Childhood Hyperactivity: A New Look at Treatments and Causes

Hyperactive children are difficult to deal with. Their schoolwork is poor, their classmates shun them, and their parents and teachers disapprove of them. But treating the symptoms of hyperactivity and alleviating the children's social and behavioral problems are two separate matters, as researchers are increasingly coming to appreciate.

Investigators have studied hyperactive children for nearly 50 years. Yet many commonly held assumptions about the causes and treatments of this disorder remained untested. Results from current research examining some of these assumptions indicate that a number of them are erroneous. These results are leading investigators to reevaluate the role of stimulant drugs in treatment programs and to discard some models of hyperactivity.

Stimulant drugs—namely amphetamines and methylphenidate (Ritalin), which acts like an amphetamine—are the most commonly prescribed treatment for hyperactivity. According to Judith Rapoport of the National Institute of Mental Health (NIMH), those who study hyperactivity are in unanimous agreement that these drugs dramatically improve hyperactive children's behavior when the children take them for short periods of time (up to 6 weeks). In fact, Rapoport says the stimulants exert what is probably the most powerful behavioral effect of any drugs she knows.

It was first noted in the 1930's that amphetamines seem to calm hyperactive children, and in the 1950's and 1960's these drugs were hailed as panaceas. Leon Eisenberg of Harvard Medical School points out that it is not hard to see why stimulants gained such widespread acceptance. They seemed to have few toxic side effects, and they diminished the overt symptoms of hyperactivity. "They allow the child to sit still and appear to pay attention in the classroom," Eisenberg says. The assumption was that the child's academic performance should improve.

Few studies have been carried out of the long-term effects of stimulant drugs on hyperactive children's academic performance and behavior. Robert Sprague of the University of Illinois explains that it is difficult to find control groups for such studies because most children who have been diagnosed as hyperactive are being treated. One of the only controlled studies was made by Gabrielle Weiss and her associates at Montreal Children's Hospital. Their control group consisted of hyperactive children diagnosed and followed for 5 years before stimulants had become the accepted treatment. Their treated group consisted of children diagnosed at a later date and treated with methylphenidate. The children were divided into three groups: 24 treated with methylphenidate for 3 to 5 years, 22 treated with chlorpromazine for 18 months to 5 years, and 20 who received no medication. The children were matched for age, IQ, and socioeconomic status.

The results of the study by Weiss and her associates, which were reported in 1975, astonished many researchers. These investigators found no significant differences among the three groups of children on measures of emotional adjustment, delinquency, IQ, visual-motor coordination, and academic performance. According to Eisenberg, no one has ever demonstrated that children treated solely with stimulant drugs subsequently do better in school.

Drugs Are Widely Prescribed

Despite these indications that stimulant drugs may not, by themselves, be an appropriate treatment for hyperactive children, the drugs continue to be widely prescribed. For example, James Bosco and Stanley Robin of Western Michigan University recently surveyed children in Grand Rapids, Michigan. Most of the children diagnosed as hyperactive were treated with stimulants, particularly methylphenidate, and were given no other treatment, such as special counseling.

The finding that stimulants do not appear to improve children's school performance is, on the face of it, surprising. Numerous investigators have reported that children given stimulants show improvement in laboratory tests of learning. According to Eisenberg, however, a correlation between laboratory and school learning has yet to be demonstrated. And even if the two were correlated, children might develop a tolerance to the stimulants when they take the drugs for long periods of time.

Sprague suggests another explanation for the poor academic performances of children given stimulants. He and Esther Sleator—who is also at the University of Illinois—have evidence that doses of stimulants that calm hyperactive children may be so high that they inhibit the children's abilities to learn.

Sprague and Sleator tested children's memories by asking them to look at a group of pictures. They later showed the children particular pictures and asked them whether those pictures appeared in the original group. The children's teachers assessed their hyperactivity by means of a commonly used questionnaire developed by Keith Connors of the University of Pittsburgh.

Sprague and Sleator found that the children's performance on the memory test peaked at a dose of methylphenidate that was less than one-third the maximally calming dose. At the maximally calming dose, the children's memory performance was actually worse than it was with placebo. Moreover, the best dose for increased learning did not increase the children's heart rates, whereas the best dose for behavior control did; heart rates rose from an average of 85.2 beats per minute with no medication to an average of 95.7 beats per minute with the maximally calming dose.

Sprague and Sleator's results are a bit difficult to reconcile with results of others, who find that children's performance on laboratory learning tests improved with the maximally calming dose of stimulants. One possible explanation for this apparent anomaly is that the drugs affect performance on different learning tests in different ways.

Sprague says that the most important conclusion to be drawn from his and Sleator's results is that children may be routinely given doses of stimulants that are too high. One common clinical practice is to increase a child's dose of stimulants until the child experiences undesirable side effects and then to decrease the dose slightly. Such high doses may not only impair the child's ability to learn, Sprague says, but will also increase the child's heart rate and blood pressure. When a child takes the drugs for many years, the increased heart rate and blood pressure may be harmful.

Sprague and many other researchers say that stimulant drugs have a place in the treatment of hyperactivity but that the drugs should be given only for short periods of time. "Seriously disturbed children are helped within a few hours after they take the drugs. This gives parents and teachers a breathing spell, a chance to start again," Sprague says. The long-term treatment of hyperactivity, many researchers believe, should include behavior modification, counseling, and changes in school curricula.

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Of course, it is much more difficult and expensive to treat hyperactive children with behavioral therapy and special education and counseling than with drugs. Investigators hope that clues to improved treatment and possibly even preventive measures might stem from an understanding of what causes the disorder.

In their search to understand the etiology of hyperactivity, investigators have tried to pinpoint the distinctions between normal and hyperactive children. This task, however, has proved difficult. According to Eisenberg, electroencephalograms don't help at all in diagnosis, and neurological examinations are uninformative. The major trait that distinguishes hyperactive children is their inability to control their movements when control is required, such as in a classroom.

Some researchers and clinicians add another diagnostic criterion to this behavioral one. They claim that most hyperactive children are calmed by stimulant drugs and that normal children are not. Physicians sometimes use this so-called paradoxical response of hyperactive children to the stimulant drugs as a confirmation of their suspicions that particular children are hyperactive.

Researchers noted that concentrations of certain neurotransmitters and neurohormones, such as dopamine and norepinephrine, are affected by these stimulant drugs, so they hoped the hyperactive children's paradoxical response might provide a key to the causes of hyperactivity. They developed animal models of hyperactivity in which, for example, various lesions in an animal's brain or injections of neurotransmitters caused it to become hyperactive and to be susceptible to sedation by stimulant drugs.

Although the notion of the paradoxical response has won widespread acceptance, a number of researchers have questioned its validity. They noted that many adults are calmed by doses of amphetamines or methylphenidate comparable to those given to hyperactive children and that adults, as well as hyperactive children, tend to do better on some laboratory tests of learning after taking stimulant drugs. The obvious way to resolve the question of whether the paradoxical response of hyperactive children is actually paradoxical is to give stimulants to normal children. But most researchers steered clear of such studies, fearing the ethical problems associated with them.

Recently, a group of investigators at the National Institute of Mental Health (NIMH) broke through this ethical barrier and studied the effects of amphetamines on normal boys, aged 6 to 12 years. The investigators, led by Rapoport and Monte Buchsbaum, report that the normal children respond the same way to a single dose of these drugs as did a group of hyperactive children. Both groups had markedly decreased motor activity when they took amphetamines (as opposed to placebos), and both did better on certain cognitive tests.

Rapoport says she thought about studying the effects of amphetamines on

Food Additives and Hyperactivity

For the past 5 years, many members of the public have been intrigued by a theory that food additives cause hyperactivity. This theory was put forth in 1973 by Ben F. Feingold, an allergist at the Kaiser-Permanente Medical Center in San Francisco. Feingold developed a diet in which foods containing synthetic colors, synthetic flavors, and salicylates are banned. He reported that 50 percent of hyperactive children dramatically improved their behavior when they followed his diet.

Last year, in response to the huge acclaim for the Feingold diet, J. Preston Harley and his associates at the University of Wisconsin tested the effects of the diet with a controlled clinical trial. Forty-six hyperactive boys who participated were observed for 8 weeks by parents, teachers, neurologists, and trained observers. Some of the children followed an additive-free diet and some did not, but neither the children, their parents, nor the other observers knew which child followed which diet. The University of Wisconsin researchers went so far as to supply all food for each child's family during the course of the trial. In addition, Harley adds, "If a child's class at school had a party, we provided all the refreshments."

The results of this study failed to confirm Feingold's claims. In fact, Harley and his associates report no effects of the additive-free diet on hyperactivity of school-age children. Most researchers accept the results of the University of Wisconsin study, although many members of the general public do not. As Robert Sprague of the University of Illinois points out, the Feingold diet is clearly less effective than stimulant drugs in modifying the behavior of hyperactive children.

Feingold, however, says that the University of Wisconsin study was biased because it was supported by the Nutrition Foundation of New York—a group he describes as "100 percent industry." He also claims that the children cheated on their diets when they were at school. (This claim is vehemently refuted by Charles Matthews of the University of Wisconsin, who is a member of the group that conducted the study.) Finally, Feingold points out that 4 out of 36 of the school-aged children's behavior improved on the diet, as rated by both their parents and teachers. Nonetheless, Matthews replies, the behavior of the other children was either rated uniformly worse on the Feingold diet or else the parents rated a child's behavior one way and the child's teacher rated it the opposite way when the child was on the additive-free diet.

Many parents still swear by the Feingold diet, and their experience cannot necessarily be dismissed. Some psychologists suggest that children's behavior improves not because of the diet, but because of the increased attention paid to the children when they are on the diet. Of course, it remains possible that the diet does help some children. Keith Connors of the University of Pittsburgh has some evidence that the behavior of a small fraction of hyperactive children might improve with the diet. He finds that the behavior of most children, however, is not affected by it.

The Feingold diet is regarded by some researchers as just another item in a long string of purported cures for hyperactivity. Sprague and his associate Esther Sleator tick off a list of suggested causes of hyperactivity, including refined sugar, hypoglycemia, fluorescent lighting, tight underwear, undiscovered organic illnesses, and, of course, food additives. The cures are to remove these causes. Sprague and Sleator remark that these treatments "are neither based on logic nor have any data which includes the essential observations on untreated controls." But it seems likely that as long as hyperactivity remains unexplained and as long as conventional treatments remain unsatisfactory, new, unsubstantiated, and sometimes bizarre treatments will continue to be adopted by the general public.—G.B.K.

normal children for 5 years before actually planning such an investigation. She and her associates ensured that the children's parents gave informed consent by choosing children whose parents are trained in the biomedical or health professions. They involved the children in the study by asking their opinions of various procedures. For example, the children did not want their blood drawn, so the NIMH investigators measured concentrations of neurochemicals in urine samples instead of in blood. Rapoport and Buchsbaum say the children enjoyed participating in the study and learned a great deal about how biomedical research is done.

Although the NIMH study demonstrates that researchers can no longer use the paradoxical response for clues to the causes of hyperactivity, another study indicates that there may well be specific biological differences between hyperactive and normal children. Mary Waldrop of NIMH and her associates find that hyperactive boys tend to be physically different from normal boys in ways that may mean that hyperactivity results from a congenital defect.

Waldrop and her associates find that hyperactive boys have significantly more minor physical anomalies of certain sorts than normal boys. Consistent with this finding, Patricia Quinn of Georgetown University and Rapoport note that children in hyperactivity clinics tend to have an unusual number of these anomalies and that fathers of these children who report being hyperactive when they were young also have an unusual number of the anomalies. The theory is that these anomalies occur during the first weeks of pregnancy and that whatever causes them could also lead to abnormalities in the development of the central nervous system. For example, children with Down's syndrome have 17 of the anomalies. The anomalies include malformed ears, assymetrical ears, a curved fifth finger, and a wide gap between the second and third toes.

One danger in predicting hyperactivity from the occurrence of minor physical anomalies is that it could become a self-fulfilling prophecy. That is, baby boys with a large number of anomalies would be expected to be hyperactive and would be treated as though they were. This could possibly "cause" the children to be hyperactive. Waldrop points out, however, that she and her associates find very few false negatives.

Girls are far less likely than boys to be hyperactive but are probably equally likely to have minor physical anomalies. Waldrop and her colleagues find that girls with more than the average number of these anomalies are often the very opposite of hyperactive. That is, they are shy, talk very little, and seem overly in control of their movements.

Investigators are still far from pinpointing the distinction between normal and hyperactive children. If the causes of hyperactivity are indeed congenital defects, it is not clear how the disorder may be prevented. For now, researchers are left with drugs and behavioral and educational counseling as means of treating the symptoms of hyperactivity. But progress is being made as researchers continue to question the efficacy of treatments and increasingly come to realize that, in Eisenberg's words, what is usual and customary in medical practice is not necessarily what is safe and useful.

—GINA BARI KOLATA

Gene Structure: More Surprising Developments

Most of what is known about gene expression comes from studies of simple, nonnucleated cells such as bacteria. In these cells, the process is relatively straightforward. First, the DNA of a gene is copied into a corresponding RNA molecule called a messenger (mRNA); then the mRNA directs the synthesis of the appropriate protein, which finally goes about its business as an enzyme or structural component of the bacterial cell. The nucleated cells of higher organisms, however, are much more complicated than bacteria and, consequently, have provided more frustration than information to researchers trying to study how they express their genetic information.

Now that situation is changing. Investigators are beginning to see some progress in their efforts to unravel the secrets of gene expression in nucleated cells. And what they are finding is significantly different from what has been learned about the process in bacteria. A current illustration is the discovery by several investigators that a number of genes from nucleated cells carry within themselves nucleotide sequences (called intervening or spacer sequences) that are not found in the messengers corresponding to the genes. In contrast, bacterial messengers, as far as is known, are direct copies of the genes, without any missing segments. Thus, the nucleated cells apparently have a mechanism, not found in bacteria, for producing mRNA's from which some gene sequences are omitted or deleted.

Similar results were reported last summer concerning the structure of the mRNA's of animal viruses (*Science*, 26 August 1977, p. 853). Because the viruses use the enzymes of the nucleated cells they infect to produce viral components, including mRNA's, investigators hypothesized that both the viral and cellular messengers are synthesized in the same way. At that time, there was already some direct—but still preliminary—evidence supporting this inference, although the researchers studying the structures of the cellular genes and messengers were not yet ready to interpret their findings in that way. Since then, however, an accumulating body of additional evidence has supported the hypothesis.

The work on the structure of eukaryotic (eukaryotes are organisms whose cells are nucleated) genes is proceeding so rapidly that a list of genes found to contain intervening sequences may be out of date before it rolls off the presses. Thus far, spacer sequences have been identified in genes for one of the protein chains (designated the β-globin chain) that form the hemoglobin molecule, in immunoglobulin and ovalbumin genes, and in genes for transfer RNA's (tRNA's) and ribosomal RNA's (rRNA's).

For example, Philip Leder and his colleagues at the National Institute for Child Health and Human Development (NICHD) discovered that two different mouse genes for β-globin contain intervening sequences encompassing some 550 nucleotides. By determining the nucleotide sequence of a portion of one of the genes, they ascertained that the intervening sequence begins immediately after the codon (a sequence of three nucleotides that specifies a particular amino acid) for amino acid 104 of β-globin. Leder and his colleagues also have evidence for the presence of a smaller spacer region near the end of the gene where initiation of mRNA synthesis occurs. Meanwhile, A. Jeffreys of the University of Leicester in England and R. Flavell of the University of Amsterdam in Holland identified a spacer sequence about 600

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