THE NATIONAL ADVISORY COMMITTEE ON HYPERKINESIS AND FOOD ADDITIVES

FINAL REPORT TO THE NUTRITION FOUNDATION

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NATIONAL ADVISORY COMMITTEE ON HYPERKINESIS AND FOOD ADDITIVES

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Preface

The Nutrition Foundation, a public, non-profit institution, is dedicated to the advancement of nutrition knowledge and to its effective application in improving the health and welfare of mankind.

In fulfilling its broad mandate, the Foundation, through symposia and workshops, seeks to obtain authoritative, scientific assessments of issues concerning food, nutrition and health. In so doing, the Foundation draws upon objective expert counsel of independent scientists for these assessments and for planning programs of support for needed competent scientific research. As these assessments of research and its significance are developed by advisory groups, The Nutrition Foundation makes the reports available publicly for the benefit and guidance of the health professions, scientific investigators, advisory and administrative bodies and those responsible for formulating public policy.

Aware of the anxiety created by the widely publicized hypothesis advanced by Dr. Ben Feingold in 1973 implicating many foods and undesignated food additives as potential factors in hyperkinesis, The Nutrition Foundation has supported responsible review of the evidence by a competent group of expert medical and behavioral scientists. The scientists who comprised the review committee were selected and identified by the offices of major scientific and medical organizations: American Medical Association's Council on Foods and Nutrition; American Psychiatric Association; American Association of Child Psychiatry; Society of Toxicology: Council for Exceptional Children; American Alliance for Health, Physical Education and Recreation; Institute of Food Technologists; American Society for Clinical Nutrition; American Dietetic Association; The National Nutrition Consortium; Life Sciences Research Office of the Federation of American Societies for Experimental Biology; Committee on Nutrition of the American Academy of Pediatrics; and the Food and Nutrition Board of the National Academy of Sciences.

The background of the Committee is such as to provide valuable guidance in assessing the design of clinical and experimental investigations of the postulated relationship between hyperkinesis and food.

The first meeting of the Committee was held January 12, 13 and 14, 1975, at Harrison House in Glen Cove, Long Island. In addition to the members of the Committee, resource personnel were invited who could provide knowledgeable information, or were involved in current investigations or were planning research in the area.

The Nutrition Foundation responded to the recommendations of the Committee by pledging continuing support for the activities of the National Advisory Committee and by inviting investigators to submit proposals for grant support from the Foundation. The Foundation followed the advice of the Committee in selecting research proposals that would receive financial support or be provided "challenge foods" described in the final report. The Foundation also encouraged and aided the free exchange of information among investigators studying this complex question, regardless of the sources of their support.

As experimental studies have progressed, the results have been reported through publications in established, edited scientific journals, at scientific meetings where peer review is encouraged, and through exchange of detailed information by correspondence and during small workshops convened by The Nutrition Foundation or by other institutions.

Over the past five years, the National Advisory Committee on Hyperkinesis and Food Additives has examined the hypothesis, the design and results of research and has considered the significance and implications of the findings. Their final report provides a detailed and authoritative critique of the research findings on the subject of hyperkinesis and food additives.

I feel confident that all individuals and organizations concerned with this issue join me and The Nutrition Foundation in our deep gratitude to the members of the National Advisory Committee on Hyperkinesis and Food Additives for the generous commitment of their time and talent, and for their wise and responsible interpretation of the significance of scientific findings for public health and policy planning. They have served throughout this period with no personal compensation other than the reward of advancing scientific knowledge and its application in improving the health and welfare of mankind.

William J. Darby, M.D., Ph.D.
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Special acknowledgements of appreciation are due to the Co-Chairmen, Drs. Esther Wender and Morris Lipton, who have diligently maintained a keen awareness and knowledge of new observations and have communicated readily with scientific, lay and official audiences in order to keep them abreast of scientific developments. The arduous task of drafting this final report was undertaken by Dr. Esther Wender and Dr. Morris Lipton. Dr. Wender has given most generously of her time not only in the drafting, but to the task of final editing of the report so that it is subscribed to unanimously by the Advisory Committee.

Without the help of an expert industry task force, chaired by Mr. Albert Karas, McCormick & Company, Inc., in designing, manufacturing, packaging and storing of the challenge foodstuffs, these investigations would not have been possible. The members of this task were: Mr. Frank P. Colten, General Foods Corporation; Mr. Bruce L. Durling, Stange Company; Mr. Frank N. Hepburn, American Institute of Baking; Dr. Robert E. Smith, Quaker Oats Company; Mr. Wayne Sweatt, Nabisco, Inc.; Dr. Alan Thomas, M&M/Mars; Dr. Barry Zoumas, Hershey Foods Corporation; and Dr. Samuel Zuckerman, H. Kohnstamm & Company.

Special thanks are due Mr. Wayne Sweatt, Nabisco, Inc., who meticulously supervised the distribution of challenge and placebo foodstuffs and maintained the rigorous double blind code essential to the success of the challenge studies.

Finally, the valuable discussions with resource personnel and observers who attended and participated in meetings of the Expert Advisory Group are gratefully acknowledged. These persons included: Dr. Michael Appleman, Department of Education, University of Minnesota; Dr. David P. Boesel, Research Division, National Institute of Education, Department of Health, Education and Welfare; Dr. Glenn H. Booth, Manager, Clinical and Pharmacological Research, General Foods Corporation; Dr. C. Keith Conners, Children's Hospital National Medical Center; Mr. Thomas Cooney, Program Officer, The Ford Foundation; Dr. Peter Eichman, Professor of Neurology,

Neurological Institute, University of Wisconsin; Dr. Benjamin Feingold, Chief Emeritus, Department of Allergy, Kaiser-Permanente Medical Center; Dr. Rachel Gittelman, Director, Child Development Clinic, Long Island Jewish-Hillside Medical Center; Dr. Charles Goyette, Project Coordinator, Western Psychiatric Institute and Clinic, University of Pittsburgh; Dr. Richard L. Hall, Vice President, Research and Development, McCormick & Company, Inc.; Dr. Robert W. Harkins, Director, Scientific Affairs, Grocery Manufacturers of America, Inc.; Dr. Preston Harley, Department of Neurology, University of Wisconsin Medical Center; Dr. George Kerr, Associate Professor, Department of Nutrition, Harvard School of Public Health; Dr. Jeffrey Mattes, Medical Director, Child Development Clinic, Long Island Jewish-Hillside Medical Center; Dr. Merrill S. Read, Director, Growth and Development Branch, National Institute of Child Health and Human Development; Dr. Donald Routh, Research Psychologist, Division of Disorders of Development and Learning, Child Development Research Center, University of North Carolina; Dr. Thomas Sobotka, Bureau of Foods, Food and Drug Administration; Dr. James M. Swanson, Neuropsychology Research Unit, The Hospital for Sick Children, Toronto; Dr. Lloyd Tepper, Associate Commissioner for Science, Food and Drug Administration; and Dr. Bernard Weiss, Professor, Department of Radiation Biology and Biophysics, University of Rochester Medical Center.

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Introduction

In response to the issues raised by Dr. Ben F. Feingold in 1973 regarding the possible role of food additives as a cause of hyperactivity and learning disability in at least half of such children,[1-3] The Nutrition Foundation, Inc. organized a critical review of Dr. Feingold's claims by a group of expert behavioral and medical scientists identified by the offices of major scientific and medical organizations. This group was charged with the task of reviewing critically any evidence then available regarding the hypothesized relationship between food additives and these common medical problems of children and recommending the kind of additional investigations which might answer some of the questions raised. This committee first met in January of 1975, and, as a result of their deliberations, The Nutrition Foundation published a report from this National Advisory Committee on Hyperkinesis and Food Additives in June of 1975[4] (*see Appendix*).

This report concluded that the Feingold hypothesis was vaguely stated and that there were, at that time, no scientific foundations for the claim. It also found that therapy based on the hypothesis was complex insofar as it involved not only eliminating putative offending foodstuffs but also changing the entire family's eating habits. Finally, it concluded that the reports of therapeutic benefits were entirely anecdotal and that no controlled clinical trials had been reported. The committee recommended that two types of controlled clinical studies be conducted. The first type would use Feingold's diet under double-blind conditions. The second type would study children who had been identified by parents as favorable responders to the Feingold diet in open (non-controlled) trials and then challenge them under double-blind conditions with the presumed offending food additives. Following the publication of that report The Nutrition Foundation coordinated the special production of two food substances (cookies and candy) containing a mixture of food colors used in American food production and identically appearing and tasting placebo food substances recommended by the National Advisory Committee as appropriate challenge materials in the type of study recommended. The Nutrition Foundation supplied this challenge material to those researchers who

submitted protocols containing appropriate scientific safeguards to assure the double-blind nature of their observations. The National Advisory Committee evaluated all such research proposals and made recommendations to The Nutrition Foundation regarding the supply of this specially manufactured challenge material. Since 1975, a group of studies employing reasonable research design have been completed. The Advisory Committee met again in January of 1979 to review this research. This report summarizes the accumulated data, comments on the significance of these and other less rigid research designs and makes specific recommendations based upon the findings.

Dr. Esther Wender, Assistant Professor of Pediatrics at the University of Utah and Dr. Morris Lipton, Professor of Psychiatry, University of North Carolina, have co-chaired the National Advisory Committee in the summary of the research and the preparation of this report.

The Feingold Claims

The claim that the ingestion of food additives is causally related to hyperactivity and learning disability was first proposed by Dr. Ben Feingold, a physician specializing in allergy. The claimed connection between food additives and hyperactive behavior evolved from his work with adult patients who are sensitive to aspirin. Such patients, who experience allergic-like symptoms in response to the ingestion of aspirin compounds, sometimes failed to improve with just the elimination of aspirin-containing medications. Therefore, a special salicylate-free diet was developed to eliminate aspirin-like (salicylate) compounds that occur naturally in some foods. The artificial food coloring, tartrazine (FD&C Yellow #5) was also eliminated because it had been shown to produce the same allergic-like symptoms in some aspirin sensitive patients.[5-8] Because not all patients responded favorably to all of these exclusions, Dr. Feingold stated that: ". . . it was hypothesized that among the thousands of food colors and flavors incorporated into our food supply, there may be other additives, although unrelated chemically which may induce adverse clinical responses. On the basis of this premise, the so-called salicylate-free diet was expanded to include not only all foods containing natural salicylates, but also all sources of artificial flavors and colors, with and without a salicylate radical."[9] Therefore, the salicylate-free diet that he used to treat these patients was devised to exclude all foods that contain artificial food colorings, artificial food flavorings and foods that contain "the salicylate radical."

The assumed relationship between aspirin sensitivity in adults and hyperactivity and learning disability in children was based upon Dr. Feingold's belief that the symptoms of aspirin sensitivity were sometimes behavioral. The scientific literature in the field of allergy has been the battleground for a continuing controversy as to whether foods and other allergens can sometimes produce purely behavioral symptoms. Though this controversy centers around the symptoms of allergy, Dr. Feingold states that aspirin sensitivity is not an allergic phenomenon but stems from an idiosyncratic reaction to a chemical of small molecular weight in a susceptible

person. So, even though he does not think aspirin sensitivity is an allergic disease (an opinion shared by others in the field), he does claim that the susceptible person's reaction to aspirin and aspirin-like chemicals may be behavioral.[10] Dr. Feingold, therefore, began using this diet to treat children diagnosed as hyperactive or learning disabled based on his assumption that their behavior might be affected by the chemicals removed in this special diet.

Reports by Dr. Feingold began appearing in 1973. In 1975 he published a book entitled "Why Your Child is Hyperactive" that spelled out his claims linking the salicylate-free diet and hyperactivity and learning disability.[11] In it he states that there has been a sharp increase in the incidence of hyperactivity-learning disability and that a "graph projecting the dollar-value increase in artificial flavors looked very much like a graph indicating the rising trend of hyperactivity-learning disability for the same period."[12] This statement, repeated in several of his articles, suggests a causal relationship between an increase in the use of artificial flavorings and colorings and an increase in hyperactivity or learning disability over the last several years. There has been a significant increase in the awareness of this disorder as reflected by the number of magazine articles, books and scientific articles devoted to the topic, but there is no evidence that the disorder has increased in prevalence.

Dr. Feingold claimed that when treated with the salicylate and additive-free diet 50% of hyperactive-learning disabled children would achieve a "full response, while 75% can be removed from drug management, even if full response to other symptoms is not achieved."[13] He summarized his findings as follows:

> "the cardinal features observed following management with the salicylate-free diet include:
>
> 1) the rapid, dramatic change in behavior. Although the history of hyperkinesis with associated disturbances are usually of many years duration (three to four years) and at times dating back to infancy, a favorable response is observed within days after instituting the dietary control. The child loses his hyperkinesis, his motor incoordination, and becomes well adjusted to his environment. The sleep pattern improves.
>
> 2) Drugs that have been administered for several years can usually be discontinued after about two to three weeks of management and rarely beyond one month.
>
> 3) Improved scholastic achievement is also dramatic. Within a single quarter at school the child will show much improvement in his reading and writing ability as well as with numbers. This is consistent with the observation that these children have either a normal or a high IQ."[14]

Dr. Feingold states that further evidence of the association between specific foods and behavior comes from "the ability to 'turn on and turn off' the pattern of hyperkinesis . . . "[15], by which he means that children who ingest the excluded foods show a return of their symptoms, followed by an improvement when they resume strict adherence to the diet. These phenomena are repeatedly described in the clinical descriptions quoted in his

articles and book. He states that the greatest improvement is seen in young children below the age of six, and he urges the entire family to participate in the diet in order to encourage strict adherence on the part of the child.[16] On the basis of these claims, Dr. Feingold recommends that legislation be adopted that would require a complete ingredient statement on all food labels and "a symbol or symbols, which would signify that no synthetic colors or flavors are present in the product."[17] He also recommends that federally subsidized school lunch programs exclude additive-containing foods.

Dr. Feingold repeatedly states that the behavior problems produced by food additives are not due to an allergic mechanism. He does suggest that some children that do not respond to the salicylate-free diet may have a behavior problem produced by allergy: "Although adverse behavioral responses attributed to allergy without apparent involvement of additives have been reported, allergy does not seem to be a frequent primary cause of hyperkinesis. When allergic disease does accompany hyperactivity-learning disability, in some cases it may be necessary to institute management for the allergy in order for the salicylate-free diet to be effective."[18] He also asks the question, "Is it possible that children who fail to respond experience irreversible damage induced by the chemicals?"[19]

As has been indicated by the foregoing review of Dr. Feingold's claims, many of his assertions are vague. The non-specific nature of his statements is summarized in a closing paragraph of his address reprinted in the Congressional Record:

> "The control of hyperkinesis with subsequent improvement in scholastic achievement has been demonstrated following management with the salicylate-free diet. The precise identification of the specific factors among the thousands of food additives has not been determined. The nature of the pharmacological behavior of these chemicals is also undetermined. The incidence of hyperactivity-learning disability among school children is not known but is generally recognized as being high and consistently rising. Nevertheless, with the recognition that this basic data is lacking (sic), in view of the critical state of the problem and its extremely wide distribution among the school children, it would seem advisable that a broad based program for the management of hyperactivity-learning disability with the salicylate-free diet be developed. The gains are many, and the risks are nil. The program involves no danger to the health and behavior of the child, nor are any drugs involved."[20]

The evidence marshalled by Dr. Feingold in support of these claims has consisted entirely of clinical case descriptions. He encourages parents to keep diaries of the child's behavior and his book and articles contain case reports extracted from these diaries.[21-22] These clinical reports include vivid descriptions of the return of hyperactive symptoms following the ingestion of specific foods prohibited on the diet. For example,

> "On July 2nd Johnny C. began the K-P diet, and on July 8th, a startling six days later, his mother reported: 'he's become very quiet, less irritable; easy to control.'

> On July 13 I noted: 'Changed child. More self control than on Ritalin. Able to reason with parents and peers, less distractable. Decreased Ritalin to once a day, at 7 a.m.: Stelazine only at night.'
>
> On the 15, Johnny C. ate a bakery doughnut at 7 a.m. and by 10 a.m. was 'hyperactive, unable to use self control.' Twenty-four hours later, after the food had cleared his system, he was back to the 'new normal.'''[23]

Such dramatic reports of improved behavior followed by deterioration with the consumption of a forbidden food is very convincing to most readers but should be viewed with great caution since the treatment (the diet) is applied with the full knowledge of both patient and physician and since the expected outcome of treatment is a change in behavior which can be strikingly affected by non-specific factors such as enthusiasm and expectation. It is important in behavioral research to ensure that the change in behavior is due only to the specific treatment given. Other, non-treatment effects, known as placebo or Hawthorne effects, can powerfully influence behavior as indicated by studies that repeatedly demonstrate a measurable improvement in 35% of patients with a sham or fake procedure.[24] In recognition of this important principle of behavioral research, the National Advisory Committee on Hyperkinesis and Food Additives recommended that studies be conducted under double-blind conditions and with the use of experimental and control diets.[25] The U.S. Department of Health, Education and Welfare's Interagency Collaborative Group on Hyperkinesis also recommended that any studies of the Feingold claims be conducted under double-blind conditions and with placebo controls.[26]

The Feingold hypothesis has been expanded by its author who has claimed improvement in the behavior of juvenile delinquents and retardates and improvement in some cases of epilepsy, enuresis and headache.[27] It should be emphasized that neither he nor anyone else has ever submitted data to support these claims.

Problems in Research Design

The vagueness of Dr. Feingold's claims made it difficult to design appropriate studies either to confirm or refute his assertions. Since the following considerations were common to all of the studies, they will be discussed before the specific investigations and their outcomes are reported.

1. Specifying the Diet

Foods are complex substances. In addition to carbohydrates, proteins, fats and minerals they contain many other chemicals which give them their characteristic taste and flavor. Dr. Feingold has not specified which chemicals and at what concentration are to be allowed or excluded from the additive-free diet. He states, for example, that one must remove all foods that contain "a salicylate radical." He refers to "old German literature" to

determine which foods contained this chemical. However, salicylate is a general chemical term that includes many compounds that have slight variations of the basic salicyl radical.[28] These variations include sodium salicylate, salicylic acid, methyl salicylate and aspirin (acetyl salicylic acid). Dr. Feingold does not specify which, or if all, of these chemical entities should be excluded and at what dose level they may produce behavioral changes. In addition, accurate studies specifying the quantitative level of salicylates in specific foods are limited. In his book Dr. Feingold publishes a list of fruits and vegetables that must be excluded because they contain "natural salicylates." This list of common foodstuffs includes almonds, apples, apricots, berries, cherries, currants, grapes and raisins, nectarines, oranges, peaches, plums and prunes. Curiously, limes, lemons and grapefruit are permitted. In the vegetable category the diet excludes tomatoes and cucumbers and all products made or containing these two vegetables. Since the publication of Dr. Feingold's book, scientists at the Del Monte Research Laboratories determined the salicylic acid content in parts per million in most of the fruits and vegetables processed by this company. They found levels that varied from less than 0.1 per million to 0.8 parts per million. In their analysis cherries, which are excluded in the published Feingold diet, contain less than 0.1 part per million while carrots and corn, which are allowed in the Feingold diet, contain greater than 0.3 parts per million. Some tomato products such as whole peeled tomatoes and tomato wedges contain less than 0.1 parts per million while tomato juice contains 0.16 parts per million and tomato sauce contains 0.30 parts per million.[29] This group's list of chemical analyses is long but the above cited examples illustrate the problem in interpreting Dr. Feingold's claims. In the absence of specific information that would allow the exclusion or inclusion of foods on the basis of scientific information, most studies have administered the diet as published by Dr. Feingold in his book entitled "Why Your Child Is Hyperactive." This has been done with the realization that the published diet may not exclude some sources of salicylate and may exclude foods that contain no appreciable amount of these chemical substances.

Though his diet was originally based upon the exclusion of salicylates, Dr. Feingold has said in recent years that salicylate-containing foods can usually be re-introduced into the diet of responsive patients without producing any deterioration in behavior.[30] Because of this decreased emphasis on salicylates as the offending foods and because the elimination of salicylate-containing foods, according to Dr. Feingold's criteria, results in a drastic reduction of available fruits and vegetables, some studies have utilized a "modified Feingold diet" which is a diet that excludes artificial colorings and flavorings but not all foods that are claimed to contain salicylates.

It is also very difficult to specify what is meant by "artificial food flavorings." Approximately 80% of the compounds listed as intentional food additives fall into the category of flavorings. The chemical components of synthetic food flavorings are usually identical to the chemicals contained in

natural foods. These synthetic flavors are usually formulated from compounds first identified in foods. The reason for excluding food flavorings is very unclear. Dr. Feingold states:

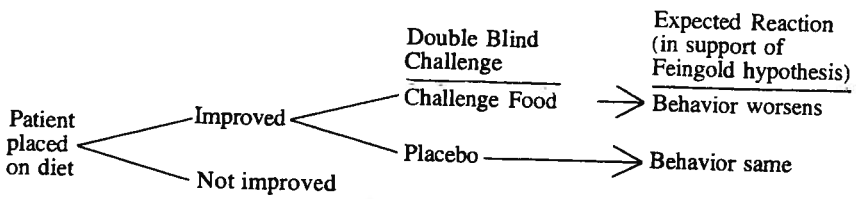
> "Following the exclusion of tartrazine, some of the failures, but not all, responded. Accordingly on the basis of the clinical relationship between aspirin and tartrazine (FD & C Yellow #5), it was hypothesized that among the thousands of food colors and flavors incorporated into our food supply, there may be other additives, although unrelated chemically which may induce adverse clinical responses. On the basis of this premise, the so-called salicylate-free diet was expanded to include not only foods containing natural salicylates, but also all sources of artificial flavors and colors, with and without a salicylate radical . . . In view of the complexity of the formulae for flavors, the necessity for the empirical exclusion of all artificial flavors can be readily appreciated."[31]

Again, as in the case of salicylates, studies have employed the diet published by Dr. Feingold which excludes all foods, the labels of which state that they contain artificial flavorings. This is done with the realization that many of the chemicals presumably excluded by this diet are actually contained in natural foods.

2. Providing a Placebo Control

In the 1975 report to The Nutrition Foundation, the National Advisory Committee on Hyperkinesis and Food Additives recommended that studies designed to test the Feingold hypothesis employ a "challenge design" which would necessitate the production of an appropriate challenge material. A typical challenge design study is illustrated in Figure 1. Subjects are placed on the restrictive diet (in this case the Feingold diet) and then, while continuing to observe the dietary restrictions, specific substances that have been removed from the diet are fed to the subjects in the form of a challenge. If the subject has improved on the restrictive diet and, if this improvement is due to the elimination of specific chemicals, the subject should then deteriorate when

Figure 1.
Research Design of Challenge Studies



those chemicals are again consumed under experimental conditions. Since deterioration in behavior might occur because the experimenter, the subject and his family are expecting that to happen (placebo effect), the challenge must be made by offering, in a double-blind situation, a placebo as well as food containing the suspected substance. The active challenge is a food that

contains the chemical previously excluded in the diet and the placebo looks and tastes just like the active challenge but does not contain the presumably offending chemicals.[32] This type of challenge study seemed particularly appropriate since Dr. Feingold repeatedly states "that any infraction of the diet, either deliberate or fortuitous induced a recurrence of the clinical pattern within two to four hours with persistence for 24 hours to 96 hours (4 days). In other words, we could turn the pattern on and off at will."[33]

The need to conduct challenge studies necessitated the production of carefully designed appropriate challenge materials. The decision then had to be made as to which chemicals and at what concentration they should be incorporated into the challenge substance. Because treatment was in the form of a diet, the decision was made that the challenge chemicals should be incorporated into a food rather than a tablet or capsule. The further decision was made to prepare a challenge food that contained only artificial food colorings as constituents not permitted on the published Feingold diet. This decision was made on the basis of Dr. Feingold's continuing emphasis on food colors as the primary offending chemicals. As previously stated, he says that salicylates can gradually be added back to the diet suggesting that salicylates seldom produce the behavioral problems of hyperactivity and learning disability. There were practical reasons why artificial flavorings were not contained in the challenge material. Such a challenge substance would have to be prepared from a list of over a thousand chemicals, and it would be impossible to disguise flavoring in the placebo food. Also, as stated in the previous section, the theoretical justification for excluding artificial flavorings is very weak since most of the chemicals contained in artificial food flavorings are identical to those that occur naturally in foods.

Artificial coloring of commercially prepared foods is accomplished by the use of nine FD&C approved colors that are used either alone or in combinations to achieve the desired results. It was possible to specially manufacture a

Table 1

Food Color	Percentage Contained in Blend	
	U.S.[1]	Canada[2]
FD & C Blue #1	3.12	3.12
FD & C Blue #2	1.70	1.70
FD & C Green #3	0.13	0.13
FD & C Red #2	—	22.27
FD & C Red #3	6.08	6.08
FD & C Red #4	0.50	0.50
FD & C Red #40	38.28	—
FD & C Yellow #5	26.91	26.91
FD & C Yellow #6	22.74	22.74
Certified Orange B	0.54	0.54
	100.00	100.00

1. From notarized letter to Mr. A.J. Karas, McCormick & Co., Inc. from Samuel Zuckerman, Ph.D., Vice President, H. Kohnstamm & Co., Inc. dated February 20, 1976.

2. From notarized letter to Mr. A.J. Karas, McCormick & Co., Inc. from Samuel Zuckerman, Ph.D., Vice President, H. Kohnstamm & Co., Inc., dated February 27, 1976.

challenge cookie or candy that contains a blend of these nine colors. The proportion of each individual color in the blend was based upon the amount of each color actually used on a per capita basis in food production. For example, 1.7% of all of the FD&C colors used by the food industry is accounted for by Blue #2. Therefore, the blend of colors used to produce the challenge material contains Blue #2 in a proportion of 1.7% of the total color used. Table 1 lists these nine colors and the proportions used in the total color blend. Since some of the challenge studies were conducted in Canada, and since Canada has banned the use of Red #40 but allows the use of Red #2, and since the U.S. has banned the use of Red #2 but allows the use of Red #40, two different color blends, reflecting these differences, were prepared for use in Canada and the United States.

The absence of color in the placebo food substance was effectively masked by a chocolate permitted in Dr. Feingold's diet. The same amount of chocolate was present in both the placebo and the color-containing foodstuffs. The placebo and active challenge material were tested by food taste panels who could not distinguish between them.

The dose of colors contained in these foods was based upon a calculation of the average daily per capita disappearance of food colors in this country. The amount of FD & C color actually used in food production must be certified by the U.S. Food and Drug Administration each year. The amount of each color certified in the years 1973 and 1974 was used in this calculation. The total amount of color certified was then divided by the U.S. population yielding the total figure of 27.29 mgs. of FD & C color certified per person per day. This calculation is illustrated in Table 2. Since this was an estimate of the amount of food coloring consumed by each person in a whole day, the decision was made to add half that amount to each portion of the challenge food since food intake is spread over several hours and the total daily amount of coloring is not usually ingested at one time.

Following the first two or three challenge studies, concern was expressed that the dose of food coloring employed may be much less than the amount of coloring consumed by children. It was argued by some that children, on the average, consume a much higher proportion of artificially colored foods than do adults. Therefore, in preparation for the California study (Weiss et al.,) a project that was funded by the Food and Drug Administration, new calculations were made of the average daily consumption of artificial colorings by children. These calculations were based on estimates of the amount and kind of foods consumed by children and calculated according to estimates of the artificial food coloring content of those specific foods. This re-estimate leads to the conclusion that children consume, on the average, 36 mgs. of artificial food coloring daily.[34] Therefore, a new challenge material was prepared specifically by these investigators for this study. This challenge material was a soda-pop drink, and the presence or absence of color was disguised using cranberry juice to mask the color difference.

It should be noted that there is a technical limitation to the amount of food

Table 2

FD & C Color	Average amount of color certified per year (lbs./year)	Average intake (mg/person/day)
Blue No. 1	143,576	0.85
Blue No. 2	78,143	0.46
Green No. 3	5,964	0.04
Red No. 2	1,025,886	6.08
Red No. 3	280,090	1.66
Red No. 4	23,206	0.14
Red No. 40	737,475	4.37
Yellow No. 5	1,239,024	7.34
Yellow No. 6	1,047,487	6.20
Orange B	24,718	0.15
		27.29 mg. (0.02729 g.)

Certification data from FDA on color additives covers fiscal years 1973 and 1974 and the first six months of fiscal year 1975. The average intake values are calculated on the basis of a U.S. population of 210 million people.

coloring that can be incorporated into a food without coloring the mouth and fingers permitting recognition of the color containing material and thus preventing the disguise of the placebo challenge. It was possible to incorporate 13.0 mg. of a color blend into a cookie and 36.0 mg. into a soft drink without jeopardizing the placebo disguise, but food technologists stated that larger amounts would begin to be noticeable.

3. Defining and Assessing the Study Population

The National Advisory Committee on Hyperkinesis and Food Additives made several specific recommendations regarding measures that should be used to define and then follow a population of hyperactive children in studies of the Feingold hypothesis. The studies reported here were all conducted by groups already involved and familiar with research involving hyperactive and learning disabled children. All of the reported studies used some type of standardized measure to define the study population. The one investigation that did not (the California study) looked at children who behaved in ways that disturbed their parents but did not necessarily meet criteria for the diagnosis of the hyperactive syndrome. In this study target symptoms were identified prior to the study and then followed during the course of the experiment. Such a research design is appropriate since the challenge was administered using double-blind techniques. The methods used in dietary manipulation are described in the reviews of each individual study.

In this report we have chosen to review only those studies that, according to our criteria, met minimal standards of appropriate research design. This means that: 1) some type of standardized measure is used to define the population and to follow the children's progress through the study; 2) the experimental variables are applied under double-blind conditions and using appropriate placebo controls; and 3) a sufficient number of children was studied to allow appropriate statistical analyses.

We have identified these studies by the first author and the geographical location of the project for the purpose of simplifying our repeated reference to different investigations. By doing so we do not imply lack of recognition of the important contributions made by the other members of the research teams that participated in the course of these studies.

Wisconsin Studies — Harley et al.

The Wisconsin group studied 46 children, 36 of school age and 10 preschool children.[35] They then conducted additional studies on 9 of the original sample of 36 school age children.[36]

This group had available resources that enabled them to devise two diets, one that contained food additives (control diet) and one that did not (Feingold diet), that were sufficiently alike to prevent families from knowing which diet the child was eating. This difficult and expensive task was accomplished by removing all food from the home and supplying all foods for the family during the diet study. The Feingold diet was disguised by including special foods that are usually eliminated in the published descriptions of this diet but, because of special manufacturing, did not contain any of the substances prohibited in the treatment diet. The regular diet was also disguised by excluding foods that the family would think should be excluded on the Feingold diet. Using this technique this group was able to provide a Feingold diet and a non-Feingold (control) diet that were sufficiently similar that no families were able consistently to identify the diets during the study.

The study design consisted of two weeks of baseline (with all children off medication) and four weeks on either the Feingold diet or the regular diet followed by four weeks on the opposite treatment. Families were assigned randomly to the possible treatment orders, e.g., Feingold diet followed by regular diet; regular diet followed by Feingold diet.

All children were diagnosed and evaluated during the experiment by a variety of measures. Trained observers rated their behavior in the classroom, activity level was measured by a laboratory test, attention and impulsivity were evaluated by several cognitive tests, and overall behavior was judged by both the father and the mother and by their teachers on standardized questionnaires designed to obtain information relating to hyperactivity and associated behavior problems. Each child included in the study had to score two standard

deviations above the norm on these questionnaires. A group of children without behavior or learning difficulties (a control group) was evaluated by all of these measures to insure that the group diagnosed as hyperactive was significantly different from normal. The group of hyperactive children studied could easily be distinguished from the control group on most of the measures used.

For obvious reasons there were no classroom observations and no teacher questionnaires on the 10 pre-school age children. There was no pre-school control group to use for purposes of comparison. As the authors point out, for these reasons findings in the pre-school group must be interpreted cautiously.

If the Feingold or K-P diet is effective in improving the behavior of hyperactive or learning disabled children, the group placed on the Feingold diet first should have shown improvement and then deteriorated when they were changed to the regular diet. The group that was placed on the regular diet first should show no change and then improve as they were switched to the Feingold diet. If only some children improve on this diet, a group of 36 children (the school-age sample) should be large enough to show that difference even if the percentage that improves is as low as 10-15% (3-5 children).

There was no consistent pattern of improvement while on the Feingold diet in any of the objective measures such as the classroom observations, the activity task and the tests of attention and impulsivity. The questionnaires completed by the teachers also showed no change. The only change seen on the Feingold diet compared to the regular diet was noted by the parents, and then only when the regular diet was administered first followed by the Feingold diet second. No differences were noted on the parent questionnaires when the Feingold diet was given first and was followed by the regular diet. Change on these questionnaires was operationally defined as a 10% or more improvement on the overall score based on ten questions that correlate most highly with hyperactivity. This degree of change (10%) is quite small.

This finding of slight improvement only by parents and only when the treatment occurred in a certain order suggests that whatever slight difference in behavior may have occurred it was too subtle to be detected by objective measures and either so subtle or not involving school related behavior, that changes were not apparent to teachers but noticeable only to parents. A difference in findings depending upon the order that treatment is given is known as an "order effect", a phenomenon often seen in behavioral studies. This phenomenon is probably produced by treatment effects combined with a factor of suggestibility which amplifies the effects of treatment when it is administered *following* a placebo. A concrete illustration will help explain this finding. If a person is in a study involving the close scrutiny of behavior and treatment starts at day one, but the person doesn't know if the treatment is a placebo or the "real thing", he is likely to be hopeful that change will occur and little differences get magnified by expectations. At the same time, he may remain wary to see if these little differences persist or get stronger. If this treatment turns out to be placebo and nothing much happens, when he

switches to the second treatment, his expectations may be even greater because he thinks that the first treatment was ineffective. If the second treatment then produces a more noticeable change it gets very much exaggerated by a sense of "Well now, I'm getting the real treatment." So treatment effects get exaggerated when the placebo is given first and the real treatment second. By contrast, if the active treatment occurred first, though noticeable changes took place, one is still at the wary "wait and see" stage and changes get de-emphasized. Then only after switching to the second treatment, and seeing even less change, is one aware that the initial changes were real. In other words, treatment effects get dampened when active treatment is given first and the placebo second. When treatment changes, compared to placebo, are definite and striking the order effect is less pronounced, since suggestibility is less of a factor.

In summary then, no findings on objective measures, plus a pronounced order-effect on subjective measures combine to suggest that some parents were able to see something. The study gives no clue as to what it was except the effects were slight and subtle and were undetected by measures that usually demonstrate treatment changes.

It is also possible that families were not completely blind to the different diets which, if this were true of only some of the parents, would have produced similar results. Though the two diets were cleverly disguised, oranges and apples are allowed on the regular diet and excluded on the Feingold diet. The sophisticated parent who has read Dr. Feingold's published diet might readily detect this difference. The Wisconsin group reported that families were asked to identify the diet treatment and none could do so, but researchers should be cautious of such statements since patients frequently seem strongly motivated to "break the code" and may be reluctant to admit their efforts at outwitting the investigators.

The pre-school children did not show changes on any of the objective laboratory or attention-testing procedures. However, on the parent questionnaires (there were no teacher questionnaires) a statistically significant number of parents did report improvement of behavior while their children were on the Feingold diet. Again, these changes were small and were not noted on the objective measures. It should be mentioned in reference to both studies that when double-blind studies of medications vs. placebo have been conducted to test the efficacy of drugs in the treatment of hyperactive children, changes that favor medication over placebo have been noted on both parent and teacher questionnaires, on activity measures, on tests of attention and impulsivity, and on classroom observations.[37,38,39]

The findings in both the school-age and the pre-school groups suggest that some parents may have been able to see differences in their children while on the Feingold diet compared to the regular (control) diet, but this difference was nothing like the dramatic improvement claimed by those advocating its use in the treatment of hyperactivity or learning disability. In fact, if such a subtle change was a real finding it seemed, in this study, to be detectable only

by some parents in a home setting.

One interesting additional result of the Wisconsin study was the careful analysis of nutrients actually consumed on the two diets. Some concern has been expressed concerning vitamin C intake on the Feingold diet since many popular vitamin C-containing foods are excluded. Vitamin C intake was lower on the Feingold diet compared to the control diet but remained well above the Recommended Daily Allowance (RDA) for that vitamin. The ingestion of carbohydrates (CHO) was also lower on the Feingold diet compared to the regular diet. One of the recommendations from both the National Advisory Committee and the Interagency Collaborative Group was that the actual diets consumed by children on this treatment be analyzed to ascertain if other important nutritional changes occurred secondary to the removal of certain food additives. The actual difference in carbohydrate intake compared to the average total intake is small and probably is not physiologically significant. On the control diet children consumed an average of approximately 330 gm. per day of CHO while on the Feingold diet the figure was 290 gm. per day.[40] This difference of approximately 40 gm. per day represents only 14% of the total CHO intake. However, it is interesting to speculate whether this difference in nutrient intakes may have been responsible for some subtle behavioral changes that might be noted by parents.

Critics of the Wisconsin study have argued that the Feingold diet may not have resulted in much behavioral change because families did not follow the diet closely. For two reasons this argument seems unreasonable. First, dietary compliance is never subject to question in the anecdotal reports of behavioral improvement appearing in the proponents' literature. In these instances the child's reported improvement is accepted as proof that the diet was followed. There is no reason to believe that the families in the Wisconsin study are any more or less compliant than those from other settings. Second, the Wisconsin group instituted several measures to insure maximum compliance. They supplied food for the whole family and provided special additive-free treats for those children having birthdays. They also monitored compliance and found no consistent relationship between detected dietary infractions and behavior.

The second part of the Wisconsin study employed a challenge design. They selected nine school-age children from the first study who showed the greatest number of changes, in the direction predicted by the Feingold hypothesis, on any of the measures used. Since findings on the first study were minimal, this group of nine cannot be said to be diet responders. This group was then evaluated over a 2-week baseline while off medicine and on a regular diet. Then the families of these children were placed on the Feingold diet and they were evaluated again over a two-week baseline. All children were then challenged twice daily with the foodstuffs containing either a mixture of artificial colorings or placebo under double-blind conditions. The challenge period was nine weeks long and consisted of two weeks on an active food challenge, two weeks on placebo, two additional weeks on the food contain-

ing additives, and ended with three weeks on placebo. Half of these children received the challenges in this order and half in the opposite order (i.e., placebo-additives-placebo-additives). Throughout this challenge period the children and their families remained on the Feingold diet with all food supplied by the study team. The same measures used to evaluate the children during the first study were employed. Again a group of non-hyperactive (control) children was followed on the same measures to insure that the study group was significantly different from "normal" children.

The results of this study are as follows: There were no differences between the active challenge periods and the placebo challenge periods on any of the measures of attention and impulsivity, the classroom observations, or the behavior questionnaires completed by both parents and the teachers. In addition to evaluating the group of nine as a whole, the data were analyzed for each child individually to see if one child, who responded in the predicted manner, might be obscured by negative results in the other eight. The Wisconsin group reports that, "Only one subject displayed a behavioral profile of parental ratings and classroom observational data that even approximated the predicted on-off effect of the challenge and placebo materials." However, examination of the raw data on this one child is not very impressive. Changes in the predicted direction were seen only on the questionnaires completed by the mother and one of her ratings during a placebo week was as high as most of her ratings during active challenge weeks.

It is also of interest, though not reported in their published article, that parents and teachers rated behavior during both 2-week baseline periods making it possible to compare behavior for the 2 weeks on the regular diet with that during the 2 weeks on the Feingold diet under non-blind conditions, (i.e., the parents and children knew they were being placed on the Feingold diet). During the latter 2 weeks of baseline, while they knew the Feingold diet was being given, mothers rated their children on the average as 4 points better (approximately 11.0 compared to 15.0) on the Conner's parent-teacher rating questionnaire. There were no differences between the father's and teacher's rating during this same baseline period and no differences on any of the objective measures. This improvement in behavior would be rated as significant if a 25% change in behavior is used as an indication of significant improvement (the figure used in several of the other studies). This finding of behavioral improvement seen by the mother when her child is placed knowingly on the Feingold diet, followed by no change seen by these same mothers during the double-blind challenge period suggests that the initial improvement was a placebo effect, i.e., based upon positive expectation.

Pittsburgh Studies — Conners et al.

This group conducted a series of studies, only some of which have been published. Its first reported study was of 15 school-age children comparing the Feingold diet to a control diet.[41] This was followed by a series of four

challenge experiments, each focusing on a different specific issue.[42-44] A total of 68 mostly school-age children was studied. In the challenge studies the researchers advertised for patients and accepted for study only those who satisfied diagnostic criteria for the hyperkinetic syndrome and those who improved according to the parents when treated with the diet in a non-blind diet trial, i.e., the patient and his family knew the diet was being given. In three of these challenge studies the only measure of change was behavior questionnaires completed by parents or teachers or both. Though reports are published on a total of 68 children there was overlap between the studies with some children participating in two or more of the experiments, so the actual number of individuals tested was 50 to 55. These authors repeatedly refer to the difficulty of completing diet studies and mention the many families who failed to complete the total program. Approximately 3 patients began the experiments for every one that completed the total study.

The first study employed a design that compared the Feingold diet to a control diet. The experiment began with four weeks of baseline followed by four weeks on the Feingold diet and four weeks on the control diet. Half of the children began with the Feingold diet followed by the control diet and the other half began with the control diet followed by the Feingold diet (i.e., a counter-balanced design). However, the Pittsburgh group's control diet was designed quite differently. Its goal was to produce a diet that required changes in shopping and food preparation comparable to that experienced while on the Feingold diet *but* without the exclusion of salicylates and artificial colorings and flavorings. This diet was created by them following, of course, guidelines of good nutritional practice. For example, some items excluded on the control diet in the category of cereal and grain products were waffles, pancakes and French toast. In the meat category, they excluded fresh fish and poultry skin and giblets. Beverages excluded were root beer, ginger-ale, lemonade and chocolate milk. As a comparison, the Feingold diet excludes all soft drinks except 7-Up and all fruit juices except pineapple and grapefruit. Families were told that two diets were being compared, that either diet, neither or both might be effective. Serious concern must be raised as to whether families were really blind to the identity of the two diets since a parent who had read Dr. Feingold's published material should have been able to distinguish between the Feingold diet and the control diet.

An improvement was seen by the *teachers* in a significant number of children when the child was on the Feingold diet compared to the control diet, but this effect was primarily due to improvement noted when the control diet was used first and the Feingold diet second. Improvement was noted by the *parents* only when comparing the Feingold diet to baseline but not when comparing the Feingold diet to the control diet. In other words, the parents saw a smaller degree of change. The amount of change as measured by the questionnaires ranged between 15% and 30% improvement over baseline. Again, this difference between the Feingold diet and baseline was accounted for only by the group that was treated by the control diet first and the Feingold

diet second (i.e., an order effect). The combination of this pronounced order effect plus the fact that these changes were seen by the teachers more than by the parents (just opposite to the findings of the Wisconsin group) lead us to interpret this finding as of doubtful significance. Again, (as was discussed in conjunction with the Wisconsin study), these findings could be explained by a very slight Feingold diet effect that was greatly amplified by the suggestibility produced when treatments are given in a certain order. They could also be produced by a placebo effect if some families were not blind to the control and experimental (Feingold) diet.

The Conner's group also completed an analysis of the foods consumed on the two diets and found the same differences as did the Wisconsin group. i.e., that vitamin C intake was lower on the Feingold diet but within the Recommended Daily Allowance and that carbohydrate intake was lower on the Feingold diet.

Following the control diet study, this group conducted a series of challenge experiments employing the specially manufactured food substance containing a mixture of artificial food colorings. The first challenge experiment was conducted with 16 school-age children who were, according to their parents, diet responders under non-blind conditions. Then, while maintained on the Feingold diet, the children were challenged with the food-coloring-containing foods and placebo foods in a double-blind fashion. No differences between the two challenges were noted by either the parents or the teachers as reflected by scores on the behavior questionnaires.

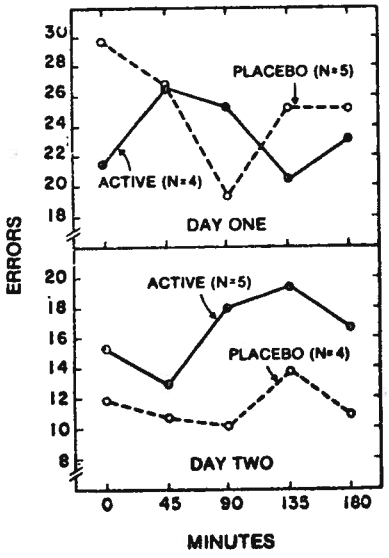
However, these children were also tested on a tracking task which is a laboratory test that requires sustained attention on the part of the child and can be made more difficult by adding distractions during the test. Some of the children performed less well on this task within the first hour after eating a food substance that contained coloring compared to their performance after ingesting a food substance that did not. Since this finding did not achieve statistical significance (i.e., it may have been due to chance) and since the measures of total daily behavior showed no differences, the study was repeated, this time requesting the parents to complete questionnaires focusing on behavior that occurred only in the three hours immediately after ingestion of the active or placebo foods. In this study of 13 children there was a significant worsening of behavior, as viewed only by the parents and only during this 3-hour period, when children ate the food substance containing coloring as compared to the placebo. Because this group was small, the Pittsburgh group did a replication study employing the same strategy, i.e. having parents rate children's behavior during the 3 hours immediately after ingestion of the food substances. In this study 30 children were tested. Again, they selected for study only those children whose parents reported improvement when placed on the Feingold diet in a non-blind trial. These children were then challenged with active or placebo foods over a 4-week-long period, receiving the food that contained coloring for one week followed by placebo for a week, then colorings and again placebo, in a counterbalanced design

(i.e., one half received colorings-placebo-colorings-placebo, and one half received placebo-colorings-placebo-colorings). In this replication study no significant differences were seen between the food coloring challenge and the placebo challenge as measured by behavioral questionnaires during the 3 hours following the challenge.[45]

Up to this point the Pittsburgh group had found no general differences in behavior in children challenged with food coloring, but they had seen a questionable difference on a laboratory task requiring sustained attention but only for a short period immediately following the challenge. They wondered if this failure to find changes in behavior might be due to the fact that the group of children tested during the replication study were less severely hyperactive than the group studied during the first challenge experiment, and they were concerned that the amount of coloring in the challenge food substance was too low, (see p. 10). Therefore, they completed one further study of 9 children between the ages of 5 and 10, selected from their previous studies on the basis of a definite response to the diet under non-blind conditions according to *both* teachers and parents, and on the basis of having demonstrated some differences in behavior as measured by parent questionnaires during the challenge experiments. This highly selected group of subjects was then studied in a laboratory setting on two occasions, with one to two weeks between testing sessions. They remained on the Feingold diet throughout this time. During the testing sessions their activity level was measured by actometers and by cushions designed to measure restless, fidgety behavior while seated. The experimenters rated their behavior throughout the testing sessions which were about 4 hours in length. Then, all children were tested on a paired-associate learning task at repeated intervals following ingestion of two of the challenge cookies or candy, either the placebo containing no colorings or the active challenge containing 13 mg. of food coloring each, for a total of 26 mg. of food coloring. On the paired-associated learning task the experimenter presents the child with pictures and an associated word (not the name of the object pictured). The child must then learn the word-picture association over repeated learning trials. This type of test is done less well by hyperactive children compared to age-matched, normal children and performance is improved by the medications (stimulants) used to treat hyperactive children. This task was chosen because another group of experimenters (Swanson et al., in Toronto, Canada), had studied the Feingold diet using this laboratory measure. The learning task was administered before ingestion of the challenge food and again 45 minutes, 90 minutes, 135 minutes and 180 minutes after ingesting the active or placebo food substance. This frequent repetition of the same task was aimed at detecting very brief-lived responses to food colorings since, in the first challenge experiments, changes on the tracking task were seen only transiently. With repeated sessions on the same task one would expect children to improve because of practice or to get worse because of fatigue. In this experiment children showed noticeable improvement during the second testing session indicating a definite practice effect. They also

saw a gradual worsening of performance over the 4 hour testing period indicating the expected fatigue effect. The results of this experiment were that no differences were seen on the measures of activity or the behavior ratings comparing food colorings to the placebo. Activity level increased during the first hour after ingestion of the food bar and then returned to baseline level for the remainder of the session, but this effect was seen with both the placebo and the food coloring challenge. This is an interesting finding suggesting that some component of food (? sugar, chocolate, calories) may increase activity level transiently. The results of the paired associate learning task are shown in Figure 2. On the first day during the baseline period the group which would later receive the food colors made fewer errors than the group which would receive the placebo. After challenge the placebo group then improved during the first two hours, but deteriorated toward baseline levels later during the session. The group receiving food colorings made more errors during the first hour and also returned to baseline level, which for them meant improvement later in the session. During the second testing day both groups improved slightly during the first hour and then deteriorated over the remainder of the testing session. There were no statistically significant differences between the placebo and the food coloring challenges on either day and both practice and fatigue effects were seen.

Figure 2



Reprinted from: Conners, K.: *Food Additives and Hyperactive Children*, New York, Plenum Press, 1980.

Toronto Study — Swanson et al.

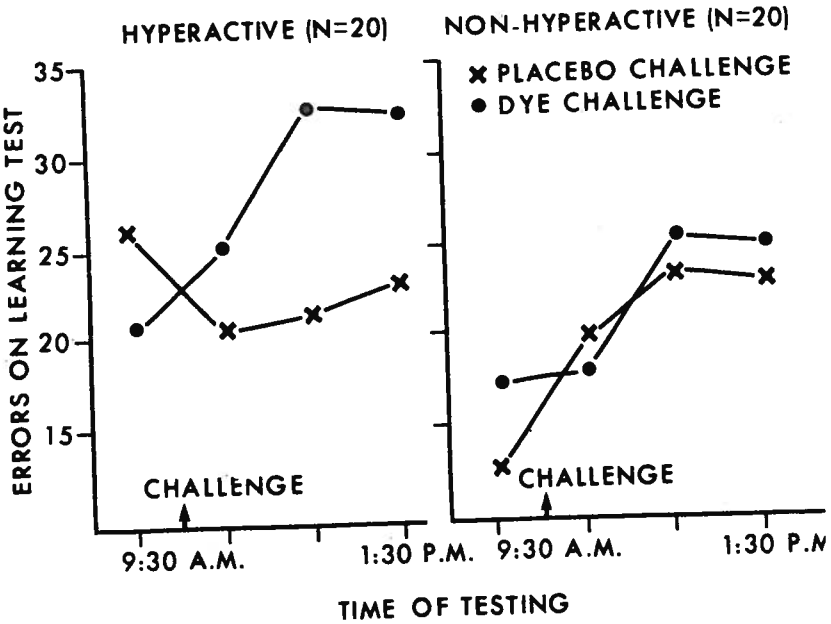
This group studied a total of 40 children, employing a research design aimed at detecting only short term effects on cognitive function rather than changes in global daily behavior in the home or school setting.[46] Children in their study were admitted to the hospital where dietary intake could be strictly controlled. They were placed on the Feingold diet and tests were administered after 3 days of dietary treatment. Tests were conducted after a challenge either with placebo or with a mixture of artificial food colorings administered as a bolus in an opaque capsule at a dose of either 100 or 150 mg. This single dose is much larger than the amount used in any of the other studies. During an earlier pilot study this group had employed a 26 mg. challenge dose and had seen no effects on their laboratory task. They justified the use of a larger dose on the basis of revised estimates of the average daily consumption of artificial food colorings by children (see p. 10). Though the revised estimates varied, in one report 150 mg. of colors was at the 90th percentile for the estimated amount of food dyes ingested daily by children[47] in the 6-12 year old age range. The reader should note that daily food coloring ingestion is usually spread over an 8 to 12 hour period of time. A single dose of 100 or 150 mg. is much more than a child would consume with a dietary infraction such as a doughnut or a soft drink.

A paired-associate learning test was used to measure the possible effects of food coloring ingestion. On this test, the child is required to learn an association between a picture and either a number or a word that is not the name of the picture. For example, a child may be asked to learn that a picture of a tree is associated with the number 5, and a picture of a bus is associated with the number 2, and so on. The experimenter can vary the length of the list of picture-number combinations to be learned in order to adapt to the child's age and learning ability. This task requires sustained attention and, therefore, is done poorly by hyperactive children compared to controls. Performance is measurably improved in hyperactive children treated with stimulant medication. These authors use this test to measure the effects of stimulant medication in a laboratory setting in order to predict those hyperactive children who will respond favorably to treatment.[48] They chose this short term measure to test the response to food coloring because the Pittsburgh group had described a transient effect of food colorings on a laboratory task requiring sustained attention (see pp. 18-20). They also argued that tasks involving cognitive performance may be more sensitive than behavioral questionnaires to the effects of food colorings.

This group studied two different populations of children referred to their Child Development Clinic. One group of 20 children they labeled "non-hyperactive" because they were non-responders to stimulant medication, according to their criteria, and had lower scores on the Conners' 10-question, parent-teacher questionnaire, compared to a second group of 20 children who they called "hyperactive" because they were stimulant medication respon-

ders and had higher scores (more hyperactive behavior) on the Conners' questionnaire. This use of the labels "hyperactive" and "non-hyperactive" should be seriously questioned. The scores on the Conners' questionnaires, for example, in their "non-hyperactive" group still fall one standard deviation above the mean. It is also a fallacy to base the diagnosis of hyperactivity on medication responsiveness. In most studies there are some children, appropriately diagnosed as hyperactive, who do not respond to stimulant medication.[49]

Swanson claims that the "hyperactive" group showed deterioration on the paired-associate learning task after the food coloring challenge compared to a placebo challenge. The first, less hyperactive, group showed no difference between placebo and food-coloring challenge. The graphs below illustrate these differences. Their interpretation of these results is subject to serious question since the difference in the pattern of placebo performance between the two groups cannot be explained and may have affected the outcome. The more hyperactive group began with a strikingly poorer performance on placebo than did the less hyperactive group. The less hyperactive group showed deterioration over time with both the placebo and the coloring challenge. This pattern of deterioration over time would be expected since children usually perform less well with frequently repeated testing. In a study reported in 1978,[50] these authors showed that children deteriorate on this test over time when given a placebo. The deterioration following the color



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challenge may be due to the ingestion of colors but needs to be distinguished from the placebo response. In the less hyperactive group the placebo and challenge performance were not statistically different. The more hyperactive group also deteriorated with the coloring challenge but the placebo pattern in these children shows improvement from baseline levels rather than deterioration over time. This difference in placebo response between the two groups would need to be confirmed with further studies before the differences between the food coloring and placebo challenges could be accepted.

In summary, this study was not designed to show changes in global behavior. Instead, these authors were attempting to demonstrate a short term pharmacological effect on cognitive function with the administration of a single, large dose of food colorings. Though they claim to have demonstrated deterioration on a learning task within 3 hours following ingestion of large doses of food colorings in a group of more symptomatic, medication responsive, hyperactive children, this interpretation must be viewed with caution since the placebo response in this group differed from the placebo response of the comparison group.

California Study — Weiss et al.

This was a study of 22 children who ranged in age from 2-7 years.[51] These children were not diagnosed as hyperactive. Rather they were behaviorally disturbing to their families or in school and had been placed on the Feingold diet by their families. Only children who were alleged by their parents to be definitely improved were selected for the study. The children were maintained on a strict Feingold diet that excluded the preservatives butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) as well as artificial colorings, flavorings and salicylates, during the entire 11 week period of study. The first two weeks were baseline with no challenges given. Then each child received either a placebo or a food coloring challenge once each day over the next 8 weeks. The challenge material was specially manufactured for this study and consisted of a soft drink disguised with cranberry juice coloring and containing either no artificial colorings or 36 mg. of an artificial food coloring mixture. This dose (36 mg.) was chosen based upon a new estimate of the average daily consumption of food colorings in a childhood population (see p. 10). The challenge material was given one day each week on different days of the week in random fashion. It was taken, however, at the same time of day for each child and the behavioral observations were made with reference to the 24 hour period after ingestion of the challenge. Both the investigators and the families were, of course, blind as to whether the challenge contained artificial coloring or only natural coloring.

Prior to beginning the 11 week study the parents — and when available, the teacher — defined a list of ten target behaviors for each child. On each challenge day the parents gave a global rating of the child's performance with

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Prior to beginning the 11 week study the parents — and when available, the teacher — defined a list of ten target behaviors for each child. On each challenge day the parents gave a global rating of the child's performance with

reference to the target behaviors. In addition, the caretaking parent used a counter to tally the total number of negative target behaviors that occurred during 15 minute observation periods. Finally, the parents completed the Conners' ten-question behavioral questionnaire on each challenge day. When available, the teachers gave a global rating and also completed the behavioral questionnaire. An independent observer periodically checked the parents' behavioral ratings during a home visit.

This group found no difference in behavior following the food coloring challenge compared to the placebo challenge in 21 out of the 22 children studied. However, in one child, aged two years ten months, the mother consistently reported deterioration in behavior following the food color challenge compared to the placebo. She correctly guessed in five out of the six times that her child had received the color challenge. There were no teacher observations in this very young child nor were there independent evaluations by trained observers. Whether this change in behavior noted only by the parent would be noticeable to other observers cannot be answered by this study. Without this information, it is difficult to tell whether the behavioral change reported by the parent is of clinical significance.

It is of interest that these authors report great difficulty in finding families that were able to complete the 11 week study. The reason for this difficulty, in many cases, was due to the strictness of the diet under experimental conditions in families that had been much less stringent in their previous voluntary adherence to the diet.

Long Island Studies — Mattes; Gittelman-Klein

These investigators conducted two studies on a total of 14 school age children whose parents volunteered to have them studied.[52,53] The children studied all came from families that belonged to the local Feingold Association, a parent organization aimed at promoting the Feingold diet treatment. All children were alleged dramatic responders to the Feingold diet and all parents reported definite deterioration in behavior with dietary infractions.

The first study involved just one 10 year old boy who was challenged with either placebo or 39 mg. per day of artificial food colorings for 2 days a week during 10 consecutive weeks. Behavior was measured by the Conners' 10-question questionnaire completed by the mother, the teacher and the boy himself. In addition, each of the three was asked to guess whether the boy had received placebo or the food coloring after each challenge. No consistent behavior change was noted by either the boy or the teacher but the mother noted an increase in irritability and fidgetiness following the color challenges and correctly guessed the nature of the challenge 8 out of 10 times, which is statistically significant. No independent corroboration of the mother's report was available.

These researchers then studied 13 additional children, all alleged Feingold diet responders, over a 3 week period. During the first week they were

challenged either with placebo or with 78 mg. of artificial food colorings taken in the form of the specially manufactured food substances, two cookies or candies 3 times a day. This was followed by a one week period with no challenge and then a final week of either placebo or 78 mg. of colors in food. Half of the group received the placebo first and the food coloring second, and the other half took the active challenge first and the placebo second. Behavior was measured by Conners' questionnaires completed by parents and by teachers, by a psychiatric examination and by a laboratory test of distractability. All measures were obtained prior to the start of the study and after each challenge period. The laboratory task was conducted 1½ hours after a food challenge.

This study design is a good one. The selection of diet responsive patients should maximize results that would support the Feingold claim, the dose of food coloring given was large and the measures of behavioral change include behavior questionnaires, which are the most sensitive indicators of behavioral change, and a laboratory measure of distractability which is highly objective. The laboratory test was administered within the time period that should demonstrate the kind of change reported by Conners in his early studies (see pp. 18-19). In these 13 children, no differences could be detected between the active and placebo challenges on any of the measures, and neither the parents nor the teachers could guess the nature of the challenge at any better than chance levels.

Though the overall results of this study refute the Feingold claim, the ability of the mother, in the first study, to accurately guess the nature of the challenge is of interest. This is similar to the finding in the one child in the Weiss study (see pp. 23-24) and the one child reported by Harley et al. during the challenge phase of their experiments (see pp. 15-16). In none of these studies was there confirmation of the parents' observations by teachers, by trained observers, or by laboratory measures. This occasional report of behavioral change seen only by the mother may be due to an occasional parents' ability to break the code and thus be aware of the times when their child is receiving placebo or the active challenge. It is also possible that in an occasional child there is a subtle behavioral effect of artificial colorings. This effect is probably clinically unimportant since it was not seen by other observers when they were available (the Wisconsin study and this study). In the Weiss study there were no other observers.

London, Ontario Study — Williams et al.

This group studied a total of 26 children ranging in age from 6 to 14 years.[54] All children had been diagnosed as hyperactive and all were being treated with, and judged responsive to, stimulant medication. Children were placed on a modified Feingold diet (excluding artificial colors and flavors, but not salicylates) for a 5 week period and were then challenged for the first four days of each week with either food coloring or placebo in the form of the

specially manufactured cookies or candy. Each child received two cookies or candies each day for a daily dose of 26 mg. of food coloring during the active challenge. During this challenge period the children also received either their regular stimulant medication or placebo medication. Therefore, each child received 4 different treatment combinations, one combination during each of 4 weeks of treatment manipulation. The 4 combinations include: (1) placebo food substance plus placebo medication; (2) food coloring plus placebo medication; (3) placebo food plus stimulant medication; and (4) food coloring plus stimulant medication. Behavioral change was measured only during the 4 weeks of treatment manipulation and only by behavioral questionnaires. The Conners' 10-item brief questionnaire was completed daily by both teachers and parents and the longer 40-item questionnaire — which includes within it the 10-items from the brief questionnaire — was completed once at the end of each treatment week. Behavior was not monitored during the baseline period when the diet was begun, so this study provides no information about the effects of the diet under open trial conditions. The 4 possible treatment combinations were administered in random order, a procedure designed to control for order effect (see pp. 13-14). This means, however, that some children received either the active medicine or the food colors over a two week period while some received these agents for only one week at a time. For stimulant medication, this is a relevant consideration since some children deteriorate in behavior immediately following the withdrawal of stimulant medication while others change only gradually over time.

The results of this study are complex. First of all, both types of questionnaires showed definite improvement in the behavior of children on stimulant medication compared to placebo. Diet effects that reached statistical significance were seen but there was no consistency between the reports from teachers and parents. The teachers saw the children as behaviorally worse during the food coloring challenge only when they were also on placebo medication and parents saw the children as worse during the food coloring challenge but only while they were on the active medication. When, instead of looking at group averages, the authors analyzed individual children's scores, they found 3 children identified by parents as responding to food coloring challenge, and 5 so-identified by the teachers but in no cases were these the same children. These authors conclude that the teacher reports are more accurate because hyperactive children are usually more symptomatic in a school setting and because teachers, who can compare each child to a classroom full of children the same age, are said to be more accurate and consistent reporters of behavioral change. However, compared to the findings of all the other challenge experiments where differences were noted only by parents, this conclusion may be unwarranted.

We would conclude that this study demonstrates that stimulant medication definitely affects teacher and parent behavioral ratings — a finding that has been demonstrated in many other studies — and that the effects of a challenge with food colorings is inconsistent and therefore questionable. The brief

periods of treatment manipulation (one week on each of 4 treatment conditions) may have contributed to the inconsistent results.

Australian Study — Levy et al.

This group studied a total of 30 children, 22 during the first study and an additional 8 in a replication study.[55,56] All children ranged in age between 4 and 8 years. Subjects were chosen on the basis of histories of chronic behavior problems typical of the hyperactive syndrome. This was a challenge study, but unlike the other studies of similar design, the challenge material was specially manufactured cookies, each containing 1 mg. of tartrazine, the chemical constituent of FD&C Yellow #5. Tartrazine was judged to be a reasonable single color challenge material since Dr. Feingold's theories are based upon his observations of aspirin-sensitive patients for whom a cross-reactivity, specifically to tartrazine, has been scientifically demonstrated.[57] The total dose of tartrazine given in the two studies was 5 mg. in the first study and 4 mg. in the second. The estimate of the average daily intake of food colorings in the U.S. population can be analyzed for each color individually and this calculation yields an average tartrazine ingestion of 7.34 mg. daily. Therefore, the dose used in these studies amounts to one-half to two-thirds of the average daily amount of this color ingested. Compared to the larger doses used in the three most recent studies (Swanson, Weiss and Mattes), this dose is small.

All children in the study protocol were followed by a variety of objective and subjective measures including the Conners' parent-teacher questionnaire completed by both parents and teachers, a measure of fidgetiness employing a stabilometric cushion, a continuous performance task, and a group of cognitive tests that measure impulsiveness and memory and have been employed in other studies of hyperactive children. Following baseline evaluation on all measures, the children were placed on the Feingold diet for 4 weeks. All tests were repeated following this period on the diet with no attempt to disguise the dietary treatment. Then all children were challenged over a 2 week period with either placebo or tartrazine in a counter-balanced order. Finally, all children remained on the diet for an additional 4 weeks, during which time no challenge was given.

For the first 4 weeks when the diet was tried in an open fashion, mothers reported an improvement in questionnaire scores. There were no changes, however, in teacher reports or on any of the laboratory testing measures. During the challenge period, there were no differences between the tartrazine or the placebo on any of the measures including the parent questionnaires. Because of the negative findings and because these investigators wished to test the Pittsburgh groups' findings of transient changes during the three hours immediately after the food coloring challenge, they re-analyzed their questionnaire data on a subgroup of the original 22 children who were most responsive to the open trial of dietary treatment. In this small group of 13

children, there were differences between the placebo and tartrazine challenge that reached statistical significance but only in the parent questionnaire. No differences were seen by the teachers or on any of the laboratory measures.

This group then attempted to replicate these findings on a small group of 8 children, this time looking only at parent-completed questionnaires. Children were challenged with either placebo or 4 mg. of tartrazine over a 2 week period. The authors do not report either the frequency or length of the challenge periods nor do they say at what point in time the parent questionnaires were completed. They report, however, finding no differences between the active challenge and the placebo challenge on the parent questionnaires. In other words, the repeat study on a small group failed to replicate their previous findings.

We would conclude that the study does not support Dr. Feingold's suggestion that tartrazine, because of its cross reactivity with aspirin, is the offending substance which causes definite and marked deterioration in behavior with dietary infractions. The improvement in behavior seen by the parents during the open trial of the Feingold diet demonstrates that behavioral improvement may be reported by parents even though there is no documentation of this change, even under open trial conditions, from teachers or from laboratory measures. This finding is entirely consistent with a placebo effect (see pp. 8-9).

Erythrosin B (In Vitro) Studies

Because work by Levitan et al.[58,59] has demonstrated biological activity produced by fat soluble fluorescein dyes, some researchers suggested that erythrosin B (FD&C Red #3), the only food color belonging to the fluorescein group, might affect behavior through an effect on neurotransmitters, chemical substances that are active in brain function and are thought to be abnormal in hyperactive children.[60] One way to study this issue is to see if erythrosin B has an effect on neurotransmitters when studied in a laboratory test (in vitro studies) in which the experimenter can directly observe the chemical's specific effect on each neurotransmitter. If one feeds the color to a person or an animal (in vivo studies) the specific effect on, for example, one kind of neurotransmitter, cannot be isolated from the effects on a variety of other tissues or chemicals. In other words, the in vivo experiment is too complex to determine specific cause and effect relationships. However, changes found in such a test may bear no relationship to what happens in the intact human or laboratory animal. For example, it might be true that a chemical in an in vitro test would produce changes in certain cells also isolated in a test tube, but the intact animal might prevent the chemical from reaching those cells thus eliminating such an effect in the live organism. Therefore, studies done in the test tube must then be tried in the animal or human before one can establish a definite relationship between the in vitro findings and effects seen in the live organism.

In vitro, i.e., test tube, experiments were conducted by Logan and Swan-

son[61] and by Lafferman and Silbergeld[62] demonstrating that erythrosin B inhibits the uptake of neurotransmitters by the nerve cell. In the Lafferman studies only the neurotransmitter dopamine was studied, but Logan also found an inhibition of uptake with seven other neurotransmitters. The degree of uptake inhibition was different in these two studies. Because of these differences Mailman et al.[63] systematically altered the conditions in the test tube to determine the reasons for these variable results. They found that the effect of erythrosin on the uptake of neurotransmitters depended upon how much protein tissue was contained in the test tube preparation. Neurotransmitter uptake inhibition was decreased in the presence of increased concentration of protein. This finding may be due to the absorption of the dye by the protein tissue making the dye less available for specific uptake inhibition. It is important to realize, however, that if erythrosin B inhibits neurotransmitter uptake in the test tube, this finding does not answer the questions about the effect of artificial food colorings on behavior *unless* erythrosin B or any other color can be shown to affect behavior in the human or animal. Swanson[64] tested this specific color (FD&C Red #3) in children by methods similar to their previous study (see pp. 20-23). They administered to 18 hyperactive children capsules that contained either a placebo or Red #3 in a dose of 1.3 mg./kg (the "maximum allowable level" of the World Health Organization), followed by hourly testing on a paired associate learning task (see p. 21). They found no differences in the test performance between those children given the color and those who received the placebo, suggesting the in vitro findings were not related to what actually happens in children.

Animal Studies

Shaywitz et al.[65] administered a mixture of artificial food colorings, prepared in the same proportions as were used in the manufacture of the challenge food substance (see pp. 9-10), by mouth on a daily basis to rat pups beginning at 5 days of age up until 26 days of age. The doses selected were ½, 1, and 2 mgs. per kilo which the authors felt approximated the quantity of food colorings ingested by children in this country. (A 30 kg./66 lb. child if fed the coloring mixture dose used in most studies would receive .8 mg./kg; if fed the dose employed in the Weiss study this figure would be 1.2 mg/kg; and if given the amount used by Swanson et. al. he would receive either 3.3 or 5.0 mg./kg.). This mixture of food colorings was given to both normal rat pups and rat pups depleted of dopamine (a neurotransmitter) by means of an intracisternal injection of 6-hydroxydopamine at 5 days of age. These dopamine-depleted animals are more active during their early growth phase but become normally active as they reach maturity. This experimentally altered animal has been proposed as an animal model of hyperactivity in children because of its increased activity level during immaturity, its poorer performance on learning tasks and because both impairments are significantly improved by the administration of stimulant medication.[66] In summary, then, both normal and dopamine-depleted rat pups were fed either a mixture of food

colorings or a placebo. The animals were tested by activity measurements and learning performances in a shuttle box. It was found that the food colors increased spontaneous activity in the normal rat pups as well as in the dopamine-depleted animals by somewhere between 10 and 25%, but there was no consistent relationship between the dose of food colorings given and the degree of activity increase measured, that is, sometimes an increase in food coloring dose was followed by a decrease or no change in activity. This finding makes it difficult to attribute the increased activity level as due only to food colorings. Usually these animals when placed in a new environment habituate as evidenced by decreasing activity level over time. Pups receiving no food colorings decreased their activity by 32% over the first 30 minutes of activity observation, but when they were given 2 mg./kg. of food coloring, the reduction was only 7.25%. Thus, the food coloring-fed animals apparently failed to habituate. In the shuttle box avoidance learning showed a transient decrease in animals fed food colorings at a dose of 0.5 mg./kg. when measured at 21 days of age, but the same group failed to show a difference at the dose of 2 mg./kg. Again, an effect which decreases with an increased dose of food colorings is difficult to explain. At 28 days of age the effect disappeared at all doses. If the dopamine depleted rat is a good animal model of hyperactivity in children — a point that is disputed by many — these specially prepared animals should have been more sensitive to food colorings in these learning experiments but increased sensitivity was not found.

Mailman et al.[63] injected 6-hydroxydopamine-treated newborn rats with large doses of erythrosin B and demonstrated an increase in the number of shocks these animals would accept in a laboratory test of punishment response. This effect is also seen when drugs are given that exacerbate hyperactivity. This group also assessed activity level in these erythrosin-B-treated animals but found no changes.

The results of these animal experiments remain difficult to interpret. Some of them need to be repeated. For example, the effects of increasing doses of food coloring on rat pup activity is inconsistent and higher doses of food coloring should be employed to see if a dose-response curve can be generated. Another problem inherent in all animal studies is that there is very little information that would allow us to extrapolate from any drug or lesion induced behavior in animals to hyperactivity in children. Also, the experimental conditions in these animal studies differ from the human situation in that food colorings are administered from early infancy while, in the human, the amount of food colorings ingested in infancy is not known, but is probably much lower than in later childhood. The findings do suggest, however, that food colorings may have some effect on animal behavior and such studies, therefore, should be continued. However, even if these findings are substantiated by further work, food coloring effects in animal studies will be of limited interest unless behavioral differences produced by food colorings can be established in humans by appropriate well-controlled investigations.

Conclusions

1) The test of the Feingold hypothesis by putting a child on this elimination diet under double-blind conditions is very expensive, time-consuming and, technically, very difficult. While in principle it may be the best test of the hypothesis, insofar as it does not assume which of several substances eliminated by the diet are the offending agents, but merely empirically tests the therapeutic effects of the Feingold diet, in practice it is so difficult and expensive that reasons for further repeating this type of experiment must be compelling. Instead, the evidence that the total Feingold diet produces improvement in the behavior of hyperactive children is equivocal. The mild and entirely subjective changes that have been reported (see pp. 13-14, 17-18, 22-24) are not, in our opinion, clinically important. None of the changes reported in the two studies that tested the total Feingold diet against a control diet are anything like the dramatic behavioral improvement described by Feingold and others. Also, it is almost impossible to provide an adequate placebo against which to compare the total diet. Therefore, the definite, but mild, differences in behavior seen in the study by Conners et al. and the subtle changes noted in the Harley study may have been due to the ability of some families to identify differences between the placebo diet and the Feingold diet.

2) Based on seven studies involving a total 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. These three exceptions include, in our opinion, the one child reported by Harley et al. (see p. 16), the one child initially reported by Mattes (see p. 24), and the one child reported by Weiss, Margan et al. (see pp. 23-24). Without the confirming evidence of objective tests and/or outside observers even these exceptions cannot be considered as definite evidence that there may be an occasional, genetically determined, sensitivity to food colorings. Though one cannot prove that no such children will be found, sufficient numbers of highly selected children have been studied to feel confident that such specific sensitivity, if found, would be rare.

3) These negative findings stand in sharp contrast to the 32-60 percent of children reported by Dr. Feingold and others to improve dramatically under non-blind conditions without the use of placebo controls. This contrast in treatment outcomes suggests that the Feingold regimen produces a therapeutic effect that has nothing to do with the removal of specific food additives. This type of non-specific therapeutic effect is known as a placebo response. A

placebo response is a change due to a component of therapy that is without specific activity for the condition being treated. In the case of the Feingold hypothesis, the specific treatment is presumably the elimination of artificial food colorings, artificial flavorings and salicylates. The components of therapy that are without specific activity for hyperactivity and learning disability would be changes in attitude about the condition, the expectation that special diets will improve the disorder and the belief that certain components of food are toxic. The Feingold regimen possesses several, non-specific treatment characteristics that would be expected to produce a powerful placebo response. First, the dietary change, while removing specific additives, also drastically alters shopping and cooking routines, and produces big changes in eating habits. Since most preprocessed foods are eliminated, the family must prepare foods from scratch. While shopping, labels must be repeatedly checked. Most favorite snack foods are eliminated, and such habits as gum chewing and the use of mints or hard candy must be discontinued. All of these changes drastically alter routines and the family must continually think about their dietary choices. These changes would be expected to increase, and alter the focus of, attention paid to the child with behavior problems. Prior to dietary treatment, these children often receive considerable negative attention. The focus on foods, rather than on the child, as the source of an unpleasant emotional atmosphere, can be expected to dramatically alter the emotional dynamics within a family. Secondly, the Feingold diet eliminates substances that many people assume to be toxic, whether or not there is scientific evidence for this conclusion. Dr. Feingold clearly makes this assumption:

> "The limited number of reports published on adverse reactions to food additives does not reflect the incidence of this problem that would be expected from the very wide distribution of additives in the food supply. This discrepancy can no doubt be attributed to the failure of the public at large as well as the profession to recognize the wide distribution of these chemicals in our food supply as well as the appreciation that food additives are frequently a cause of various clinical patterns."[67]

The belief that food additives are toxic would be expected to produce changes in behavior based upon the expectation that behavioral deterioration will result from their ingestion. This expectation is most dramatically conveyed by Dr. Feingold's statement, "Whenever a change in behavior occurs, suspect an infraction."[68] Finally, the conditions of hyperactivity and learning disability possess characteristics that lend themselves to placebo effects in treatment. Both are disorders characterized primarily by behavioral symptoms that provoke considerable guilt on the part of parents since these behaviors are often interpreted as signs of poor parenting. In this atmosphere of guilt there is an emotional need to perceive the disorder as caused by sources outside the home and family. These needs can be expected to increase the potency of placebo effects based upon the belief that foods rather than family interaction are producing the child's problem.

4) The evidence that artificial food colorings may, in large doses ingested

at one time, produce adverse behavioral reactions is, at best, uncertain. Only the Swanson studies suggest such behavioral toxicity in human subjects, and their findings must be questioned (see pp. 20-23). Though animal studies have suggested that behavioral changes in the experimental animal may be seen as the result of artificial food colorings fed during the neonatal period, conclusions based upon these experiments are also subject to question (see pp. 28-30). There is some evidence that erythrosin B affects biological systems in vitro, but the only evidence, as of yet, that this biological activity may result in behavioral symptoms stems from the animal studies by Mailman et. al.[63] which have very questionable applicability to hyperactivity in children. The preliminary findings by Swanson[64] suggest that no relationship will be found between erythrosin B and hyperactivity or learning disability.

Recommendations

1. The studies reported here represent the efforts of dozens of investigators over more than a four year period at a cost which has probably exceeded the million dollar level. It is our opinion that the studies already completed provide sufficient evidence to refute the claim that artificial food colorings, artificial flavorings, and salicylates produce hyperactivity and/or learning disability. We see no indication based on this evidence for the continuation of high priority, specially funded programs for further investigation in this area. We also see no need for changes in public policy with regard to the use of artificial food colorings in the food industry based upon the putative relationship between artificial colorings and behavior problems in children. There is insufficient evidence to suggest a ban of food containing artificial food colorings in the federally supported school lunch program.

2. Because of the lack of evidence for a causal association between the specific food additives mentioned in this paper and hyperkinesis or learning disability, there is no special need for a symbol on food labels indicating the presence or absence of these food additives for the purpose of treating these behavioral disorders. There may be other reasons for indicating the presence of certain food additives on food labels, but the larger issue of what constitutes an appropriate food label lies outside the scope of this committee's deliberations.

3. Food coloring effects demonstrated in animals and by means of in vitro studies may lead to evidence of behavioral toxicity and therefore should continue. However, biological activity confirmed in the test tube or in animal studies must then be shown to relate to hyperactivity or learning disability in human subjects if this phenomenon is to be related to Dr. Feingold's claims.

4. There is a general need to remain vigilant regarding the safety of food colors but this issue should stand on its own merits and bears no relationship to the specific disorders of hyperactivity and/or learning disability. In addition to the studies mentioned here, investigations of lifetime feeding of food colorings to animals are underway and should continue.[69]

5. Since the food-additive-free diet has no apparent harmful effects, and

since the non-specific (placebo) effects of this dietary treatment are frequently very beneficial to families, we see no reason to discourage those families who wish to pursue this type of treatment as long as they continue to follow other therapy that is helpful. If the family asks, however, for the clinician's advice he or she must cope with the ethical issues involved in recommending a treatment for its placebo effect while the family believes that the treatment is based upon scientific evidence.

(n.b.) As this report was in press, we received the book entitled, *Food Additives and Hyperactive Children* by C. Keith Conners (Plenum Press, N.Y., 1980). The material referred to in our references numbered 43 and 44, are reviewed in Chapter 6 (pp. 87-93) of that book.

We find ourselves in close agreement with Dr. Conners' conclusions and wish to acknowledge the contribution made by his review and summary.

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Appendix

The National Advisory Committee
on Hyperkinesis and Food Additives

— Report to The Nutrition Foundation
June 1, 1975

The Nature of Hyperkinesis

The terms "hyperactivity, hyperkinesis and hyperkinetic syndrome" have been loosely employed in both lay and professional writings. Strictly speaking, hyperactivity is one of the symptoms of the hyperkinetic syndrome. Frequently, the latter term is mistakenly used interchangeably with that of the syndrome of "minimal brain dysfunction," which syndrome is of itself ill-defined. Indeed, Strother (3) has opined that "greater attention should be paid to classifying the very heterogeneous group of children now included under this rubric into more specific and homogeneous categories." There is no agreement—and little good evidence—as to the extent to which several seemingly related syndromes overlap. Definitive separation of these conditions has not been made in the writings of most physicians, behavioral scientists, or educators, including Dr. Feingold.

In an effort to clarify "the murky realm of nosology" P. H. Wender (4) notes that there is evidence for several etiological subgroups, and that the "hyperkinetic behavior syndrome" includes a number of clinical features: hyperactivity; short attention span and poor powers of concentration; impulsivity and the inability to delay gratification. There is diminished ability to experience pleasure and frequent refractoriness to disciplinary measures of any sort. Variably affected are perceptual-cognitive functions and neurologic function and coordination. These problems produce significant school underachievement in most children with the disorder. In school it contributes to classroom disruption; at home it is disruptive to family relations. Estimates of its incidence in U.S. schools range widely, frequently from 3 to 10%. Feingold (1) quotes some estimates as high as 25% or more of all children in certain schools. Others estimate a similar percentage of children as receiving drugs for the disorder (5). These variations reflect the inappropriate equating of different conditions "under the rubric of learning disabilities (i.e., hyperkinesis and reading retardation)" as well as other influences (6).

The origin and development of the disorders have not been established. Indeed, it is not even certain whether this is a discreet illness or a syndrome of many causes. There is evidence to support the hypothesis that some minimal brain dysfunction is genetically determined, produced

by subtle central nervous dysfunction of biochemical nature (4). It is also hypothesized that some minimal brain damage may result from intrauterine factors or from difficult birth process (7). In rare instances low level lead encephalopathy may contribute to such a syndrome, if one can extrapolate from experimental animal models (8, 9).

The lack of clarity in regard to these conditions is emphasized by the statement of The Council on Child Health of the American Academy of Pediatrics (10):

> "One must be cognizant of the fact that there is probably more confusion in relation to diagnosis and appropriate criteria for the use of medication for the treatment of hyperkinetic children than there is regarding the actual medication. Many physicians, as well as the general public, do not truly appreciate the differential diagnosis of the overactive child. It may be the result of basic personality, anxiety, subclinical seizure disorders, strictly in the eyes of the beholder, or true hyperkinesis; the latter is the only condition in which stimulants might be expected to be beneficial."

The Council on Child Health of the American Academy of Pediatrics (10) further notes that:

> "The hyperkinetic child is typically one of normal intelligence who fails to learn at a normal rate even though he is given the same educational opportunities as children with equal intelligence. He usually exhibits to some degree (1) short attention span, (2) easy distractibility, (3) impulsive behavior, and (4) overactivity. Although other behaviors ofttimes are seen in children with normal intelligence and academic lag, stimulant drugs seem to be most effective in the four behaviors just mentioned. Little is known about the effect of stimulant drugs on such things as poor motor integration, deficits in the perception of space, form, movement and time, and disorders of language or symbol development."

Response to drug therapy is unequivocal when it occurs and after satisfactory response to short term treatment, omission of the drug is immediately evident to those around the child, because he rapidly returns to the base line abnormal behavior (10). After long periods of control, discontinuance of drug therapy may be followed by remission in some 25% of patients. It is the practice of "many clinicians [to] discontinue the use of medication over each long school vacation; this

allows the child to start a new year without medication. The medication is resumed only if the syndrome that initiated the original treatment hinders satisfactory school progress" (10).

There is little reliable information about the prognosis or natural course of hyperkinesis, how long the average child may benefit from medication, or whether taking stimulant drugs alters the ultimate prognosis in a substantial way. As an example, in a study recently published (11) in JAMA, data were summarized on 42 children, 13 of whom had been followed for two years, and 29 for one year. The subjects had been part of a double blind placebo study on the effect of different dose levels of Ritalin on behavior and school performance and were tested at one month intervals. Thus the population employed were known to be Ritalin responsive.

Twenty-six per cent of those taken off medication exhibited no deterioration of performance. This observation is important to interpretation of any studies of the effect of newly instituted regimens because the previously occurring symptoms do not always return immediately when medication is discontinued.

In a study at the University of North Carolina designed quantitatively to measure the motor activity and interest span of children diagnosed as hyperkinetic, Dr. Routh (12) reported that of 78 referrals from physicians, teachers and parents, 47% of the children were judged to be overactive and 53% were not. This, despite the fact that all of the children were considered to be "problem children" by those referring them to the testing service. Difficulties are inherent in all measurement techniques. Behavior perceived as hyperactivity may be more accurately described as non-goal directed activity. There is a sub-group of children with many of the other characteristics of minimal brain dysfunction who are in fact hypoactive.

Examples are numerous to illustrate the inconsistencies in rating of a child's activity by observers with different relationships to the subject, i.e., mothers, fathers, teachers, physicians, independent observers. Differences in perception by the observer do not follow a consistent pattern determined by the relationship to the child. For example, in a study in Iowa of teacher ratings of hyperactivity, it was found that older age teachers rated more children hyperactive than did young teachers (13).

Clinical experience indicates that many factors alter the activity patterns of such children or the perception of them by parents. Such factors range from the presence or absence of breakfast, weather conditions and resultant seasonal cycles that alter activities during cold seasons, to the interpersonal family relationships or existence of disruptive family problems. Age of the child appears to be another determinant of detection of the syndrome of hyperactivity. The majority of cases are noted at about the age of entry to school and there usually is a gradual diminution in the hyperactivity approximately at puberty or slightly

thereafter. While some observers cite isolated cases of identifiable hyperkinesis in older individuals, this not the usual pattern. The syndrome is not recognized as a problem by school authorities in some areas of the world—again an example of differences in perception or of occurrence.

The diagnosis of hyperkinesis depends primarily upon the trained clinician's judgment, based upon history and observation of behavior. Some studies have employed trained classroom observers to help confirm the diagnosis. Again, behaviors which can be objectively measured may not adequately reflect the kind of problems that different children have. Objective measures of attention span have been developed (usually continuous performance tasks) and have been employed in making the diagnosis in some studies. Standard questionnaires completed by parents and teachers and involving observations at several different points in time provide useful evaluatory techniques.

The Feingold Hypothesis

In June 1973, Dr. Ben Feingold, a pediatric allergist from San Francisco, orally presented a preliminary report (14) in which he stated that hyperkinesis was associated with the ingestion of salicylates, of compounds which cross-reacted in the body with salicylates, and with common food additives.* This presentation was followed by a signed editorial in October, 1973 (1). The October 30, 1973 Congressional Record (16) contained the text of a paper given by Dr. Feingold at a meeting in London the month before and an account by a writer for the *Washington Post*. Dr. Feingold's paper printed in the Congressional Record yielded calls for the elimination of "food additives" from school lunch programs. He later restated his position in a book (2) entitled,

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* The term "food additive" is of itself a broadly encompassing one which is too often loosely used. The Food Protection Committee of the Food and Nutrition Board, National Academy of Sciences/National Research Council defines food additives (15) as "a substance or a mixture of substances, other than a basic foodstuff, that is present in a food as a result of any aspect of production, processing, storage or packaging. The term does not include chance contaminants." It does embrace such diverse substances as many essential nutrients (vitamins, minerals), flavoring agents (naturally occurring or synthetic), functional ingredients, preservatives and antioxidants (naturally occurring or synthetic), etc.

The U.S. Food and Drug Administration has defined "food additive" as: "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or

Why Your Child is Hyperactive. This book not only advocates the hypothesis, but also describes his dietary method of treatment. The presentation and the publication of the book have attracted a great deal of publicity. It has resulted in hundreds of letters to pediatricians, especially from parents seeking assistance, and although Dr. Feingold advocates his diet under medical management, it probably will lead to self-treatment programs.

Dr. Feingold currently advocates that a special label, identifying foods "without additives," be made available to be placed on all foods sold to the American public. By implication, of course, foods not so labeled would be considered by the interested consumer to contain "synthetic" additives.*

Dr. Feingold has not presented a specifically focused hypothesis. He depends upon the empirical observations he has made with patients under his therapeutic regime and on his special diet. He has reported that his management regime and an elimination diet (the Kaiser-Permanente or K-P diet), which was designed to be low in salicylates and free of "food additives," effectively treats 48% of the children presented to him with hyperkinesis. Of the children who respond, under his guidance, about ⅔ do so dramatically; the other third "favorably." It is important to note that Dr. Feingold claims (2) a response in *only half* of the children treated and dramatic response in but ⅔ of these. Thus his percentage of success is of the same magnitude that occurs following cessation of drug therapy (11).

Although Dr. Feingold's claims may prove valid, and, if so, may represent a major breakthrough in the treatment of this complex condition, the fact remains that his hypothesis is subject to serious criticism on several grounds. Of especially critical significance is the fact that no double blind controlled experiments have been conducted which permit the conclusion that dietary constituents are the critical variables. His observations, therefore, have served as a basis for generating an hypothesis, but they are inadequate for rigorous testing of the hypothesis. They do not justify definitive conclusions.

holding food; and including any source of radiation intended for such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use."

The distinction between "naturally occurring" and "synthetic" is usually vague and often relates to origin, not identity of the compound or mixture. For example, chemically synthesized β-carotene, the precursor of vitamin A, is "synthetic" while the chemically identical material biologically present in the carrot is "natural." Similarly, a mixture of three or so synthetic chemical components of a natural flavoring agent is termed "synthetic," while the "natural" agent contains these same components plus an additional number of compounds. Thus, the separation into "natural" and "synthetic" *per se* has no biological significance.

According to the Feingold regimen, not only the children, but their entire families are placed on the diet and regimen in order to ensure compliance. Parents are instructed to spend Saturday mornings making additive-free candy and cake with their children. There can be no question but that the total regimen significantly alters the structure and dynamics of the families by the introduction of the diet and its restrictions upon the child and his family. Since in many children hyperactive behavior is associated with family problems, it is quite possible that the alterations in the family dynamics may be causally related to the reported improvement in the child. Second, hyperactive behavior and its rating on a severity score are both subject to suggestibility. Dr. Feingold is charismatic and certain of the value of his program. It is possible that the confident expectations generated in the patient and the family affects the syndrome itself, or at least the parents' ratings of the altered severity of the behavioral pattern. Third, parents or teachers who rate the children know that they are on the diet and this knowledge may influence their ratings. Fourth, objective rating scales like that developed by Dr. Keith Conners (17) have not been systematically employed to measure the parameters of the disorder or improvement. Dr. Feingold's improvement ratings are global, not specific.

The exact additive and nutrient content of the Feingold elimination diet remains difficult to assess. The proscriptions invoked may eliminate important and as yet unidentified food constituents. Knowledge of the chemical composition of foodstuffs is fragmentary. A number of common sources of important nutrients are proscribed, making it especially important that careful planning and food selection pertain to assure that nutrient requirements are met for any long term period of restriction to the regimen. Development of information on nutrients supplied by the regimen are currently underway in order to evaluate dietary patterns under the restrictions imposed and to determine if they may meet the long term nutrient needs of children. Until this question is answered, the committee feels that this regimen should not be used without competent medical supervision.

The initial rationale of the elimination diet advocated by Dr. Feingold was to avoid salicylate and salicylate-like compounds which occur naturally or as a result of processing. Data upon the naturally occurring salicylate compounds are notably incomplete and the dietary plan is based upon studies utilizing old and less-than-definitive methodology. The K-P diet calls for elimination of many commonly eaten members of the widest variety of food classes, with and without food additives, of all categories. There is *no* identifiable single substance or group of substances which the diet specifically removes and to the absence of which any observed effect might be attributed. The validity of this assessment by the Committee is indicated by Dr. Feingold's shift of emphasis from a suspected role of salicylates, aspirin-like compounds, to other food ingredients. It is noteworthy also that the K-P regimen (2)

proscribes a wide variety of sundry items including over-the-counter medications, toothpastes and tooth powder, mouthwashes, cough drops, throat lozenges, antacid tablets and perfumes. Accordingly, the regimen markedly modifies other ingestibles as well as food.

A review (18) of the preliminary studies on eight patients by the Pittsburgh group studied in relation to the K-P regimen revealed that the majority of those subjects were judged by the parents to have exhibited improvement, sometimes continuously, regardless of which of two dietary regimens (the K-P diet or a "control") they were following. There were discrepancies, however, between the assessment by parents and by teachers of perceived behavioral changes in a portion of the studies and the teacher assessment was absent in a considerable number of the observational periods reported. Although the data were inconclusive, the preliminary results of the pilot studies were consistent with an interpretation of placebo effects and of variations in perception on the part of different observers, both of which are known to occur in studies of hyperkinesis.

Summary

The Committee concludes that data from critically designed and executed studies, free of the deficiencies of design noted, must be available before firm conclusions can be reached on the Feingold hypothesis. Accordingly, the Committee has considered at length the experimental design characteristics necessary to obtain definitive, interpretable data which may permit a decisive interpretation.

Guidelines for Experimental Design

While a variable number of experimental approaches may contribute to resolution of these complex questions, certain approaches will be more informative and feasible than others. The possibility of producing a wide variety of dietary products in identical pairs containing, or free of, specific chemical ingredients and indistinguishable to the consumer was considered. To execute effectively a program utilizing many such foods and to maintain the regimen as a complete double blind study would involve an enormous expenditure. On the other hand, the utilization of alternate dietary plans, i.e., the K-P diet and a "control," even when randomly administered, precludes strict double blind testing and introduces the variable placebo effect.

Patient compliance is difficult to control and monitor and might most easily be assured in a totally institutional or residential population. Potential methods for controlling compliance might be detection of metabolites or a marker in urine, but committee members are doubtful that appropriate technology may be available for such monitoring. This is being explored.

In order adequately to test the Feingold hypothesis, it is desirable that an "exclusion" diet planned for nutritional adequacy and in keeping with the K-P proscriptions be designed and utilized. Strong preference was expressed by the Committee that in a home setting there be used but one diet, i.e., no "control diets," because of anticipated difficulties in assuring compliance and the impossibility of avoiding the placebo effect. The use of a control diet would be more acceptable in a residential or institutional setting.

In any study it is essential to establish a valid behavioral base line before any manipulation is tried. The multiple and manifold nature of symptoms make it mandatory that the base line be established by having more than a single point and a *minimum* of two observations are required. The observations and evaluations should include assessments by the same observers in at least two different points in time and the observers should be the same as those who will subsequently assess the patient's behavioral pattern during the remainder of the study.

It was agreed that, after establishment of the behavioral base line and institution of the dietary regimen, a well designed double blind study utilizing, as a test or challenge, conventional foods prepared to be free of, or to contain, a single challenge ingredient or group of ingredients, would be most informative. The "challenge foods" should be made available for daily consumption by all members of the family. Such foods are more acceptable than capsules and the Committee recommends that at least two forms be developed. Each of these forms should be prepared in separate lots, one free of challenge material and another containing the challenge substance(s). They should be packaged in such manner as to preserve the double blind nature of the observations. Sequentially identified individual units should be packaged for consumption by the family, utilizing randomization and an unindicated code.

Behavioral observations of subjects will be made throughout the course of the experiment and only upon conclusion of individual studies will the challenge code be broken. In the event of adverse somatic reactions or deterioration of behavior, of course, the eating of the "challenge food" may be interdicted. A direct comparison of observed behavioral patterns with consumption or non-consumption of the "challenge substance" will permit definitive conclusions. These studies demand adequate independent monitoring and an appropriate number of participating families with hyperkinetic children.

The Committee emphasizes the necessity for utilization of quanti-

tative base line measurements of behavior and of behavioral changes. As a minimum it is agreed that the Conners scale should be adopted and that assessments should be made by the use of independent (non-parent, non-teacher) classroom observers (such as graduate students in psychology) as well as by teachers and parents. In addition, there should be a clinical assessment by a physician at the beginning of the experiment and at least at monthly intervals throughout and additional measurements as feasible within the resources of the research team.

At least two weeks of base line data are recommended, the exact circumstances of which will depend upon the prior treatment (medication, diet or none), if any, of the patient. The frequency and quantity of observations during the base line period and the experimental periods should be such as to assure adequate assessment of individual variations. The reliability of all observations, including the initial observation, should be maximized by having the same observers rate the child throughout. Because of the known effect of medication on the symptoms being observed, the Committee felt that whenever possible any study should include a significant preliminary period of approximately two weeks during which there is no medication. It was agreed it would be advisable for at least one study to evaluate children who had never received drug medication. The period of observation following the base line should be a minimum of one month for the diet.

The code for the challenge materials should not be broken until the study is completed and the behavioral data are available for direct comparison with the data on the consumption of the challenge or control food. The advantage of the proposed approach is that interdiction is possible at any point simply by stopping the "challenge food." Careful records should be maintained of all such instances.

Ethical Considerations

The question of ethical acceptability of such studies has been carefully considered and the Committee agrees upon the following points:

The subject and the family will benefit from participation in such experiments whether:

(a) a challenge material can be incriminated, and thereby the opportunity of avoidance of a specific offending material results; or

(b) there is confirmed in a well controlled setting the value of the restricted diet as opposed to other factors; or

(c) no benefit occurs and thereby a troublesome exclusion diet of indefinite duration is avoided.

studies are in humans, but the estimates include modest funding for initiation of projects utilizing animal models. The Committee estimates that a total investment of $400,000—$500,000 is required. It is hoped that these funds may be obtained from a number of sources and that their utilization may be coordinated within the framework of the guidelines identified by the Advisory Committee.

Potential sources, in addition to the food and food related industries, logically would appear to be the Food and Drug Administration, National Institute of Education, National Institutes of Health, the National Science Foundation and other foundations. The role of The Nutrition Foundation would appear to be two-fold: a) the continuing support of the Advisory Committee for purposes of assessing and coordinating research program activities and evaluating overall developments and, b) direct support of recommended grants utilizing funds available from a variety of sources. Industry as well as other support for these activities could well be coordinated through administration by The Nutrition Foundation.

The most economical and expeditious initial test of the hypothesis would be to determine, in keeping with the requisite design, the behavioral response to "challenge foods" of known hyperkinetic children currently maintained on the K-P regimen. Dr. Ben Feingold has agreed to cooperate with the Advisory Committee in exploring such an initial study of patients in his series. Other cooperative centers of investigatory work are being explored.

Development of Challenge Food Vehicle

A task force from industry participated in by the staff of The Nutrition Foundation has, during the period beginning from the January 1975 meeting of the Advisory Committee, undertaken the preparation of appropriate challenge and placebo vehicles as recommended by the Advisory Committee. It is anticipated that these coded materials will be ready for utilization by investigators during the spring of 1975.

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