teacher attention. J School Psychol 17:317–324, 1979. Reproduced with permission of Grune and Stratton.)*

Figures 4–2A and 4–2B show the alteration in the quality of a second-grade boy's desk work resulting from treatment with methylphenidate.

The succinct statement in the conference report has been amply confirmed by a body of research, much of it well-controlled, that is staggering in quantity and repetitively consistent. For those inter-

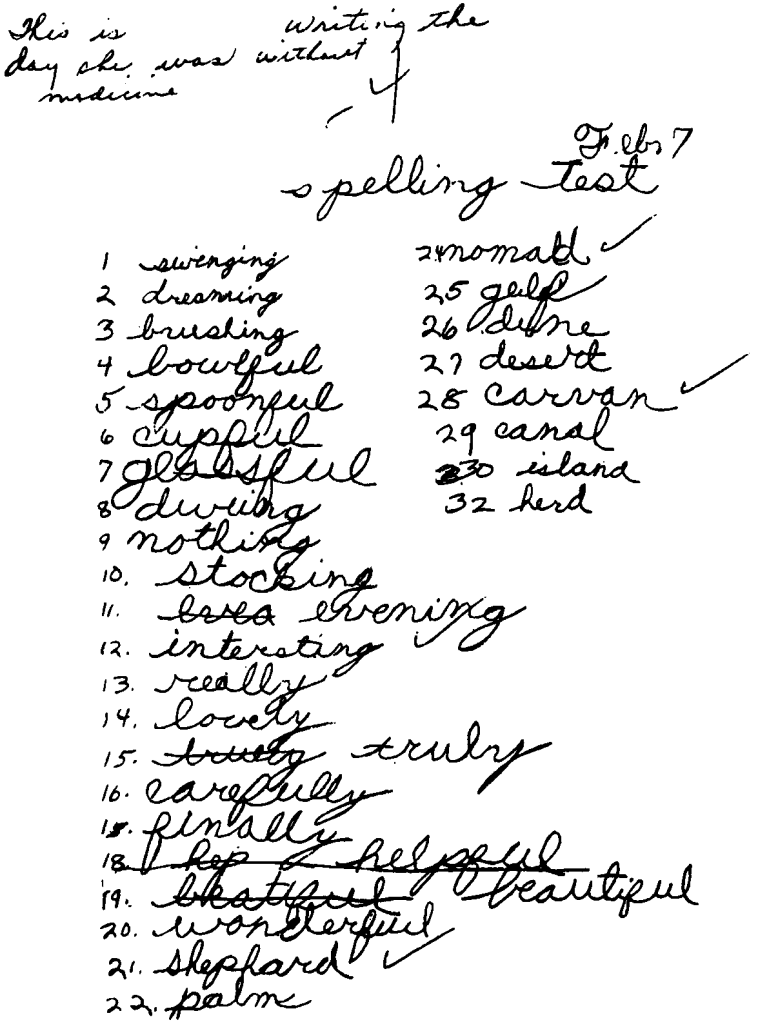



**Figure 4–1.** *(cont.)*

ested in a detailed review of the literature, a chapter by Conners and Werry on the subject (with 280 references) can be recommended.[4] Any pediatrician who has used stimulants for ADD has already had personal experience with the changes these drugs can produce. The happy reports of relieved parents can be one of the most gratifying experiences in a pediatric practice, particularly when one compares

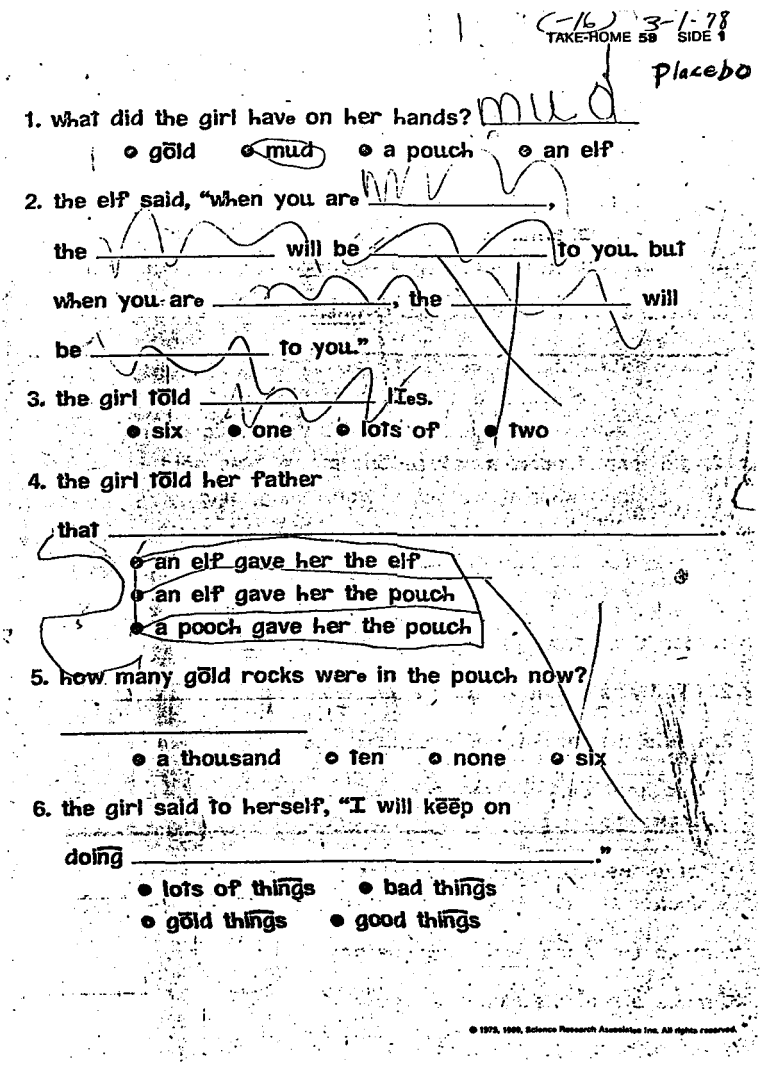
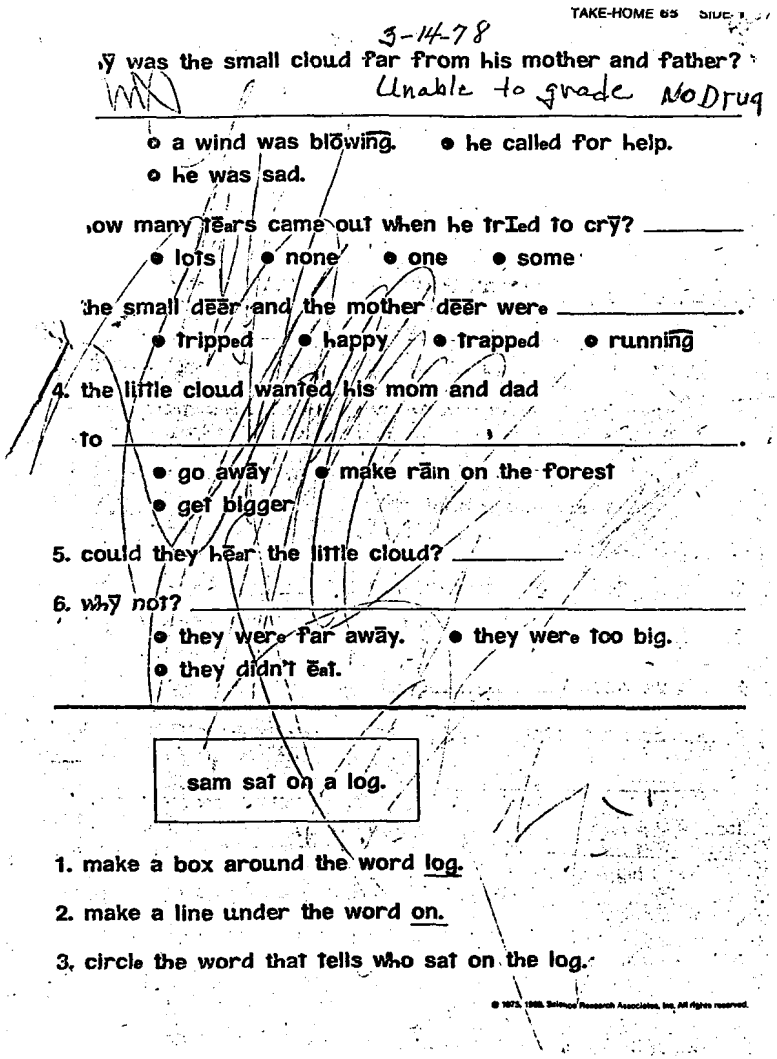



**Figure 4–2A.** The workbook of a second-grade child during his placebo period and several days later when his mother neglected to give his medication.

the overnight effect of medication to the therapeutic intransigence of behavior disorders with other inventions.

It must be kept in mind, of course, as with almost any drug, that the effects vary a good deal from one child to another. The range is from no effect at all to remarkable improvements in the targeted problem. And as will be discussed later, the drugs are, alas,


TAKE-HOME 6S SIDE

3-14-78

Why was the small cloud far from his mother and father?

Unable to grade No Drug

- a wind was blowing.
- he called for help.
- he was sad.

How many tears came out when he tried to cry? _____

- lots
- none
- one
- some

The small deer and the mother deer were _____.

- tripped
- happy
- trapped
- running

4. the little cloud wanted his mom and dad to _____.

- go away
- make rain on the forest
- get bigger

5. could they hear the little cloud? _____

6. why not? _____

- they were far away.
- they were too big.
- they didn't eat.

sam sat on a log.

1. make a box around the word log.
2. make a line under the word on.
3. circle the word that tells who sat on the log.

**Figure 4–2A.** *(cont.)*

by no means solutions to all the child's life problems and there are very few research data supporting long-term beneficial effects (again, a topic that will be discussed later).

Rating scales from the teacher are the most expedient way of finding out how medication is affecting the patient, but encouraging the teacher to add any descriptive notes he or she wishes can enrich

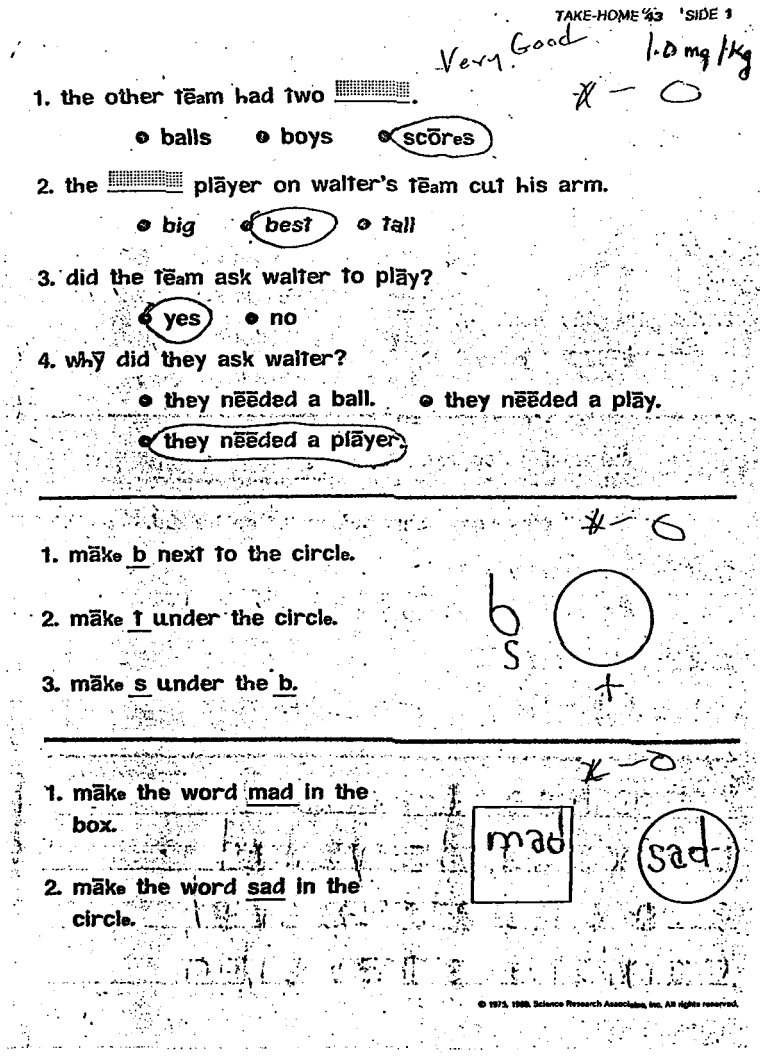



**Figure 4–2B.** The workbook of the same second-grade child while on methylphenidate, done within a few weeks of the pages shown in Figure 4–2A.

our understanding of the child and impresses one with the sensitivity, concern, and keen observational power of many teachers. Two examples of information volunteered on the rating scale form used at the University of Illinois follow:

> George is much improved the last few days. He is calmer and thinks and speaks more kindly and rationally toward his fellow

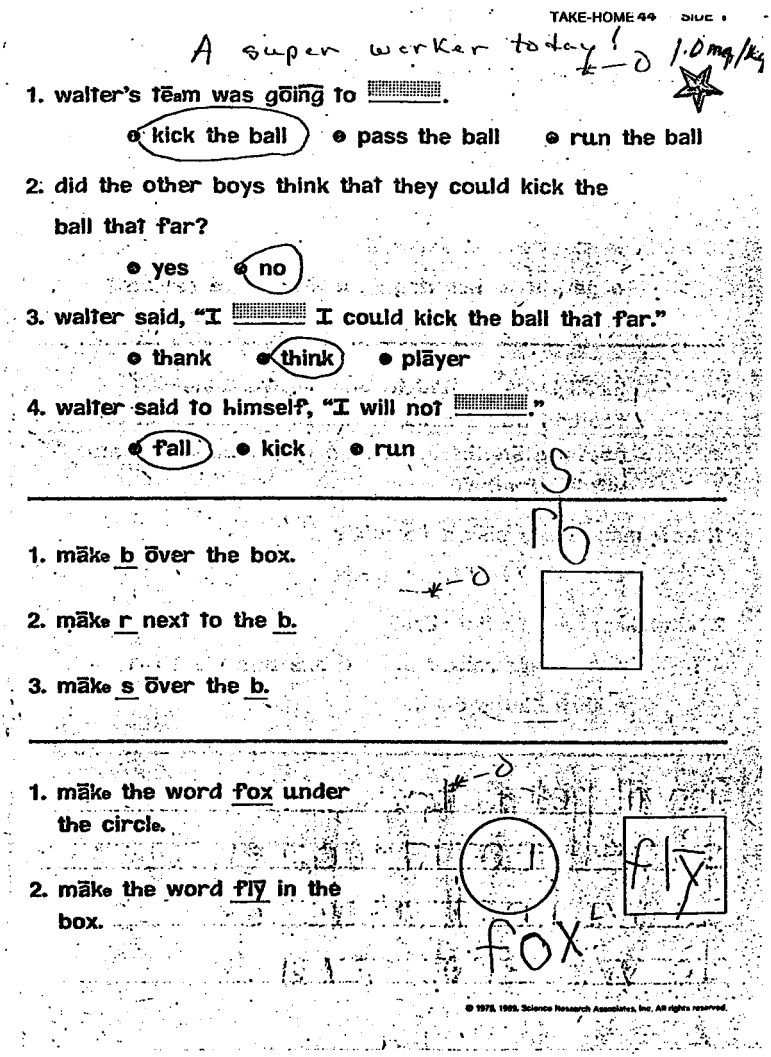



**Figure 4–2B.** *(cont.)*

students. He still shouts out but not angrily nor abusively. He seems to enjoy the activities instead of wasting energy in pouting and self-pity. He is trying to make friends and play football and chess with other 5th grade boys. He is not always successful because his past performance makes some kids leery of him. But he keeps trying. This was a good day!

Last week George was a bright, alert, reasonably calm and cooperative boy. He noticed it himself, and discussed how nicely

things were going with me. He remarked on some of the nice friendships he is making, and is currently developing a code system with several of these boys. One especially intelligent and witty boy *asked* to move his seat next to George!

*During the placebo week:* Now, this week with George was a nightmare! His eyes shot fire most of the day. He lost his temper repeatedly, was loud and abusive in language. Finally, when asked to work in the hall for a time he nearly broke the glass in the door going out. When asked to return, he chose to sulk in the hall about one-half of the rest of the day.

Raoul is now more tractable; his attention span has increased and *he is eager to try to work without help* (italics added). Tuesday he did 11 pages in math; he did 14 pages at home Wednesday evening (usually he averages 2.5 to 3.5 pages). He still is involved in some disagreements with his peers, but the number has been reduced approximately one quarter to one third. He read a complete story aloud for various people which was a first. He seems much more confident of himself in the reading and math.

I have never seen a finished paper of any kind that Raoul was supposed to do on his own until he was on medication. I am looking forward to the conference with his mother because I have so many good things to tell her for the first time.

## Paradoxical Effect

Expressions of astonishment from laypeople that stimulant drugs are used to treat hyperactive children are still not at all unusual. Parents may still come to the physician expecting a sedative to be prescribed. The old explanation that the stimulants have a "paradoxical effect" in hyperactive children can no longer be used as a convenient, brief explanation. The facts are that they have the same spectrum of effects in hyperactive children as they do in normal (or hyperactive) adults or normal children.

How the myth of the paradoxical effect arose is difficult to understand, in view of the extensive knowledge that had been accumulated by 1962 from work done back in the days when research on the effects of amphetamines was common in college students and soldiers. Weiss and Laties[5] summarized the research that had been done up to 1962, and much of it is remarkably similar to current findings of the effects of methylphenidate and amphetamines on hyperactive children.

Weiss and Laties reported that both caffeine and the amphetamines prolonged the amount of time during which an individual could perform physically exhausting work. After reviewing the research on athletic performance, Weiss and Laties stated: "There is little doubt, then, that amphetamine can produce a significant en-

hancement of athletic performance, even in events in which, like putting the shot, one cannot see where endurance or fatigue would play a major role." They found evidence showing that caffeine impaired hand steadiness, and that amphetamine improved it. Amphetamine improved tasks requiring coordination, "especially the more complex ones." An example of such a task would be a tracking task in which subjects must follow in various ways a moving target or compensate in some way for deviations in movement of the target.

Another area in which the effects of stimulants had been studied in adults by 1962 was monitoring or responding appropriately to information read from an electronic device. Investigators did not find the usual decrement in performance over time in such monitoring when the subject, under blind conditions, was given amphetamine. Vigilance tasks, a popular device to the present in looking at the effects of stimulants on hyperactive children, had already been well-studied in normal adults on amphetamine or placebo back in the 1950s. Amphetamine administration maintained vigilance and decreased errors just as it does in hyperactive children.

The performance of simple arithmetic tasks was improved, with greater improvement occurring if the task continued for a long time. However—and this is certainly important—performance of intellectual tasks, such as solving syllogisms or anagrams, was not enhanced. Genuine intellectual performance did not seem to be improved in normal adults. However, the ADD-H child often cannot be given an accurate standard IQ test until made capable of attending to the test by stimulants—at least this situation is frequently reported by school psychologists.

In adults there is little doubt that amphetamines have a major effect on mood. Weiss and Laties reviewed work in which mood effects of a variety of drugs were studied by having the subject fill out a mood questionnaire: "Amphetamine surpassed all other drugs in its ability to create a pleasant state in normal subjects. . . . It also was the most popular drug when subjects were asked to rate them all on a 'most pleasant' to 'most unpleasant' scale."

Weiss and Laties conclude that amphetamines have two independent effects: alterations in performance and in attitude. Another conclusion, pertinent in this day of the omnipresent office coffee pot: "At dose levels that clearly enhance performance, the amphetamines seem not only more effective than caffeine, but less costly in terms of side effects."

A landmark paper which finally put to rest the curious belief in the paradoxical effect was published in 1978 by Rapoport and her colleagues.[6] They had the good fortune to find 14 normal children whose parents were willing to cooperate in this important piece of research. The children were carefully selected to be free of major

problems; they had a mean IQ (Peabody) of 131 ± 18 and a mean age of 10 years and 1 month.

After collection of baseline data, each child took placebo or a mean dose of 15.8 mg of dexedrine elixir before the first experimental session, and the other preparation at the next session. During each of the three sessions motor activity, reaction time, vigilance tasks, and cognitive tests were performed, the subjects completed a mood scale, and behavior was rated during a one-half-hour psychiatric interview. Parents also recorded the child's behavior during the rest of the day.

Amphetamine decreased motor activity, and the laboratory tests showed improved attention, increased reaction time, improved memory and vigilance. During the on-amphetamine interview, the psychiatrist noted that the children were unusually inactive, with increased task-related descriptive talking but less talk which was not task-related. As stated by the investigators: "These results are entirely consistent with those reported for hyperactive children on stimulant medication in previous studies."

Although 12 of the 14 children knew which day they were on active medication, there were no significant effects on apparent mood reported by observers, nor were the children's self-reports significantly different from placebo when they were on stimulants. The investigators found the only self-report differentiating drug and placebo days was, "I feel funny, not like myself." Of the stimulant effects studied by Rapoport, only with respect to the mood created by stimulants was there difference between the effect on adults and that on children. The euphoria described by adults was entirely absent from the self-reports of these children. An interview study of children on stimulants by Sleator and colleagues[7] showed similar results.

Another myth, happily demolished by the Rapoport work, is that response to stimulants has diagnostic significance. Clearly it does not. A good analogy may very well be the anti-inflammatory effect of steroid ointments. As all pediatricians know, improvement of a skin lesion by such an ointment does not prove that the patient had eczema. Nor is its usefulness in eczema diminished because the effect is nonspecific.

## DRUGS USED FOR THE TREATMENT OF ADD AND ADD-H

The use of medication by physicians for the treatment of ADD increased steadily from the years 1971 through 1981. Safer and Krager[8] accumulated these data through biennial surveys using a "head

count" of all public and parochial elementary school children in Baltimore County taking medication. Even at the last count, however, the percentage of school children on medication was hardly sufficient to result in condemnation of physicians for being all too ready and eager to use the easy route of the prescription pad for the solution of difficult problems. They found that by 1981, 2.6 percent of all public elementary school children had been prescribed medication for hyperactivity.

The difficulty of garnering good prevalence data of this sort is amply demonstrated by Gadow's[9] extensive review of all such attempts. Surveys conducted in six different geographical locations showed prevalence rates varying from 0.75 to 2.56 percent. The results of Safer and Krager's 1981 survey correspond to the highest level found in other surveys, so that one can have confidence that the use of drugs for hyperactivity is certainly no higher than 2.6 percent of all school children.

The drugs used for the treatment of hyperactivity are relatively few. They are the stimulants methylphenidate (Ritalin), dextroamphetamine (Dexedrine), pemoline (Cylert); the tricyclic antidepressant imipramine (Tofranil); and the phenothiazine thioridazine (Mellaril). In 1981 in Baltimore County,[8] of all children prescribed medication for hyperactivity, 91 percent were given methylphenidate. Although there are as yet no data on the subject, we feel we can legitimately assume that the percentage of methylphenidate use has actually increased since the recent introduction of a slow-release form which eliminates the necessity for the abhorrent midday dose.

## Who Responds to Stimulants and How to Find Out

Considerable research has been devoted to attempts to develop predictors that the clinician can use to determine before a drug trial whether a patient will be helped by medication—that is, if the patient will be a "responder." Safer and Allen[10] found in their summary of research that from 15 to 20 percent are reported to have demonstrated no benefit from stimulant drugs. The contrast between the "magic potion" effect of stimulants on some ADD children and no improvement in others is so striking that the extensive and documented efforts to find predictors[11] are understandable. However, the chance of finding a predictor sufficiently precise to be of value for clinical use is remote. Group design (pooling results over many subjects) used in predictive studies inevitably means that the research will not aid clinicians in knowing whether the very child sitting in the office will be helped by a stimulant drug. Physicians only know that if the child has been diagnosed as ADD, there

is a 70 to 80 percent chance that such treatment will alter behavior for the better.

If the physician has decided that medication is the treatment of choice for his or her patient, the only way to find out if it will help is to *try it*. Good clinical practice does not require the physician to determine before the fact that medication will be beneficial, but it does require that the trial of medication be done in such a way that the physician can be confident that the benefits of prescribing outweigh the cost—the cost in dollars, in side effects, in distress to the child if the word gets out in school that the child has to take medicine because he or she is "hyper," and in just the general all-around nuisance of taking medication daily.

If the physician wants to accurately monitor drug effects he or she has no choice but to make arrangements to obtain teacher reports, preferably on a quantified rating scale. This emphatic statement has been supported at length in the previous discussion on diagnosis (Chap. 2). Collecting such reports is simplicity itself. Physicians (or their office help) put dates on a number of scales, and give them to the parent to deliver to the teacher with instructions to fill out the scale on the assigned date and mail them to the physician in envelopes that the parent has stamped and addressed. To ascertain the feasibility of this method, the University of Illinois has carried out the procedure exactly as described and the rating scales arrived with gratifying regularity. The physician should already have a baseline (pretreatment) rating as a necessary part of the diagnostic process, to know in what areas the child is having problems and to have a score with which to compare changes brought about by therapeutic interventions.

For research purposes the operational definition of a responder at the University of Illinois is a child who improves 20 percentile points on the profile for the attention factor on ACTeRS and whose attention rating drops at least 20 percentile points during his or her placebo trial. Such a definition is essential for a research report but is not necessarily the rule the physician should follow in deciding whether or not to continue medication. The ACTeRS provides the physician with quantified information about four important types of behavior. The physician may also have some descriptive information from the teacher, and will have the opportunity to talk to the parents about their observations and the kind of feedback they may be getting from the teacher. No simple formula can be provided to help make the choice of whether medication should be continued. However, if all the information suggested has been collected—most particularly rating scales from the patient's teacher—it can be safely predicted that the physician will have new confidence that the information necessary to make an informed decision is at hand.

It is important that the physician keep in mind that when treating a behavior disorder even under blind conditions, there will frequently be some placebo effect. For example, during the 1983–1984 research year at the University of Illinois, where a practice has been made of two blind placebo periods, with the second randomized but the first always the first drug condition, it was found that 10 percent of the subjects responded to the first-dose placebo period with sufficient improvement reported by the teacher to be classified as a "responder" according to the research definition.

In the research laboratory all drug trials are conducted under double-blind conditions. In some children being treated by clinicians the alteration brought about by medication is so striking that the physician can be confident the child is responding to the medication. However, there are instances in which the clinician may wish to carry out a double-blind study on a particular child. This is entirely feasible, and parents are usually cooperative and even pleased because of the reassurance it will provide them that the medication is really worth giving. The truth is that many research subjects' parents are fugitives from a practitioner whom they felt was insufficiently informed about their child's response to medication but continued to prescribe. They will quickly understand the concept of a double-blind study and, in fact, may find it intriguing as well as reassuring.

The clinician may choose to do such a study where there is some response to medication but it is not striking, and a double-blind study is necessary to determine if the effect is, perhaps, a placebo effect. If it is, the physician certainly would not want to continue active medication. Varley and Trupin[12] recommend the physician make a practice of double-blind studies but "particularly in difficult family or clinic situations," and they provide three interesting case reports in which a double-blind study was indispensible.

Case 1 was a 10-year old who had severe ADD. His parents had never been willing to even consider medication but did agree to a double-blind study after 3 years of psychotherapy had not resulted in change. The dramatic change on medication and the reversion to his old self on placebo was sufficient for them to request continuation of medication with a regular placebo trial.

Case 2 was a 5.5-year old child who, according to the mother, had been a difficult child since birth. The mother demanded medication, threatening to seek another doctor if she did not get the prescription. It took a double-blind study to convince the mother that the child was a nonresponder. The 2 days in which the mother insisted there had been great changes for the better turned out to be placebo days—the mother was finally convinced that medication was ineffective.

Case 3 was a typical ADD child who also had poor intellectual abilities. His dose had been gradually increased up to 120 mg a day, apparently in a constant effort to seek a better outcome. He was not gaining weight but the parents felt he needed the large dose. A double-blind study showed that he was, indeed, helped by medication, but there was no discernible difference between 120 and 60 mg.

There are a few other important admonitions for the physician to keep in mind when prescribing daily medication. First of all, if the parents want a real trial of the effect of medication it is necessary for them to take extraordinary precautions to be certain that the medication is taken. One of the parents or some other responsible person must hand the pill to the child and watch the child swallow it. If the bottle is left on the kitchen table for children to help themselves, it is not only a menace to other children in the family but there is excellent likelihood the child will not take it. If one neglects to supervise the swallowing, we know from experience it may be "cheeked" and land in the cat or dog food dish, down the drain, or in the grass as the child heads out the door for school. The rather sad fact is that most children dislike taking the medications used to treat ADD. Sleator and associates[7] have documented this dislike and the philosophical dilemma that the attitude of the child-patient (particularly after long-term use of stimulants) poses for the therapist:

> The intensity of the dislike of many hyperactive children for taking stimulants is a troubling phenomenon. The problem is made more difficult by the fact that many of the most vigorous objectors are greatly benefited by medication in school achievement, in freedom from the open disapproval of elders at home and at school, and in improved peer and sibling relationships. Our observations that such improved behavior and functioning occur frequently are confirmed by an abundance of well-controlled published studies which support the view that there is an important role for stimulant drug treatment of hyperactive children.
>
> Is it justifiable to urge children to follow what is to them an aversive regimen whose benefits are perceived by associates but not by themselves? The dilemma is not unique to stimulant therapy: few children realy enjoy receiving necessary immunizations and many dislike attending school. Our culture is replete with examples.
>
> One device we have used is to stop medication, and agree not to start, as a goal (and reward) for continued satisfactory performance. Regardless of the techniques used, it is, above all, important for the clinician to understand any distress or confusion the child may be experiencing and to enlist his cooperation in structuring the medical regimen so as to aid in developing new behavior patterns.

> Although each drug presents unique problems and is given to achieve different ends, there seems little doubt that any child given chronic medication can be benefited by physician concern and his knowledge of the child's attitude toward prescribed medicine.*

## PRESCRIBING METHYLPHENIDATE

The close to exclusive use of methylphenidate for the treatment of ADD is understandable because it brings to the physician reports of a very rapid and striking improvement, and, for such an effective drug, it is remarkably safe. The physician can feel comfortable in prescribing methylphenidate. In the rare situation in which undesirable side effects do occur, the medication is so short-acting that on withdrawal of medication the children return to their old selves in a few hours. Dextroamphetamine is equally effective and is also relatively free of side effects, but methylphenidate has almost replaced dextroamphetamine.[8] This may well be, as Safer and Krager[8] speculate, because dextroamphetamine is no longer advertised and because it is under more stringent government regulations (in Illinois every prescription must be written in triplicate on forms purchased from the Illinois Bureau of Investigation). Its notoriety as a drug of abuse no doubt has also resulted in some reluctance to prescribe the drug to children.

In order to individualize dose according to the needs and responses of the patient, the physician must have a reliable method of monitoring drug effect. The dose requirement does vary widely from one patient to another and some children are not helped by any dose. How best to find out?

By far the most revealing method, as well as the least expensive and most convenient to implement, is to obtain repeated ratings from the teacher on a well-designed rating scale. It follows, of course, that the first trial of stimulant medication should be done during the school year. *The summer vacation is not an appropriate time to start medication on a school age child, for it is really impossible under summer vacation circumstances to get a solid grip on whether or not the treatment is effective and what dose is optimum.*

The method of "titrating" dose as described in PDR is reasonable but only if the physician has a good method of determining an end point. A device such as a teacher rating scale is essential if the concept of titration is to have any meaning.

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The question of whether or not it is important to determine dose in mg/kg when medicating ADD children has been actively discussed by investigators since the appearance of a controversial paper by Sprague and Sleator[13] in *Science* in 1977. The Sprague laboratory played an innovative role in the use of mg/kg doses as a research tool, and a productive tool it has proven to be. However, they have not claimed that using milligram per kilo (mg/kg) doses is essential to good clinical practice.

The issues raised by the Sprague and Sleator *Science* paper are pertinent to a discussion of the optimum dose of methylphenidate. The important finding of that paper, again using group data, was that most children did best on a cognitive task (short-term memory) on 0.3 mg/kg, but received the best ratings from their classroom teachers on the ATRS when they were on a dose of 1 mg/kg. This was not, of course, true of all 20 subjects. As the authors specifically stated, only 65 percent of the subjects received their best scores on the short-term memory task at 0.3 mg/kg. The main point of the paper was that it showed different doses were optimally effective for different target behaviors. This is major pharmacological information for any drug that is used for more than one purpose (e.g., one uses very different doses of phenobarbital for anesthesia than for seizure control). Unfortunately, in the case of ADD this point is not yet of great clinical importance because of the lack of availability of a highly reliable, highly specific, readily available test for cognitive function that can be used repeatedly without a practice effect. For determining the best dose for the individual child we are still left with the teacher rating scale as the best instrument available to the clinician.

And there are at last some real data on whether or not taking methylphenidate before or after meals makes a difference. Gualtieri and associates[14] determined serum levels of methylphenidate in 6 normal adults who took the drug either in a fasting state or immediately following a full meal. There were no differences. Absorption of methylphenidate is not altered by the presence of food in the gut.

After the physician has determined that the young patient is substantially benefited by medication and has settled on the optimum dose, there are further decisions to be made. Should the child be on medication on Saturday and Sunday? Should medication be taken over the summer? How long should the child be continued on this medication?

But are these decisions going to be made by the physician? Of course not. This is not exactly news to the experienced physician, but in a monograph in which one goal is to deal with the clinical situation as it truly exists out in the world, we cannot simply de-

scribe optimum procedures as if there were no doubt that the physician can implement them at will.

During the early stages of intervention there is usually eager compliance, but in the chronic phase, the decisions will be made by a complex interaction between parents, child, and to some extent the teacher. The physician has only one real power, to withhold prescriptions; but it is a limited power. The family, if they wish, can usually find another physician who will prescribe.

Compliance will be discussed in some detail when we deal with outcome of drug treatment, but in the few research papers in which an attempt has been made to assess compliance in this clinical situation it has invariably been found to be mediocre to terrible.[15–20] Compliance in most chronic medication situations has been shown to be poor,[21] but treatment for ADD is particularly vulnerable. The patients dislike taking stimulants and with a peculiar ferocity as they approach the teen years.[7] As the treatment is for a behavior disorder which the parents deal with daily and the physician at relatively rare intervals, parents feel (often correctly) that they are more competent to make decisions about dosage, and stopping and starting medication, than the doctor; and an uneasy feeling on the part of some parents about giving this, by some, abhorred medication, are all factors in the physician's lack of control. Families will give medication irregularly, leave the bottle on the table for the child to take on his or her own, or discontinue giving it for various reasons and simply no longer appear in the doctor's office. There are parents who increase the dose at will, and those who insist with a desperate passion that the child cannot function without medication, even though they and the teacher have been unable to detect changes in the child's behavior during a placebo period.

Making the assumption that the physician is able to determine how the child will be medicated, what are the optimum procedures? The recommendations made here are based on many years of experience with stimulants in ADD children under research conditions and 8 years of meticulous prospective follow-up with detailed periodic reports from teachers and parents collected both routinely and spontaneously whenever a difficult situation arose. As with much of this section on how best to administer stimulants, there are few scholarly references and it should be made clear that we are calling on clinical experience, fully recognizing the pitfalls of such source material. However, nothing better seems to be available, and the assumption is made that the distillation of years of experience with carefully watched ADD children could be of some value to the busy practitioner.

In a frequently cited paper by Sleator and associates[22] it was re-

ported that 26 percent of the subjects in a prospective long term follow-up study who were "known hyperactive, drug sensitive" were able to function satisfactorily without medication as determined by teacher-reported response to a double-blind month on placebo. Eleven of the 42 children on follow-up showed essentially no deterioration for the entire month on placebo. The study has methodological weaknesses (small number of subjects, not all subjects had a placebo trial, no follow-up on ability to continue off medication), but it does at least indicate that some children may require medication for good school performance for a relatively short time, and this is a fact that the doctor must take into consideration in his or her handling of children being chronically medicated with stimulants.

If the child is doing reasonably well on medication, the only way the physician can determine if medication is no longer needed is to recommend to the parents a drug-free period some time after school is well under way. The physician would be well advised to urge such a trial as early as the second year the child is on medication. Parents frequently will start a child back to school off the medication after a reasonably good summer, as their own trial to determine if medication is still needed. This is a poor time for such a trial. The facts are that after two weeks to a month in school the mother is often on the phone with a plaintive cry for a new prescription immediately, or the call may be from a desperate teacher reporting that the child is out of contol and requesting advice or help. It is a common-sense opinion that a good start at the beginning of the year can establish the child as a tolerable student and companion; a disastrous beginning can be very difficult to overcome.

Because implementing a double-blind placebo-controlled "drug holiday" would be very difficult for the practitioner, there seems no choice but to simply take the child off medication and admonish the mother not to notify the teacher of the change. Unfortunately, it is not at all rare for teachers, seeing altered behavior, to ask the child "Did you take your pill today?" (not always done, alas, in privacy). This is an unfortunte practice at any time in the drug treatment, and the mother should be instructed right at the beginning of medication to request that the teacher never ask the child this question at any time. Any concerns the teacher may have about faithfulness of drug-taking should be addressed to the mother. If the teacher does call the mother during the off-drug period describing deterioration in behavior, drugs can be restarted immediately. Some alarmed teacher calls to parents come during the first morning of placebo period! Curiously, the teacher, now accustomed to orderly behavior, sometimes interprets the placebo behavior as the result of a toxic dose of

drugs. However, neither parents nor teacher may detect a change during the off-drug time, and in that case drug treatment should end. The doctor is warned that even in this situation, parents are fearful of taking their child off drugs and will, after the fact, insist they really did see subtle changes. The doctor should have the strength of character to resist this plea. It may be difficult.

As for medication on weekends and during the summer, that is a decision to be made with the parents, and depends on how disruptive the child is in the home. If medication decreases conflict with siblings and peers and creates a generally happier atmosphere for all, daily medication is reasonable. Many parents feel they can "handle" the child at home and that the difficulties are mainly in school, and those parents prefer to keep the stimulants to a minimum. Not infrequently permission is given for parents to give the patient a tablet before a Little League baseball game to cut out impulsive throwing of the bat and abusive talk to the other players. Sometimes a pill is given on the weekend for church only, or perhaps during the summer when the child is at camp or on a long automobile trip.

## Pharmacokinetics of Methylphenidate

Knowledge of the pharmacokinetics of drugs can and frequently does make major contributions to all aspects of drug use, and is of great help in clinical prescribing and monitoring of some medications. However, because of the great difficulty of determining blood levels of methylphenidate, the drug came into widespread use without the benefit of pharmacokinetic studies. Only recently have reproducible methods of determining blood levels become available. Using a sensitive and reliable gas chromatographic-mass spectroscopic method for measuring methylphenidate blood levels, the pharmacokinetics of methylphenidate have now been described in ADD children, normal adults, and some laboratory animals. Shaywitz and her colleagues,[23] writing in *Pediatrics*, deplore the "primitive" quality of prescription practices with methylphenidate, implying this is due to the lack, until very recently, of availability of methods of determining methylphenidate blood levels.

Shaywitz and associates[23] found a fivefold range in absorption-rate constants between subjects, but relatively little variation in elimination of the drug. Levels of methylphenidate peaked between 2 and 3 hours. Most interesting, they found a correlation between the blood level of methylphenidate and the ratings the child received on

the Conners 10-item abbreviated rating scale (although it is not made clear who rated the children). They also found that the children who were considered nonresponders to methylphenidate all had low peak blood levels. The authors feel that blood-level determination of methylphenidate (suggesting one sample 2 or 3 hours after drug administration would be ample) will eventually prove helpful in determining if a poor clinical response is due to inadequate dosage.

But before speeding to the laboratory to insist that methylphenidate blood or serum level determinations be made available, it is necessary to report that—as in so many aspects of research with ADD—other investigators have not replicated previous findings. In a most impressive paper by Gualtieri and colleagues[24] five meticulously performed and analyzed studies are reported. They found no correlations between serum levels of methylphenidate and ratings on the Conners 10-item scale, on laboratory measures of attention, on activity levels, pulse rate, blood pressure, or direct behavioral observations in the classroom. In addition, they found that 1-hour serum levels varied greatly from day to day in the same individual on the same dose (in subject 1 the serum level ranged from 6.7 ng/ml to 15.5; subject 2, 7.9 to 23.1; subject 3, 9.3 to 21.7; subject 4, 1.6 to 6.0), and the variation in performance that one commonly sees in ADD children was not correlated with serum levels. They concluded that blood levels will not predict any more about the patient's clinical response than dose, and that blood or serum levels are not now, nor are they likely to be, clinically helpful. As there was also no correlation found between blood levels and side effects, they found no reason to believe that such blood levels will prove useful even in predicting the development of toxic reactions.

Gualtieri and associates speculate that this lack of correlation may be due to the selective affinity of methylphenidate for different tissues (there is, for example, greater and more consistent affinity for brain tissue than other tissues), or due to the fact that present methods do not distinguish between the d- and l-isomers, which may have differential activity.

The findings of Gualtieri and colleagues are not at all unusual in drug research: "This lack of an exact relationship between drug metabolism and therapeutic action is not surprising in light of the many factors that can influence the effects of drugs, including binding to receptors, storage in body tissues, and the influence of extraneous environmental factors in precipitating symptoms."[24] This is a complex and difficult area of research. It can be safely stated that, at present, determination of blood and serum levels plays no role in the treatment of ADD children.

## Generic Methylphenidate

Because prescribing by brand name during the span of exclusive rights understandably tends to become habitual with physicians, it is worth pointing out that methylphenidate, in all doses currently available under the Ritalin brand name, can now be obtained generically at considerable savings to the patient. This is not true of the sustained-release methylphenidate, which is available only under the brand name.

## Ritalin SR (Sustained Release)

Although an appreciable number of our subjects at the University of Illinois are able to manage the school day on a single morning dose of methylphenidate, the number who eventually require bid doses increases the longer they are on the medication. But attempts to even try a single dose of the short-acting methylphenidate are most unusual. The necessity for bid or even tid doses is taken for granted by most practitioners. Unfortunately, the short-acting quality of methylphenidate constitutes a serious disadvantage because hyperactive children, already suffering from a poor self-image, must be administered an in-school midday dose. This seems to invariably inform the entire school that the patient is "hyper" (a currently popular epithet among grade-school children) and has to take pills in order to behave. Children have articulated[7] specifically their embarrassment at the necessity of being medicated at school. Such feelings are one factor in the poor compliance that is already a problem in children who are very much helped by stimulants.

In September of 1982, CIBA began to market a long-acting form of the drug, Ritalin SR 20 mg (sustained release) which is said to be equivalent to a standard 10-mg dose twice a day. The claim is made that with the SR form once-a-day dosage can be effective for the entire school day. The advantages of such a formulation are obvious. Now the medication can be given once in the morning in the privacy of the child's home. If the claims are true, it constitutes a leap forward in the treatment of ADD children. But, unfortunately, the practitioner has insufficient information available to know if the sustained-release form is as effective as the familiar two or three doses a day regimen when using the standard form. The package insert of Ritalin SR gives a brief paragraph on the urinary excretion of the major metabolite of methylphenidate. The peak time of excretion is a little over 2 hours longer in the SR form than the standard form (with very wide variations). A duration of action is claimed of ap-

proximately 8 hours for the Ritalin SR, but substantiation of this claim does not seem to exist.

There is exactly one research paper published on the subject of the clinical effectiveness of the SR formulation,[25] but this paper is so inadequate that it can hardly be considered an improvement over the remarkably sparse information in the package insert. Some of the problems with this study are:

1. The number of subjects, research design, and duration of the experiment were inadequate to generate enough statistical power for meaningful analysis.
2. No information is supplied about how the subjects were diagnosed as having Minimal Brain Dysfunction (MBD), an outmoded rubric but beloved by CIBA.
3. Although verification of the longer duration of behavioral effects is the central concern with the SR form, no monitoring of duration was reported. There is one sentence in the closing paragraph in the results section stating that three parents reported "the effects of the SR fomulation *may not* have lasted as long as expected" (italics added) although what expectations the parents had (or why) is not clear. Nor do we know whether the behaviors that led the parents to the conclusions that the effects had worn off were observed by the parents or reported to them by teachers, or even what behaviors were being monitored that allowed the three parents to reach their stated conclusion.
4. There were neither placebo nor no-drug comparisons.
5. The parents and teachers completed unidentified questionnaires so the reader has no idea what the rating scale scores mean.
6. The only doses studied were the 20-mg SR and two 10-mg doses of standard methylphenidate. This is an inadequate dose for many subjects.

The SR formulation is potentially an extremely useful medication for ADD children. However, a recent write-up on Ritalin SR in *The Medical Letter*[26] calls attention to the very weaknesses described above in the supporting data for Ritalin SR, and the writers conclude:

> No adequate studies have been published to show that Ritalin-SR is effective or safe, or even truly long-acting. Until more information becomes available, particularly on safety, standard formulations of methylphenidate are preferred.

Clearly, under present circumstances, the admonition of *The Medical Letter* cannot be faulted. However, because the advantages of an effective long-acting form are so great, it is no doubt being widely used. In a drug with such an inadequate published track record it is of particular importance that the practitioner take special pains with the monitoring of drug effects. At the University of Illinois laboratory, spectacularly good as well as a number of poor results followed Ritalin SR use. It has been found that the dose of Ritalin SR can be safely adjusted to suit the individual patient just as is done with the short-acting form. That is, it is not necessary to limit the dose to one SR tablet in the morning.

In the meantime, the practitioner eager to use the longer-acting form will receive, if he or she makes inquiries of the Medical Services personnel at CIBA (as many have done), a copy of the uninformative Whitehouse and associates[25] paper described above.

## Side Effects of Methylphenidate—Short-Term

Shader and DiMascio,[27] in what must now be considered a venerable book on psychoactive drug side effects, were struck by the fact that, compared to the other psychotropic drugs "remarkably few reports document adverse reactions to the drug" (i.e., methylphenidate). They list the well-known insomnia, usually transitory if it occurs at all, and anorexia in some children. Five cases are described in which visual and auditory hallucinations or twitching of dyskinetic movements appeared following use of methylphenidate, and all terminated when the drug was stopped.

Barkley[28] thoroughly reviewed all side effects of stimulant treatment generally, not limited to methylphenidate, up to the time his paper was published in 1977; he also noted those most frequently reported were insomnia and anorexia. Next in frequency were weight loss, irritability, and abdominal pain. Less frequently he counted headaches, drowsiness, sadness, dizziness, nausea, proneness to crying, euphoria, nightmares, tremor, dry mouth, constipation, lethargy, depression, dazed appearance, nervous tics, anxiety, and others: "Many investigators found these side effects to be temporary and easily modified by adjusting dosage downward." Four reports of psychosis following methylphenidate treatment are covered in Barkley's review, but all psychotic episodes subsided after discontinuation of the drug.

A very few children, usually those with a history of allergy, have developed urticarial reactions after taking methylphenidate.[29] Again, withholding medication, as would be expected, resulted in clearing of the lesions.

A more consistent but also transitory effect, as shown by Ballard and associates,[30] is the significant increase in heart rate and blood pressure when methylphenidate is compared to placebo. The increase in heart rate was significantly dose-related; the increase in blood pressure tended to increase with dose. The marked effect of dose was shown by the fact that elevated blood pressure and pulse rate was fully evident at the end of 5 hours after a 1.0 mg/kg dose, whereas it was no longer present at the end of 3 hours when the child had been given 0.3 mg/kg. What the pathological results of this effect, if any, might be is not known. However, the clinician must take these data into consideration if he or she has a patient whose blood pressure is in any degree elevated before medication is begun. If the clinician decides to go ahead with methylphenidate treatment, monitoring of blood pressure at the time of peak drug effect (about 2 hours after the standard form is administered) is certainly indicated.

The evanescent quality of some alarming signs and symptoms that can appear after the administration of methylphenidate is demonstrated in a case report in a letter to *Pediatrics*.[31] A large child in his early teens was participating in a research trial using randomized doses and received his largest dose first. Forty mg were given at 1:30 P.M. for a special study on learning. By 3:00 P.M. he was dizzy, pale, speech slurred, unable to focus, and ataxic. He was distressed, frightened, experienced true vertigo as well as constant twisting of his facial muscles, movements of the tongue in and out of his mouth, and impaired hand–eye coordination. At 6:30 P.M. with extreme suddenness the subjective distress vanished, and the abnormal movements showed marked diminution; they were gone entirely by 11 P.M. The child slept soundly, wakened next morning entirely well, and attended school the next afternoon. There were no sequelae and no subsequent administration of methylphenidate. The abnormal response was, indeed, temporary, but it was not an experience that any child, parent, or physician wants to have. The recommendation in the Ritalin package insert to start with a small dose, and increase as indicated, is sound and should be heeded.

## Side Effects of Methylphenidate—Long-Term

### *Growth*

The possibility of growth retardation secondary to methylphenidate administration should be troubling to the conscientious physician because this is one of those side effects that could have permanent consequences. The lack of day-to-day impact as obtains with other side effects makes growth problems easy to ignore. Compounding

the difficulty of maintaining a high level of concern is the fact that the data are simply not yet sufficiently convincing to influence many doctors to refrain from using a therapy that is so often at least a temporarily effective solution for both the physician and the family.

One might expect that we could, when dealing with a matter as simple as height and weight, know whether or not a chronically given drug altered the growth pattern of a group of children. Indeed not. The difficulties are, in fact, great. First of all, most physicians—and this seems to apply to investigators as well—do not know how to accurately measure height. The usual office balance scale with a movable bar is insufficiently accurate in measuring height to be used in the doctor's office, let alone as a research tool. This position is convincingly supported by Owen in his *Pediatrics* paper,[32] and yet some of the published papers purporting to study growth effects of methylphenidate used exactly the movable-bar method. In addition, longitudinal studies are always full of pitfalls: they take years to accomplish, subjects have the annoying habit of disappearing, and it is most difficult to develop the clear patterns of drug dosage (and reliability in taking medication) that can be used for effective calculations. Nevertheless, well over a dozen courageous investigators have made the attempt and the result is still uncertainty. The best review paper is the report of the Pediatrics Subcommittee of the FDA Psychopharmacology Advisory Committee.[33] The first author is Alex F. Roche of the Fels Institute of Yellow Springs, Ohio, who has devoted a life of meticulous research to studying growth. His conclusions are worth repeating:

> Despite their defects, in combination, these studies provide reasonable evidence that stimulant drugs, particularly in the "high-normal" dose range, moderately suppress growth in weight. There may be some minor suppression of growth in stature during the same period but the evidence is less certain. However, the effects of treatment during pubescence and early adolescence have received little attention.
>
> The literature indicates that incomplete "catch-up" occurs if treatment is discontinued during the summer early in treatment, and that the early growth suppression during treatment is no longer evident in adulthood. Because these conclusions are based on studies of small groups, the risk of larger effects in a few children is unknown. Therefore, careful monitoring is necessary during treatment, particularly if the child is already small or delayed in maturity for age. The expected benefits and risks should be judged before treatment is commenced; the present growth and maturity status of the child should be considered when this judgment is made.

This is certainly good advice and the monitoring can be easily accomplished by charting growth (properly measured) on the National Center for Health Statistics growth charts before the beginning of stimulant drug therapy and perhaps twice a year thereafter. There are no guidelines that can be provided to the clinician in deciding how to handle an ADD child on methylphenidate who has dropped into a lower channel. The clinician will have to evaluate all possible causes and make a decision based on his or her own judgment of the situation.

*Tics and Tourette's Syndrome*

Special attention to the development of tics as a side effect of methylphenidate is indicated, also because of the possibility that the tics may develop into a permanent disability.

The most complete overview of tic development secondary to methylphenidate was published by Denkla and her associates.[34] The total number of children on methylphenidate in their data pool was 1520. Forty-five of the children had tics before methylphenidate was administered, and in 6 of these children the tics became worse. There were 14 children who developed tics for the first time when on methylphenidate (a total of 20 children in whom the tics either became worse or appeared for the first time). One of the children was diagnosed as having Tourette's syndrome, but it is not clear from the report if this child was one who had tics before or only following the administration of methylphenidate. The appearance of the tics varied from 1 day after the beginning of medication to 1 year, and the doses on which the tics appeared or became worse varied from 10 to 60 mg daily dose.

When medication was stopped the tics returned to their previous level of intensity in the children who had had tics before medication, and the tics stopped in all but one of the children in whom tics developed after medication was begun.

In summary, Denkla's data do not suggest that tic occurrence is one of the serious threats of methylphenidate use, but other authors do not agree. Lowe and his colleagues[35] (a group of neurologists and psychiatrists) reviewed the literature and deplored the fact that "in spite of recognition of the relationship between use of stimulants and the development of clinically recognizable motor tics, children continue to receive stimulant medication in the presence of tics or when vulnerable to Tourette's syndrome." They reviewed a series of 15 patients whom they evaluated for Tourette's syndrome following administration of stimulant medication. The review includes four case histories. One of the four developed Tourette's while on pemoline. Of the other three, two had already manifested tics before medication was begun. In one of the case histories a full-blown Tou-

rette's appeared after 2.5 years on stimulant medication. Withdrawal of the medication did not alleviate the Tourette's symptoms, and haloperidol therapy was unsuccessful. The authors do not take a position on whether or not stimulants can be the actual cause of Tourette's in a child who would not have developed it otherwise. This is an unanswered, and possibly unanswerable, question. However, their advice to the practicing physician makes good sense:

> Our data support two general principles regarding the use of stimulants in children with hyperactive or attention-disorder symptoms. First, motor tics or diagnosed Tourette's syndrome in a child should be a contraindication to the use of stimulant medications for alleviation of hyperactive symptoms. Second, the existence of motor tic symptoms or diagnosed Tourette's syndrome in the parents, siblings, or other family members of the index patient should be viewed as a relative contraindication to stimulant therapy. In the second group, if the decision is made to use stimulants for relief of attentional or hyperkinetic symptoms, the physician should proceed with careful observation for the first indications of development of motor or phonic tic behaviors. Stimulants should be withdrawn immediately if such signs develop. In addition, the development of motor tic symptoms in any child receiving stimulants, with or without a positive family history of tics or Tourette's syndrome, is a clear indication for immediate discontinuation of stimulant therapy in an effort to minimize the possibility of eliciting a full-blown case of Tourette's syndrome.

*Psychological Side Effects*

An interesting group of disadvantageous psychological behaviors have been described as side effects of methylphenidate by a number of investigators. These are reduced responsiveness, reduced curiosity, and an increase in subdued, apathetic behavior. Fiedler and Ullman,[36] uniquely, made a systematic effort to measure curiosity behavior empirically. Using measures said to quantify various aspects of curiosity, they rated 20 hyperactive children both on and off methylphenidate and compared the results with similar measurements on 20 normal controls. The "object curiosity" task measured the number of times a child manipulated each of a group of objects, and the number of questions asked about the object. The ADD children were found to do less object manipulation and to ask fewer questions about the objects when on methylphenidate than when on placebo; the normal controls manipulated less and asked fewer questions than the ADD children on either medication or placebo. The investigators drew admirably cautious conclusions from these results: "The present findings also clearly provide some initial empirical support for the possibility that stimulant drugs are affecting more

than just the symptom behaviors (e.g., attention span, activity) of hyperactive children." Considering that manipulation of things and talkativeness are among the manifest characteristics of ADD children, and that the medication resulted in behaviors of ADD children significantly more like normal children than were the nonmedicated ADD children, it is difficult to consider that these data demonstrated a deleterious side effect of methylphenidate. Further investigations along the same lines will undoubtedly follow, and may prove eventually to be of considerable interest.

### *Addiction or Dependence*

The possibility of addiction to or dependence on methylphenidate is of great concern to many parents who must make the decision for or against a stimulant drug trial for their ADD child. Will their child be more likely than are children not treated with behavior-modifying drugs to practice so-called "substance abuse" as they mature? Barkley[37] succinctly answers this question as best it can be answered at present:

> There are no reported cases of addiction or serious drug dependence to date with these medications. Several studies have examined the question of whether children on these drugs are more likely to abuse other substances as teenagers than those not taking them. The results suggest that they are not, although more research is needed to rule this out conclusively. Nonetheless, the possibilities are viewed as remote by most investigators in this area.

The experience of the investigators at the University of Illinois indicates that a much more difficult problem is to keep children on stimulant medication as they approach or reach the teen years. Many children of that age are still demonstrably helped by medication in important ways, and yet taking stimulants is so aversive to many patients that if they do not intransigently refuse to take the medication, they may resort to subterfuge.[7] A group of 52 patients, representative of the several hundred children who had been followed over a period of 8 years, were interviewed in depth and their records were carefully examined to determine accuracy of the information provided the interviewer. Three-quarters of the interviewed group who were 12 years of age or older expressed a powerful dislike of taking the stimulants, or their records provided repeated evidence of efforts to avoid taking them. Their reasons for disliking medication are revealing and surely have a place in this discussion of side effects of methylphenidate (Table 4–1).

**TABLE 4–1. SPECIFIC REASONS GIVEN IN INTERVIEWS FOR DISLIKING MEDICATION**

| Reason/Example(s) | Number[a] |
|---|---|
| Does not need | 15 |
| Physiological side effects | 10 |
| Anorexia | |
| Stomachache | |
| Insomina | |
| Causes depression | 6 |
| "It makes me sad and I like to eat" | |
| "I don't want to participate" | |
| "I wouldn't talk or smile or anything" | |
| "I don't want to play" | |
| Causes drugged feeling | 7 |
| "Spaced out" | |
| "Makes me feel strange" | |
| "It numbed me" | |
| "Like I was under hypnosis" | |
| "It takes over of me; it takes control" | |
| Changes perception of self | 10 |
| "Taking it meant I was dumb" | |
| "It makes me feel like a baby" | |
| "Makes me feel like I was different from others" | |
| "Don't feel like myself" | |
| Embarrassing | 4[b] |
| Decreased ability in gym class | 4 |
| "Slows me down" | |
| School performance actually worse | 1 |
| "Drugs are bad for you" | 1 |
| "Wild" after medication wears off | 1 |
| Dislikes but cannot articulate reasons | 2 |
| "I don't know how to explain it, I just don't want to take it anymore" | |

[a]Some children gave more than one reason.

[b]Although only 4 subjects specifically gave embarrassment as a cause for dislike of taking medication, the coders felt that 16 of the 52 subjects interviewed communicated the idea that taking medication was a source of embarrassment to them.

*In Sleator EK, Ullmann RK, von Neumann A: How do hyperactive children feel about taking stimulants and will they tell the doctor? Clin Ped 21(8):474–479, 1982. Reprinted with permission of Clinical Pediatrics, published by J. P. Lippincott Co.*

It is not unusual for a physician who is willing to prescribe stimulants to the primary school child to refuse to provide such medication to children of 12 or older. There seems to be no research support for this practice and the reason for its prevalence is a mystery. If a teenager is helped by medication, and is willing to take it, there is no reason why he or she should not have it. A teenager would never be denied behavioral interventions for behavior disorders, so why should the patient be denied another treatment of known efficacy?

## DRUGS OTHER THAN STIMULANTS USED IN THE TREATMENT OF ADD

There are two classes of drugs which, in at least some medical circles, are considered useful in the treatment of ADD. These are the tricyclic antidepressants, especially imipramine (Tofranil), and the major tranquilizers thioridazine (Mellaril), a phenothiazine, and haliperidol (Haldol), a butyrophenone. According to the Safer and Krager[8] 1981 head count of all Baltimore County public and parochial elementary school children taking medication for hyperactivity, 2 percent were taking nonstimulnt drugs; thioridazine is mentioned as one of those drugs. They have been studied in ADD children (although vastly less so than have the stimulants) and, somewhat unexpectedly, produce stimulant-like effects. As these drugs are capable of causing devastating side effects, the physician needs to know, should he or she consider prescribing them, if they have important advantages over the stimulants.

### Tricyclic Antidepressants

A brief review of the reports of two well-done studies will suffice to give a picture of the range of research results.

Rapoport and associates[38] carried out a double-blind study comparing imipramine, methylphenidate, and placebo given to 76 hyperactive grade school boys. Both drugs were significantly more effective than placebo, but "all measures favored the stimulant drug," and on "objective" tests, improvement was confined to children on methylphenidate. There were many more side effects with imipramine than with methylphenidate: much greater appetite decrease, much more constipation, more insomnia, much more drowsiness, more headache, much more nausea, and much more sadness. The investigators were constrained from titrating dose to what they thought may have been a more effective therapeutic level of imipramine because of side effects. Maximum dose was 80 mg/kg.

Werry and associates,[39] limiting dose to 1 mg/kg in one group and 2 mg/kg in another, found that imipramine resulted in behavior and performance remarkably similar to that of methylphenidate—that is, it produced a stimulant-like effect. Increasing the dose from 1 to 2 mg/kg did little more than increase side effects; the authors suggest that commonly approved doses may be too high.

Werry and associates found the cardiovascular side effects especially noteworthy. Mean pulse rate was 77 per minute on placebo, 79 per minute on methylphenidate, and 95 per minute on imipramine.

Elevation in blood pressure was small and essentially the same for methylphenidate and imipramine.

The cardiovascular side effects are troublesome. Winsberg and associates[40] found marked tachycardia and heart block in seven children following 5 mg/kg/day of imipramine. Three of the children developed first-degree atrioventricular block. There is a report in the literature[41] of a 6-year-old girl being treated with imipramine for school phobia who, recalcitrant to treatment, gradually had her dose increased. Given a 300-mg dose at bedtime, she was found dead 3 hours after administration of the drug. The final cause of death given by the medical examiner was Tofranil intoxication.

In 1972 an article appeared in a British journal with the arresting title "Poisoning as a Complication of Enuresis."[42] At that time, imipramine, widely available in households for the treatment of enuresis, was the second most important cause of poisoning of children after aspirin!

Dr. Thomas Hayes, Chief of the Psychopharmacology Unit of the FDA, and his colleagues published in the *American Journal of Psychiatry* an important statement on the subject of imipramine use.[43] Recognizing that the drug is used clinically in a variety of conditions other than the approved enuresis, often at higher doses than recommended, they expressed concern about the attendant toxicity with the possibility of the administration of a fatal dose. They feared that the doses being used in a variety of conditions had "merged with the range of hazardous doses." Recognizing that more requests for investigational use of imipramine in children would be forthcoming, Hayes and associates stated the FDA plans to limit the allowable dosage: 90 mg for a 40-lb child, 110 mg for a 50-lb child, 135 mg for a 60-lb child, 150 mg for a 70-lb child, and 180 mg for an 80-lb child. They also plan to recommend regular EKG monitoring when doses approach these limits. Despite this expressed willingness in 1972 of an authoritative representative of FDA to allow more research on imipramine for various pediatric conditions, it is most interesting that in 1985 the only approved indication for imipramine in children is still nocturnal enuresis.

## Major Tranquilizers (Antipsychotics or Neuroleptics)

A similar situation to that described for antidepressants in the treatment of ADD obtains for the major tranquilizers. Most of the studies looking at the efficacy of these drugs in ADD find change in the desired direction. Again, a brief review of two reports should suffice to give an adequate conception of the nature of the effects of these drugs.

Gittelman-Klein and associates[44] found methylphenidate, thioridazine, and a methylphenidate/thioridazine combination superior to placebo. Methylphenidate alone and the methylphenidate/thioridazine combination were most effective.

Werry and Aman[45] systematically studied and compared the cognitive effects of methylphenidate and haloperidol in ADD. They found that methylphenidate and, to a lesser extent, the low dose of haloperidol (0.05 mg/kg) facilitated performance, whereas there was a trend toward the high dose of haloperidol (0.25 mg/kg) causing a slight deterioration in cognitive performance.

But the potential side effects of the major tranquilizers are far from trivial. The most feared complication is tardive dyskinesia (TD). The American Psychiatric Association's Task Force Report on Dyskinesia[46] provides a vivid description of the condition:

> Tardive dyskinesia (TD) is an involuntary movement disorder that may appear after several months of treatment with antipsychotic drugs. It may be either permanent or transient and is characterized by a variable mixture of orofacial dyskinesia, chorea, athetosis, dystonia, tics, and facial grimacing. Orofacial and lingual dyskinesia and dystonia are traditionally considered the most characteristic and well recognized features of TD. Typically insidious in onset, such movements may initially be detectable only as mild forward-backward (snail-like contraction) or lateral tongue movements when the patient is asked to hold his mouth wide open with the tongue lying on the floor of the mouth. In some patients, however, tic-like movements of the lips or face or frequent blinking are earlier signs of TD. Later, more obvious protruding, twisting, and curling movements of the tongue; pouting, puckering, sucking, or smacking lip movements; retraction of the corners of the mouth (bridling), bulging of the cheeks, and various forms of chewing or lateral movements of the jaw may occur individually or in various combinations. Blepharospasm, brief upward deviations of the eyes, arching of the eyebrows, and a variety of facial grimaces may also occur.

The facial distortions described above are clearly disturbing to the patient and grossly disfiguring. However, the dyskinetic movements often extend to all parts of the body as well as to the muscles of deglutition as described above.

These drugs are a particular menace when used chronically which, of course, is often the case in ADD. However, according to the task force, TD may appear after as little as 3 to 6 months of use or even a shorter period of time. The danger of TD in children after treatment with Mellaril is not hypothetical. Gualtieri has seen 2 cases of severe and persistent TD in hyperactive children who were

treated as outpatients for several years with large doses of Mellaril (personal communication).

Gualtieri, in a letter to the editor of the *Journal of the American Academy of Child Psychiatry*[47] discussing the clinical use of the antipsychotics, says: "A drug must be effective indeed, and alternative remedies particularly unavailable, to warrant that kind of risk."

It has been found that 18 of 41 children, adolescents, and young adults withdrawn from chronic neuroleptic treatment developed tardive dyskinesia, nondyskinetic withdrawal symptoms, or transient behavior deterioration.[48] Nevertheless, one of the approved indications for both thioridazine and haloperidol is in the "short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorder."[49] It is clear that the antipsychotics should be used in children only by those extensively experienced in its use and committed to meticulous monitoring of treatment effects.

It is possible, certainly, that when behavioral abnormalities are present in addition to ADD, imipramine or thioridazine might be indicated. For example, if panic attacks and hyperactivity are both present, imipramine, felt to be helpful in panic, might be useful.[50] Or if psychotic aspects were present in a child with ADD, thioridazine treatment might well be considered, but such a child would very likely be under the care of a psychiatrist.

Would the antipsychotics or antidepressants be effective therapy in the case of an ADD child who did not respond to stimulants? Winsberg and associates[51] have examined this question for imipramine and have found it to be ineffective in children who failed to respond to methylphenidate.

## DIETARY TREATMENT

### Feingold Diet

It is tempting to discuss the history of the Feingold diet at some length because it is representative of a kind of sociological phenomenon that can have a major impact on the health care practices of the American public. As a result more space will be allotted to this diet than is warranted by its role in the clinical management of ADD. Not only is it controversial, but there has been a good deal of interesting research devoted to evaluation of the diet. Unfortunately, one vital piece of information relevant to the importance of the diet is missing: there seems to be no information on the extent of the use (or attempted use) of the diet now or in the past. Nevertheless, one can

safely assume that some knowledge of the research foundation that determined its nature and proved or disproved its efficacy will at one time or another be of use to the practicing pediatrician.

Dr. Ben Feingold was a pediatrician and allergist at Kaiser-Permanente in California. The highly public portion of his career began when he gave a presentation at an American Medical Association meeting in 1973 and described some observations he had made as a practitioner. His claim was that about half of all the hyperactive children he treated with his salicylate and artificial color- and flavor-free diet showed greatly improved behavior, other treatment became unnecessary, and that even a minor infraction of the diet would turn a calm, attentive child into his old uncontrollable self for up to 72 hours.[52]

The Feingold claim hit a responsive chord with first the press, and then other media, and then public officials and the public. His presentation was given extensive media coverage, it was read into the Congressional Record, he was interviewed by newsmen, and he began to appear on talk shows. He subsequently wrote a book called *Why Your Child Is Hyperactive*[53] and finally a K-P diet cookbook.[54] Although there are no numbers, it was believed that a great many people put their children on the K-P diet, reported gratifying effects, and some organized themselves into vocal groups of passionate Feingold devotees.

Feingold's diet grew from his observations of adults who were sensitive not to food dyes but to salicylates. When aspirin was eliminated, some of these adults continued to have the symptoms which Feingold felt had been elicited by aspirin. He then eliminated foods that he believed to contain naturally occurring salicylates. The same individuals also demonstrated hypersensitivity to tartrazine (yellow dye no. 5) and, as the chemical structure of several artificial flavors contain a segment that is similar in appearance to salicylates, he theorized that these additives were likewise involved. On this basis, he constructed a "salicylate-free diet" that excluded food containing natural salicylates, artificial flavors, and all forms of aspirin. Because Dr. Feingold observed that some of the symptoms of aspirin sensitivity were behavioral, he developed the hypothesis that hyperactivity and learning disabilities were also due to salicylates.[55]

The Feingold diet, published in the 1975 book by Feingold, *Why Your Child Is Hyperactive*,[53] excludes among other foods almonds, apples, apricots, tomatoes and all tomato products, cucumbers, many berries including raspberries and strawberries, cherries, currants, grapes, raisins, oranges, peaches, plums, and prunes; all manufactured cakes, cookies, pastries, sweet rolls, doughnuts and piecrusts; bologna, salami, frankfurters, sausages, meatloaf, ham, bacon, pork, self-basting turkeys, and frozen fish; manufactured ice cream, des-

sert mixes, and chocolate syrup; flavored yogurt; all manufactured candies, hard or soft; cider, soft drinks, and prepared chocolate milk; and oleomargarine, colored cheeses, mustard, and catsup.

The nuts, fruits, and vegetables listed above are excluded from the K-P diet because Feingold believed they contained high levels of salicylates acquired naturally, but the Del Monte Research Laboratory scientists found lower levels of salicylates in many of the excluded fruits and vegetables than in fruits and vegetables that were not excluded.[55] The University of Wisconsin Food Research Institute also found that most fruits do not contain significant amounts of salicylates and, on inquiry, the Wisconsin investigators learned that Feingold based his exclusion of fruits on a study done in Germany at about the turn of the century![56]

The exclusion of fruits and vegetables was not a popular aspect of the K-P diet, and Dr. Feingold eventually modified it: salicylate-containing food could be gradually reintroduced if there were no adverse reactions as they were eaten.

Both the FDA and the Nutrition Foundation (a food industry organization) assembled committees whose members had impeccable credentials to examine the Feingold claims. Both committees reported that Feingold's method of subject selection and evaluation of results were not clear and there were no double-blind studies or adequate controls.

A series of studies were then performed and published, some of excellent quality. The research was of two kinds, crossover studies and challenge experiments. In the diet-crossover study, a group of hyperactive children is selected and placed on either the K-P diet or a placebo diet disguised to resemble the K-P diet but containing salicylates, artificial colors, and artificial flavors. After varying amounts of time the children are switched from one diet to the other; during the entire experiment, observational and laboratory test measures are taken.

In the challenge experiments a group of children who appear to be improved to some extent by the K-P diet are maintained on the restricted diet. They are occasionally fed a challenge food (e.g., cookie, soft drink) that contains the forbidden additives, or a placebo; measurements and observations are made. Crossover experiments have in several cases been followed by challenge experiments.

The earliest experiment to have much impact was done by Conners, an established investigator in hyperactivity research, who together with associates conducted a diet crossover study on 15 children.[57] The teachers found significant improvement when the subjects were on the K-P diet. This study, however, has been criticized for looseness in blinding and poor supervision of dietary intake of the subjects.[58] In addition, Sprague at the University of Illi-

nois[59] reanalyzed the Conners data and found a pronounced interaction between diet and diet order. His conclusion was: "The strongest statement that should be made is that the K-P diet did improve teacher ratings in only the groups which received the control diet first and the K-P diet second." Such data suggest that something other than the diet was influencing results.

Conners' crossover study was followed by a challenge study.[60] The 15 school-age children who appeared to respond to the K-P diet were, under double-blind conditions, challenged with the experimental cookies; deterioration in behavior did not occur in any of the subjects in either teacher or parent observations, or in the results of a visual-motor tracking test. In another challenge study with 8 preschool children who had, according to their parents, improved on the Feingold diet, the parents saw a deterioration in behavior when the children were given the artificial dyes. Conners concluded that their data "suggested that artificial dyes do act to impair and disrupt the behavior of children . . . and may be particularly disruptive to younger children."[60] Stare and associates[61] comment on this work: "With such small samples and a clear conflict in experimental results, the qualification of their conclusions with the term 'suggest' is absolutely necessary. Unfortunately, many have ignored that antecedent when interpreting the significance of the work conducted by Conners and Goyette in Pittsburgh."

Harley and his associates[62] at the University of Wisconsin performed two diet crossover studies and a challenge experiment. A major effort was made to maintain blind conditions on the part of all participants and observers. During the first crossover study each group was on each diet for 3 weeks; during the second crossover study there were 4-week periods on each diet. Before the special diets began (and all children had been off medication for 2 weeks), each child had a neurological and physical exam, neuropsychological data were collected, and laboratory observations were obtained. An average of 3 classroom observations were carried out on the subject and a normal control by trained observers each week throughout the study; weekly ratings by parents and teachers on a standardized scale were also obtained on subjects. Special efforts were made to obtain dietary compliance, including special meetings with the parents and documentation of infractions of the diet. All previously purchased foods were removed from the house, and each family's entire food supply was delivered to the homes weekly. All family members were placed on the diet to reduce the temptation of the subject to eat other foods. Arrangements were made by the research dietician to deliver the birthday treats usually provided by the birthday child in any classroom in which there was an experimental subject. Pseudo-dietary manipulations and distractions were incorpo-

rated into the diets (e.g., hot dogs, potato chips, and cookies might be provided one week and absent the next week, although these items as provided by the research dietician were permitted on both the control and experimental diets). The neuropsychological evalutions made at the end of baseline and each diet period included tests of general intelligence, memory, motor speed and coordination, reaction time, vigilance, concentration/attention, and basic academic skills.

Their research led to a conclusion that was quite different from that of the Pittsburgh team. Only parent ratings showed a significant diet effect; only 4 of the 36 children were rated by both parents and teachers as improved on the K-P diet; the improvements found, although statistically significant, were small; and, as with Conners' data, positive effects of the diet were primarily restricted to the sequence of control diet first and experimental diet second. The reason for the persistence of this finding is not clear; work done by Werry and Sprague[63] found analogously that second baseline ratings by parents and teachers consistently scored the children better than the first rating although there had been no therapeutic manipulations whatsoever.

The second diet crossover study done in Wisconsin[62] had 10 preschool children as subjects and used, therefore, only parent rating and neuropsychological tests to measure diet effects. The parents' ratings showed a significant diet effect, with all mothers rating the children as improved when salicylates, artificial colors, and artificial flavors were eliminated from the diet. The neuropsychological tests showed no diet effect.

The Wisconsin challenge study[64] included 9 children who had appeared to respond to the Feingold diet with a reduction in hyperactivity. Parent and teacher ratings, classroom observations by trained raters, and neuropsychological test scores obtained during baseline, challenge, and placebo did not show deterioration by the artificial color challenge material. There was a suggestion that one child may have had some adverse effects when results were individually analyzed.

Stare,[61] who compared the Pittsburgh to the Wisconsin research in his *Pediatrics* article, stated:

> The conclusions of the Wisconsin and Pittsburgh researchers differed. Interpreting their data, a reviewer must consider several factors. The Wisconsin study had closer diet supervision and was much more effective in disguising the diet. In addition, they had more measure of the dependent variable and a larger sample than the Pittsburgh experiments. These differences lead one to attach greater importance to the data of the Wisconsin researchers.

Williams and associates[65] in Toronto compared the beneficial effects of stimulant drugs with those of the K-P diet on 26 school-age hyperactive children. Both parent and teacher ratings showed that stimulant medications were clearly more effective than diet. The diet effects were inconclusive in the parents' ratings. Minor beneficial effects of diet were found in teachers' ratings only when the children were receiving placebo medication. Williams concluded that the diet had small but ambiguous effects.

Weiss and his colleagues[66] used as their subjects 22 children between the ages of 2.5 and 7, none of whom had been diagnosed as hyperactive. However, their parents felt they had some problem behaviors, had placed them on the K-P diet, and reported improvement in the behaviors. The parents selected, in each individual case, seven behaviors which they found aversive and on each day of the study they conducted two 15-minute observation periods, one within 3.5 hours after the challenge was taken and one at a later time. During these observation periods they recorded the frequency of occurrence of the seven target behaviors. A soft drink was taken daily on each of the 77 days of the study. On 8 days randomly distributed among weeks 3 through 10 of the study period, each child received the challenge drink. The challenge material was a soft drink containing 35.6 mg of artificial colors. During the entire time the children were otherwise maintained on the strict K-P diet although some parents did not restrict the designated fruits and vegetables, claiming their children were not sensitive to them.

Parents of only two children reported results that could be considered to show any effect of the additives; one of these can hardly be considered significant. In that case, a 3-year-old boy showed an elevation in two of the seven target behaviors during three episodes. In one 34-month-old child the results were felt to be dramatic: five of the seven aversive behaviors were worse after challenge, and the mother correctly recognized the challenge soft drink five out of eight times it was given. Weiss and associates reach the same conclusion from these results that they had drawn before the experiment was actually complete (personal observation)—that is: "These data further strengthen the accumulating evidence from controlled trials [here they quote Conners and colleagues] supplemented by laboratory experiments that modest doses of synthetic colors, and perhaps other agents excluded by elimination diets, can provoke disturbed behavior in children." No doubt with one child showing what appear to be unequivocal results, this statement is strictly true, but it is certainly a powerful overstatement with respect to the clinical usefulness of this dietary intervention.

According to Stare[61] writing in *Pediatrics*, the nine investigators conducting the Weiss and associates research differed among them-

selves in their interpretation of the significance of this one child's response, and some of them felt the findings should not be used to either negate or support the hypothesis.

For the reader who is sufficiently interested in this subject to go to the original literature, an excellent beginning would be a paper by Mattes and Gittelman[67] published in 1981 in the *Archives of General Psychiatry*. Not only is there a complete, succinct, and objective literature review but the experiment they conducted is particularly intriguing.

Their subjects were obtained by solicitation of chapters of the Feingold Association; children were accepted only if parents reported that the child was cooperative in limiting food intake to acceptable foods, and that ingesting artificial food colors produced behavioral deterioration quickly and dramatically. The children were maintained on the diets that had so successfully controlled their behavior, and given under blind conditions either placebo or challenge cookies. The dose of food additives was larger than in other experiments, and corresponded to that which is said to be consumed by the average American child (earlier studies had been criticized for giving inadequate doses of additives). In addition, "to maximize the likelihood of finding a significant diet effect, all children were given a nonblind one-week trial of placebo cookies prior to the double-blind investigation. Children who reacted adversely to the placebo were eliminated from further study." This is an unusual but admirable precaution.

Results? "None of the ratings by parents, teachers, children, psychologists, psychiatrists demonstrated significant differences between placebo and artificial colorings. Moreover, no type of rater (parents, teachers, psychiatrists, nor children) guessed beyond chance the type of cookie. . . . This study, which was designed to maximize the likelihood of detecting a dietary effect, found none." The possibility that the challenge cookies were not properly labeled was suggested by members of the Feingold Association. Ten cookies were then analyzed blind; in every instance the analysis corresponded to the research code.

A summary of seven challenge studies is provided in the final report of the advisory committee.[55] To quote directly:

> Of approximately 190 children there have been no instances of consistent, dramatic deterioration in behavior in hyperactive children challenged, under double-blind conditions with artificial food colorings following treatment with the diet that removes these substances. There are three instances that constitute exceptions to these generally negative conclusions, but, in all three cases, the deterioration is reported only by the mother with no other objective, confirming evidence available.

Despite the raising of the shibboleth of "objective evidence" when it is obvious that in behavioral disorders the best, if not the only worthwhile evidence of the nature and severity of the problem in children is observation of the behavior, the quality of the data in these three cases *is* poor. Two of the three who were felt to deteriorate on the active challenge cookie were school children and the teacher did not see a change. This suggests that in those cases the changes were minor and very subtle. In the case of the nonschool-attending child, the mother was able to identify the challenge food in five out of eight cases, which is quite impressive. This 3-year-old was very likely the only true responder, which means a percentage of responders of 0.5 percent. However, liberally accepting all three as responders, we get a percentage of 1.6 percent responders when the effects of food coloring were studied under blind condition. This is a far cry from Feingold's claim that 50 percent of hyperactive children showed greatly improved behavior when on this diet.

Apparently, many parents have seen wonderful changes in their children when the Feingold diet is imposed. Why is this? One must recognize that the Feingold regimen possesses many nonspecific treatment chracteristics that would be expected to produce a powerful placebo response. The whole family is urged (and such devoted families are likely to comply) to go on the diet to give moral support to the child and eliminate any forbidden fruits from the household. Everybody has to change their eating habits and, as most preprocessed foods are forbidden, the family must prepare food from scratch; Feingold urges that the child assist in this time-consuming food preparation. All of these changes alter routines and the family must think about dietary choices much of the time. Food, rather than an annoying child, becomes the culprit. And as any family that has the fortitude to go on this diet must consist of true believers to begin with, *they will greatly desire that the diet prove successful: they will be actively looking for and responding positively to any evidence of improved behavior in the child.*

It appears that most of the therapeutic effects of the Feingold diet are a nice demonstration of the wholesome effects of expecting the best to happen and the benificent effects on the behavior of children (as well as adults) of love and praise. The placebo effect can be of great benefit to those in need and the physician should never say a discouraging word to those who are benefiting. The accumulation of valid and reliable knowledge is the goal of investigators and such knowledge will not be advanced unless we clearly distinguish between nonspecific and specific effects of intervention. This is not to say, however, that the practioner who listens to parents describing the great benefits of eliminating one thing or another from the

child's diet should not look pleased, nod his or her head wisely, and congratulate the parents.

## Sugar as a Cause of Behavior Disorder

Wolraich and associates[68] feel that there has been a lessening interest by parents in using the onerous Feingold diet in an effort to improve their child's behavior. But in our culture, so seemingly determined to attribute much of life's difficulties to the modern diet, can another villain be far behind? Indeed not. Testimonials on the part of parents claiming the conversion of little child monsters to little child angels by the restriction of sweets (never honey, which contains some sucrose, for honey is not only benign but profoundly beneficial) are commonly heard. According to Wolraich, "the conviction that parents feel concerning the role of refined sugar in accounting for their child's problems appears to be both more strongly held and more widespread than that associated with additives." Parents are said to report that eating refined sugar produces dramatic change within one-half hour.

None of the few systematic studies testing the sugar hypothesis have produced results supporting the concept that sugar is the culprit in ADD children. Gross[69] found and reported one child (and his mother as well) who by blind tests were found to have definite unpleasant behavioral and subjective reactions to sugar. In 50 other ADD-H children whose mothers were sure their behavior deteriorated when sugar was taken, the mother was unable to distinguish between behavior following a lemonade challenge, sweetened randomly with sugar or saccharin. Gross concluded that hypersensitivity to sucrose can exist but it is rare. He suggests a simple blind challenge experiment be done if there is some "compelling reason" to suspect sucrose hypersensitivity.

Wolraich and associates[68] maintained 16 ADD-H boys on a sucrose-free diet in a live-in clinical research center for 3 days. Baseline laboratory tasks measuring learning, attention, and impulsivity, as well as baseline systematic playroom observations were made on the first day. On the second and third days, a challenge drink was given after lunch, and the drink contained either 1.75 mg/kg of sucrose or an equivalent sweetness of aspartame. One-half hour after the challenge drink the measures performed at baseline on the first day were repeated. In a second study, the boys received the challenge drink the first thing in the morning in the absence of any other foods. This was to rule out the possibility that taking the challenge after lunch might have attenuated the effect of the sugar intake. One

analysis was done on all subjects and a second analysis was done on just those boys whose families were restricting sugar intake to improve behavior.

Wolraich and associates found no significant differences or even trends under the two conditions of a sugar or aspartame challenge, and they concluded that "sucrose does not adversely affect the behavior of school-age children."

Behar and associates[70] studied 21 boys who were felt by their parents to show adverse behavioral effects after eating dietary sugars. Nine were ADD, four ambiguous problems, and eight had no psychiatric diagnosis. Challenge doses of 1.75 mg/kg of glucose or sucrose were alternated with a saccharin challenge. Far from supporting the sugar-producing-hyperactivity hypothesis, their main positive finding was that the sugar produced a significant *decrease* in motor activity at 3 hours. Behavioral ratings and measures of attention and memory showed no consistent or significant change following sugar challenges.

The pediatrician will surely meet parents who are eloquent on the subject of the beneficial behavioral effects on their children of withdrawing sweets from the diet. Again, it will be wise to refrain from attempts at enlightenment by describing controlled research results. Such statements will not be believed and the physician's wisdom will be questioned. It is also likely that if the parents see the child as improved and express pleasure and approval resulting from the change the child is, indeed, better off.

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