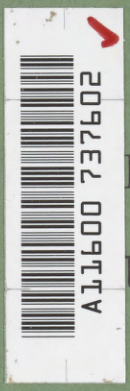
NUTRITION AND HUMAN NEEDS



HEARINGS

BEFORE THE

SELECT COMMITTEE ON
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OF THE

UNITED STATES SENATE

NINETIETH CONGRESS

SECOND SESSION

AND

NINETY-FIRST CONGRESS

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NUTRITION AND HUMAN NEEDS

PART 13E—NUTRITION AND PRIVATE INDUSTRY

WASHINGTON, D.C., AUGUST 5, 1969

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APPENDIX

NUTRITION AND HUMAN NEEDS

TUESDAY, AUGUST 5, 1969

U.S. SENATE,
SELECT COMMITTEE ON NUTRITION AND HUMAN NEEDS,
Washington, D.C.

The committee met at 10:15 a.m., pursuant to recess, in room 4200, New Senate Office Building, Senator George S. McGovern (chairman) presiding.

Present: Senators McGovern, Ellender, Percy, Dole, and Dominick.

Staff present: William C. Smith, general counsel and staff director, and Gerald S. Joseph Cassidy, professional staff member.

The CHAIRMAN. Good morning, ladies and gentlemen.

Our first witness is Mr. Steven Mason, vice president of the International Minerals & Chemical Corp., located in Senator Percy's State.

OPENING STATEMENT BY HON. CHARLES H. PERCY, A U.S. SENATOR FROM THE STATE OF ILLINOIS

Senator PERCY. Mr. Mason, perhaps you would just like to take a seat at the table.

Mr. Chairman, I am very pleased this morning to welcome the International Minerals & Chemical Corp. to participate, through their representatives, in these hearings. I appreciate this opportunity to talk about a company valued very highly in Illinois. I personally have been well acquainted with it because of its proximity to my own business location through the years.

International Minerals & Chemical has its headquarters in Skokie, Ill., a suburb of Chicago, and has achieved a worldwide reputation for its leadership in supplying agricultural chemicals to farmers since its founding in 1909.

However, it is much more than an agricultural supplier. IMC today is a diversified company that produces hundreds of products for industry and the home as well.

A growing share of IMC's business is in the food field where products are produced for retail, processing, and institutional markets. That aspect of the company's growth has developed since 1942 when IMC began producing monosodium glutamate. Today it is ranked as the Nation's leading producer of MSG, which is known as Accent.

In effect what IMC has been trying to do is what every housewife in America, including every Senator's wife, is trying to do—simply make food taste better, which is a large part of cooking.

IMC produces products serving many uses in the food industry and away-from-home feeding by schools, hospitals, restaurants, and other

institutions. The company's chief executive officer and president, Mr. Nelson White, very much wanted to be present at today's session. As I understand it, he just arrived in the country last night from a long trip, including Australia, so he is represented today by R. Steven Mason, vice president in charge of the food area of this major corporation's business.

It will be interesting to the committee to know that Mr. Mason's life experience in business has been essentially with companies that we have heard from in these hearings. He came to IMC from Ralston Purina Co. Before that he was with General Mills in various sales and marketing positions. He is a graduate of the University of Alabama.

We are very happy to welcome you this morning. I know the committee is pleased to have you as a witness, Mr. Mason.

Senator ELLENDER. Mr. Chairman, I wish to join the Senator from Illinois. I have just learned that these good people have a plant in my own State. They bought out a plant that was owned by the Bulliard family. I understand you are expanding that and I wish you much success.

The CHAIRMAN. Mr. Mason.

STATEMENT OF R. STEVEN MASON, VICE PRESIDENT, INTERNATIONAL MINERALS & CHEMICAL CORP., ACCOMPANIED BY DR. A. G. EBERT

Mr. MASON. Mr. Chairman, distinguished members of this committee.

International Minerals & Chemical Corp. is pleased to have an opportunity to testify before this select committee. As the Nation's largest producer of the flavor-enhancer monosodium glutamate, we feel a strong obligation to all users of MSG, to our industry, to the scientific community, and to this committee, to come forward to present our data relevant to the use and safety of one of our products.

Monosodium glutamate has a long history. Its flavor-enhancing properties were first recognized in Japan in 1908. However, various natural products rich in glutamate have been used for their flavor-enhancing properties for thousands of years. Our own interest in the product dates back to 1942. From the time of that initial involvement, we have felt a sincere and strong sense of responsibility to establish and insure the product's effectiveness and safety.

Glutamic acid, of which monosodium glutamate is the sodium salt, is a natural component of protein foods. Its natural occurrence in proteins is closely linked to the fact that most foods of basically protein origin are improved in flavor with the addition of MSG. Included are such foods as soups, meats, poultry, seafoods, vegetables, and certain snack foods.

Recognizing that there are pitfalls in talking about per capita or average food intake, particularly in a nation of over 200 million people with a wide range of eating habits, we estimate that the per capita glutamic acid consumption in this country, as a natural component of the foods we eat, is about 15 grams per day. When the housewife or food processor adds MSG to enhance the flavor of foods, they are adding to a natural component already present in those foods—on the average only one-third gram or an additional 2 percent—a relatively insignificant amount.

Let me explain further that in terms of percentages, monosodium glutamate is added to appropriate processed foods in levels ranging from 0.2 to 0.4 of 1 percent of that food. Expressed another way, a product on the high side of that range, some soups for example, might contain as much as 6 ounces per 10 gallons.

The committee has expressed an interest in the nutritive value of MSG. To the extent that the product is utilized by the body, MSG does have nutritional value. But our product is sold to improve flavor. We like to think though, as suggested by earlier witnesses, that improved flavor is at least indirectly tied to nutrition. The most nutritious food provides no nutrition, unless it is eaten, and improved palatability certainly encourages eating.

Concerning the safety of monosodium glutamate, this corporation has viewed with increasing concern and, in fact, shock, the reports which have appeared in the popular press as a result of certain testimony before this select committee which implied that monosodium glutamate might be deleterious to humans and particularly infants in its use with food, and that no toxicologic studies or safety evaluation work has been done.

The question of the safety of monosodium glutamate has always been viewed by our corporation as an ongoing study which continues in the light of new scientific evidence and technology.

In our search for new applications, and to zero in on the best use-level in a given food, we have conducted a continuous program of taste panel evaluations in a wide variety of food products for a quarter of a century. This usually necessitates adding monosodium glutamate in what we would regard as both low and high levels. Never in any of these studies have we had a physiological complaint which might be related to the addition of MSG. Speaking conservatively, we have conducted hundreds of such consumer preference taste panels involving thousands of responses. I mention this as evidence of the product's safety under normal use.

Further, we have sponsored studies through independent and highly reputable research laboratories which establish the safety of monosodium glutamate. These studies were conducted using laboratory test animals. Clinical work has also been done on humans involving extremely high levels of glutamate in the treatment of certain central nervous system disorders, with no toxic effects reported.

As a result, we have an extensive fund of research which establishes the effectiveness and safety of monosodium glutamate for human consumption as a food flavor enhancer. And recent studies mentioned and testimony given before this committee did not refute or discredit these data.

With your permission, I would now like to ask Dr. Andrew G. Ebert, manager of pharmacology and Government registration in our corporate research division, to describe in somewhat more detail the results of several safety evaluation studies on monosodium glutamate, specifically:

1. A 2-year chronic feeding study in rats.
2. A 2-year study on mice by A. D. Little, Inc.
3. A 90-day feeding study in rats.
4. The effect of MSG on the reproduction and development of rabbits.

Dr. Ebert will summarize each of these studies and then expand on them as the committee desires. His comments will bring you up to date on past research projects relevant to the safety of MSG. Let me emphasize, once again, that these research efforts are continuous and ongoing, whether spurred by our own interest in the product, or by the creation of the slightest doubt, reasonable or unreasonable, as to the safety of this natural food commodity.

Dr. Ebert?

Dr. EBERT. Mr. Chairman, as a member of research management for International Minerals & Chemical Corp., I am one of the scientists who has recently been involved with studies on the safety evaluation of monosodium glutamate in conjunction with its use as a flood flavor enhancer. Research on MSG has been carried out over the past two decades by outstanding men in the field.

Qualified scientists had been convinced of the safety of MSG for its intended use and placed it on the GRAS list after adoption of the Food Additive Amendment to the Federal Food, Drug and Cosmetic Act. However, prior to and subsequently, our company sponsored appropriate tests to demonstrate the safety of MSG.

In chronological order, the first long-term toxicity study sponsored by IMC was carried out in 1950–51 by A. D. Little, Inc. In that research three compounds were evaluated. The L-isomer of MSG which is the material sold commercially, plus two related compounds: DL-monosodium glutamate, that is the racemic mixture, and L-glutamic acid, the acid form of MSG.

Test compounds were incorporated in rat diets at levels of 0.1 percent of 0.4 percent by weight of diet. Note that these concentrations are equal to or slightly greater than the typical use levels of MSG added to the diet of humans.

These diets were administered to Sprague-Dawley rats for 2 years; that is, their anticipated lifetime. During the study, each of the 600 rats in the tests were examined for any signs of toxicity. Body weight gains and food consumption were frequently measured. Hematologic examinations were carried out, as were blood-glutamate levels. Any animals that died during the course of the research—plus those sacrificed at the end of 2 years—were subjected to gross and histopathologic study.

The following quote from the summary of the report describes the results:

"On the basis of our observations made in living animals and at post-mortem examination, it is our conclusion that we have seen no evidence of chronic toxicity to be exerted by L-monosodium glutamate, DL-monosodium glutamate, or L-glutamic acid."

I think it would be worthwhile to add parenthetically here that the 0.1 percent and the 0.4 percent used were equivalent to 1 teaspoon per day in man at the low level and 4 teaspoons per day in man at the high level.

We believe a second study would be of interest to the committee. It deals with the safety of the product beyond the toxicological aspects previously discussed at these hearings.

This was a 2-year evaluation in mice using the black C–57 strain of mouse which had been shown to be extremely susceptible to known

chemical carcinogens. The dose of MSG was 1 percent and 4 percent of diet, 10 times the amount used in the previously described research in rats. On the basis of a 30-gram mouse eating about 5 grams of chow per day, this would be a dose of over 6 grams per kilogram of body weight. In a 150-pound man, this dose would be equivalent to consuming about one pound of MSG a day at the high level. The scientists were looking primarily for possible tumors in these animals. There were none, nor were there any toxic effects.

Monosodium glutamate has been studied with respect to reproduction and teratology, which is the study of offspring malformation. Our corporation sponsored research in 1966 following publication of a paper which claimed that glutamic acid was teratogenic to rabbits.

In our studies carried out by Hazleton Laboratories, Inc., various concentrations of MSG were used. These concentrations were low, intermediate, and high: 0.1 percent, 0.825 percent, and 8.25 percent of the diet. These levels, in food, were fed to rabbits for 2 to 3 weeks, after which the animals were mated.

Parents and offspring were studied for signs of adverse effects on reproduction, or for malformation of the young. No abnormalities were observed that could be attributed to MSG. Further, following the Olney paper on brain damage in mice receiving MSG subcutaneously, the preserved pups on the 8.25 percent MSG levels, plus controls from our studies, were reexamined for evidence of brain damage.

The 8.25 percent MSG concentration in feed was equivalent to a dose of 2.5 to 3.5 grams per kilogram per day, in the same range as that administered in a single subcutaneous dose in Dr. Olney's experiments. When the Hazleton scientists examined the same areas of the brain where Olney reported damage, they observed no evidence of neuronal necrosis or other pathology.

Senator PERCY. Could I interrupt the witness at this point? Regretfully I must now leave for a markup legislative session.

I would just like to ask one question. Have you reviewed carefully all of the adverse testimony that has been given before this committee relating to harmful effects of MSG?

Dr. EBERT. Yes, sir; I have.

Senator PERCY. Could you explain to the committee how extensive your own investigations have been as to possible harmful effects as against the investigations that have been carried on by those other witnesses who have testified? How much more do you think you know about your own product than the other witnesses who have appeared before this committee?

Dr. EBERT. The protocols used in our studies have been specifically designed to demonstrate the safety or lack of safety of a food additive or any additive administered for a long period of time. This was not the protocol, as I understand, that was utilized in the papers reported here.

Further, the studies that we carried out were of a longer duration utilizing means of administration by which the product is consumed by man, and at normal levels of consumption of multiples thereof. We look with interest upon data where the product is, you might say, abused such as being given at high levels, subcutaneously, to the immature animal, in this case the mouse, and while these data are interesting, we feel that they in no way refute our extensive safety evaluation work I have described here.

Senator PERCY. Will all of your data be made available to an independent panel for the purpose of establishing an independent evaluation?

Dr. EBERT. Yes, sir; this information is now with FDA and certainly will be available to an independent panel.

By no means has our corporation been the only industrial company carrying out research on glutamate safety. Yonetani of the central research laboratories of the Ajinomoto Corp., the world's largest manufacturer of MSG, has carried out reproduction and teratology studies in rabbits at an oral MSG dose of 25 milligrams per kilogram. He also reports no adverse effects.

I would next refer you to a Japanese paper by Hara, et al., which also reported no toxic manifestations when MSG was fed to rats for 90 days at levels up to 10 times those used in our 2-year feeding study in rats.

To put this in better perspective, the level in the Ajinomoto study was the equivalent of about a quarter teaspoon per day in man, and in the Hazleton work we reported here, the three-levels studied ranged from a low of the equivalent to one-third teaspoon per day in man to a high of about one-third pound per day in man.

We do not wish to imply that these studies are the "last word" in toxicology, nor do they preclude the necessity for further studies as various technical advancements in toxicology evolve. However, we do believe that these data provide strong evidence of the safety of MSG when used as a food flavor enhancer, evidence that has not been refuted by the data presented here by other witnesses and appearing in the recent scientific literature.

We wish to submit the detailed reports of the studies I have described for inclusion in the record, Mr. Chairman.

The CHAIRMAN. Those reports will be made a part of the record.

(The reports follow:)

ARTHUR D. LITTLE, INC.,
Cambridge, Mass., March 15, 1953.

Dr. PAUL D. V. MANNING,
International Minerals & Chemical Corp.,
Chicago, Ill.

DEAR DR. MANNING: We are sending you herewith a report of an investigation of the toxicity of L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid. The work was carried out over a two-year period during which these compounds were fed to albino rats as supplements to nutritionally adequate diets. A control group of rats was fed on the same diet without supplement and maintained under identical conditions. The acute toxicity of these compounds was determined by administering a single large dose orally to rats. The doses found to be lethal to fifty per cent of the rats to which they were administered (LD_{50}) were as follows:

L-monosodium glutamate	19.9 grams per kilogram body weight
DL-monosodium glutamate	10.3 grams per kilogram body weight
L-glutamic acid	More than 23 grams per kilogram body weight

The concentrations of the test materials fed to rats were 0.1 per cent and 0.4 per cent of the total diet. Observations were made on growth, nutritional and general physical status, and fertility. The mortality rates for each group were carefully recorded as well as the occurrence of abnormalities such as dental anomalies, abnormal eye conditions and occurrence of tumors. Post-mortem examinations were made of all rats, and evaluation of tissues and organs made by microscopic examination as well as by gross inspection.

No evidence was seen of chronic toxicity resulting from the administration of the materials under test. The incidence of abnormalities was approximately

the same in control animals, and the survival rates showed no significant differences. The lesions seen after death were consistent with the advanced age of the animals, and were chiefly low-grade inflammatory lesions in the lungs and kidneys.

A number of tumors (in every case benign) were seen. These were chiefly fibroplastic in type. They were more numerous in female than in male anlmals, but were not more numerous in test animals than in the control group. No adverse effect was manifested by the test materials on the fertility of the rats to which they were fed.

The report is presented in two parts. The first describes the organization of the experimental work, the results of post-mortem examinations and the general conclusions. The second part contains a detailed description of the tissue examinatons for record purposes.

It is our conclusion that we have observed no chronic toxic effect to be exerted by L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid, and that such abnormalities as we observed in the living animals and at autopsy existed in approximately the same incidence in the control as in the test animals. The anatomical tissue changes which we observed and which are described in detail are more properly relatable to the age of the animals than to the test materials.

Respectfully submitted.

ARTHUR D. LITTLE, INC.

REPORT ON AN INVESTIGATION OF THE TOXICITY OF L–MONOSODIUM GLUTAMATE, DL–MONOSODIUM GLUTAMATE AND L–GLUTAMIC ACID TO INTERNATIONAL MINERALS & CHEMICAL CORP.

PART I

INTRODUCTION

The controversial position of "intentional" food additives in recent years has made objective investigations of their so-called "chronic" toxicity a matter of necessity. Investigation of the toxicity of the substances which are added to food differs materially from the toxicity of drugs, for the use of the former may extend throughout the life span of the consumer, whether human or animal. For many chemical substances, there may exist a large body of data covering pharmacodynamic action, biochemical fate and therapeutic value, but definitive and descriptive information regarding the effect of repeated ingestion in small amounts may be lacking. Into this category fell glutamic acid and its sodium salt, although there existed extensive information acquired on an empirical basis.

The purpose of the investigation reported here was to acquire under controlled conditions, objective information regarding the effect of feeding L-glutamic acid, L-monosodium glutamate and DL-monosodium glutamate to laboratory animals. The feeding program was carried out over more than two years during which time observations were made on the general physical condition and behavior, growth, fertility, mortality rates, and gross and microscopic changes in body organs and tissues by post-mortem examination. Determinations were made of the lethal dose (LD_{50}) when administered via the gastrointestinal tract. The species used was the albino rat, and observations were made on control groups as well as on rats fed a standard diet supplemented by one of the compounds under test.

The chronic toxic effects of a chemical substance may be manifiested in a variety of forms, either as alterations in normal phsiological and biochemical processes observable during life, or they may be expressed as anatomical alterations which are perceptible only after death or sacrifice of the subject animal. Nutritional changes may result from the inadequacy of the diet due to the addition of large amounts of supplementary material. Changes may be seen in cardiorenal, neuromuscular, or gastrointestinal function. It is only by comprehensive observation and recording of all such changes plus any random observations that a total picture of the presence or absence of chronic toxicity can be established.

If chronic toxicity is high and manifests itself early in the course of controlled observations, it is probably adequate to limit the duration of experimental work. When no evidence of toxicity is seen or the evidence is so limited as to make early generalizations of nontoxicity hazardous, the feeding of the

test material should be extended over two years, or the approximate life span of the animal, whichever is shorter. The director of the Division of Pharmacology of the U.S. Food and Drug Administration has stated that any toxicological data on a feed additive based on work of less than two years duration can be given extremely small weight.

Almost any chemical substance can be said to be toxic if the dosage be sufficiently high. In general, *toxicity* is considered to be the capacity of a substance to produce injury, while *hazard* is the probability that injury will result from the use of the substance in the quantity and manner proposed. From our findings with respect to both acute and chronic toxicity of L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid, it is apparent that a wide and adequate margin exists between the amount which will produce damage and that which will be ingested by humans under reasonably normal conditions. No evidence was derived that normally adequate diets were reduced in nutritional value by adding any of the three substances examined.

Glutamic acid is a normal constituent of mammalian tissue, and is found in free form in brain, cerebral cortex, heart, spleen and thymus. It is a non-essential amino acid, although a major constituent of body proteins and enters into many normal metabolic processes. It is an intermediate in the synthesis of folic acid and a growth accelerator. Glutamic acid was first isolated in 1866 by Ritthausen and is said to be the only chemical substance other than certain of the carbohydrates which can support the metabolism of isolated brain tissue. The Asiatic peoples, notably the Japanese and Chinese have used monosodium glutamate as a food additive for several centuries without suspension of associated toxicity.

ACUTE TOXICITY

The data covering the determination of the acute toxicity of the three compounds examined in this investigation was described in detail in a previous report dated August 4, 1950. It is summarized here for reference purposes. The single lethal doses for 50 per cent of rats (LD_{50}) to which the compounds were administered by a stomach tube were found to be

L-monosodium glutamate	=	19.9 grams per kilogram weight.
DL-monosodium glutamate	=	10.3 grams per kilogram weight.
L-glutamic acid	=	(*a*) more than 30 grams per kilogram body weight in rats. (*b*) more than 23 grams per kilogram body weight in rabbits.

No exact lethal dosage level was found for glutamic acid. According to the classification of Hodge,[1] these compounds can be considered "Practically non-toxic" in the case of DL-monosodium glutamate and "Relatively harmless" in the case of the other two compounds.

Rats and rabbits were used to determine the LD_{50} for L-glutamic acid and rats only in determining this level for DL-monosodium glutamate and L-monosodium glutamate.

L-Monosodium Glutamate

To each of 28 albino rats was administered a solution of the compound in distilled water (90–95 percent). The dosage level tolerated by 50 percent of the rats to which it was administered was 19.9 grams per kilogram of body weight.

DL-Monosodium Glutamate

To each of 57 albino rats was administered a solution of the compound in distilled water (50-60 percent) by stomach tube.

This compound was less soluble in distilled water than was L-monosodium glutamate and when the calculated dose exceeded a volume of 12 ml, it was given in divided doses with an hour interval between. The LD_{50} was found to be 10.3 grams per kilogram body weight.

L-Glutamic Acid

To each of 36 albino rats was administered L-glutamic acid as a suspension in 1.0 percent carboxymethyl cellulose (which is known to be non-toxic). For

[1] Hodge, H. C. and Sterner, J. H.; *Tabulation of Toxicity Classes.* Am. Ind. Hyg. Assoc. Quart. 10.93, 1949.

levels requiring a volume greater than 12 ml. it was necessary to give an additional dose after an interval of one hour. Administration of the calculated amount of L–glutamic acid of rats was never completely accomplished for, even with uniform suspension, the compound settled out in part and was difficult to extrude from the delivery syringe through a catheter.

L-glutamic acid was tolerated by rats at all levels ranging from 8.1 to 30.3 grams per kilogram body weight. The low solubility of L–glutamic acid and the difficulty of administration in concentrations sufficient to produce toxic effect necessitated the repetition of the procedure in another species. Rabbits were used and the dosages administered ranged from 3.8 to 23.0 grams per kilogram. One animal died during administration and at autopsy, fluid was found in the lungs. Presumably death resulted from asphyxia rather than from the toxic effects of L-glutamic acid. Administration of the suspension of L-glutamic acid in 1.0 percent carboxymethylcellulose was more successful than in rats for a larger stomach tube could be used, which minimized the "settling" of the suspended material before being deposited in the animal's stomach.

CHRONIC TOXICITY

Young, adult, albino rats obtained from Sprague-Dawley, Inc., Madison, Wisconsin, were used as test animals. Six hundred rats weighing approximately 250 to 350 grams and aged about three months when the experimental work started, were divided according to age and sex and caged in sub-groups of 7-8 rats. Female rats were born between August 21 and 31, 1949 and the male rats were born between August 3 and September 12, 1949. Six test groups of 75 individual rats each and one control group of 150 rats were established. The rats were divided as evenly as possible according to sex among the six test groups; the control group contained a slightly larger number of females than males. For each supplement to be tested two groups of rats were set aside; one group was fed on a standard diet adequate for their nutritional needs with added supplement to the extent of 0.1 percent of the total weight of the ration. The second group received 0.4 percent supplement added to the standard diet. The distribution of rats according to sex is indicated below:

600 ALBINO RATS USED AS TEST ANIMALS, DISTRIBUTED AS TO SEX

Supplement	Number of animals		
	Males	Females	Total
0.1 percent L–MSG [1]	40	35	75
0.4 percent L–MSG	35	40	75
0.1 percent DL–MSG	40	35	75
0.4 percent DL–MSG	35	40	75
0.1 percent L–GA	40	35	75
0.4 percent L–GA	35	40	75
Control diet	61	89	150

[1] Throughout this report, the following abbreviations, when used, are intended to indicate the following: L–MSG: L-monosodium glutamate monohydrate. DL–MSG: racemic DL monosodium glutamate monohydrate. L–GA: L-glutamic acid.

The rats were housed in wire mesh cages in groups of seven or eight. Food in pellet form was offered in mesh feeders which were accessible ad libitum to the rats. Water was supplied from non-dripping bottles (providing a "demand" supply) so attached that only the outlet projected into the cage. A sliding metal tray containing sawdust was in position under a mesh floor to catch droppings and waste. The sawdust was renewed each day. Cages, feeders, and water bottles were thoroughly cleaned periodically.

The cage room was maintained at constant temperature of 74° F. and approximately 50 per cent relative humidity. The lighting conditions were made constant by rendering the windows opaque and regulating the daily period during which artificial illumination was in use. The feeders were refilled as required.

It should be noted here that the Sprague-Dawley strain of rats used by us is highly inbred. This has the advantage of producing uniformity of response, but at the same time exaggerating any tendency to which the strain is particularly susceptible.

NUTRITIONAL DATA

The test supplements were mixed with the food and incorporated into pellets at the Experimental Ration Laboratory of the Ralston Purina Company, St. Louis. The supplements were obtained from Dr. M. J. Blish, Research Division, International Minerals and Chemical Corporation, Rossford, Ohio, who also arranged for assays of the actual pellets consumed. The Ralston Purina Company was not able to prepare a pellet the same size as that of the basic ration. It was shorter (½-1 inch) and slightly smaller in diameter (⅜-½ inch) but was acceptable to the rat. The only differences between the pellets fed to animals in the test and control groups were the presence of the supplement and slightly different size. The Ralston Purina Company reported some difficulty in getting a uniform concentration of the supplements into pellet form in lots weighing less than a quarter of a ton. Preparation of such a quantity was undesirable because of probable vitamin loss before such a large lot of food was entirely consumed.

Representative samples of the unsupplemented food were sent at intervals to the Rossford plant where they were analyzed for the appropriate supplement under the direction of Dr. M. J. Blish. For the reasons stated above, the actual content of dietary supplement varied from the intended concentration because of the relatively small lot which was prepared at one time. In all cases, the actual concentration was greater than the intended concentration so that all animals received more supplement during the course of the experimental work than either 0.1 or 0.4 per cent would have furnished. The theoretical and actual intake daily and for the two-year feeding program is shown in Table I. These data are based on the average amount of food consumed during a controlled measurement survey upon which comment is made elsewhere in the report. The results of the assays for supplements are shown in Table II. The maximum variation from the intended concentration is not outside the limits of tolerable error in this type of experiment.

The glutamate supplement concentrations of 0.1 and 0.4 per cent were selected as those approximating the probable average daily range of intake for a human subject using monosodium glutamate in the concentrate recommended, in all suitable foods; these levels were established on the recommendation of Mr. L. B. Sjöström and Dr. S. E. Cairncross.

TABLE I —INTAKE OF SUPPLEMENT, DAILY AND OVER 2-YEAR PERIOD

Supplement	Amount of supplement (in grams) received daily				Amount of supplement (in grams) received over the 2-year feeding program			
	Theoretical		Actual (average of assay values)		Theoretical		Actual (average of assay values)	
	Male	Female	Male	Female	Male	Female	Male	Female
0.1 percent L–MSG	0.04	0.02	0.08	0.04	30.29	16.79	59.1	32.7
0.4 percent L–MSG	.17	.09	.18	.10	121.18	67.16	132.9	73.2
0.1 percent DL–MSG	.04	.02	.11	.06	30.29	16.79	80.3	44.5
0.4 percent DL–MSG	.17	.09	.23	.13	121.18	67.16	166.0	92.0
0.1 percent L–GA	.04	.02	.06	.04	30.29	16.79	47.5	26.4
0.4 percent L–GA	.17	.09	.18	.10	121.18	67.16	132.1	73.3

Note: In all instances the actual amount received in grams was greater than the theoretical amount.

TABLE II.—ASSAY DATA FOR SUPPLEMENTED RAT FOOD

[In percent]

Supplement represented	Date of report and percent of supplement found								
	Jan. 30, 1950	Feb. 21, 1950	June 7, 1950	July 13, 1950	Oct. 16, 1950	Feb. 28, 1951	June 6, 1951	Sept. 26, 1951	Average
0.1 percent L–MSG	0.20	0.39	0.16	0.18	0.17	0.12	0.17	0.17	0.195
0.4 percent L–MSG	.43	.43	.42	.48	.47	.43	.40	.45	.439
0.1 percent DL–MSG	.29	.29	.30	.24	.24	.28	.21	.27	.265
0.4 percent DL–MSG	.51	.57	.50	.59	.59	.61	.47	.55	.549
0.1 percent L–GA	.13	.16	.17	.14	.19	.16	.14	.17	.158
0.4 percent L–GA	.42	.49	.41	.43	.45	.44	.40	.45	.436

VITAMIN ASSAYS

Vitamin assays for vitamin A, B_{12}, niacin, riboflavin and thiamine were made on samples of supplemented rat food used in this study at the Food Technology Laboratories, Massachusetts Institute of Technology under the direction of Dr. Samuel A. Goldblith. A summary of the results is presented in tabular form. The samples assayed had been stored for various periods of time. (Tables III–VIII).

An effort was made to exhaust a lot of food before starting to feed a newly prepared lot to minimize vitamin loss and general deterioration. The assays were made between October 8–28, 1950, of two lots of food supplemented with 0.4 percent L–monosodium glutamate and on three samples with 0.4 percent L–glutamic acid prepared at different times. Each vitamin assay was started on the same day, in order to favor consistent results. This is especially important in microbiological assays, so that the same standard curve can be used for all data.

Vitamin A

There was loss of vitamin A in some samples, but in no case did the loss reduce the amount present to less than the minimum nutritional requirement of rats, i.e. 40 U.S.P. units/100 gms. of food.

Niacin

There appeared to be a definite loss of niacin on storage, except in the case of the sample containing 0.4 percent L–monosodium glutamate. Any variation less than $\pm$ 10 percent is not significant due to inherent errors in microbiological assays.

Riboflavin

The extent of riboflavin loss is of the same order of magnitude as that for niacin. As with the niacin assays, there was more loss in the sample stored for eight months than in the sample stored for three months (0.4 percent L-glutamic acid).

Thiamine

With respect to thiamine, the losses, if any, were not great. In some samples, a slight gain was shown, probably due to errors in the experimental method or loss of moisture.

Vitamin B_{12}

The B_{12} losses may be actual in the case of the sample containing 0.4 percent L-monosodium glutamate as well as in that containing 0.4 percent L-glutamic acid. In both cases, however, because of the inherent inaccuracies of B_{12} assays, the actual extent of the losses cannot be stated with exactness. However, it was apparent that no animal showed the effect of B_{12} avitaminosis.

An appreciable loss of riboflavin and niacin occurred in less than eight months' storage of the rat food containing 0.4 percent L-glutamic acid. A small loss occurred in three months storage of that containing 0.4 percent L–monosodium glutamate. This did not affect the nutritional status of the rats appreciably since a new lot of food was ordered every three months. Thiamine appeared to be stable on storage of the food, although there seemed to be a slight loss on storage of the 0.4 percent L–monosodium glutamate sample. When losses occurred on storage, the extent of loss appeared to bear no relation to the glutamate derivative present.

Variations in the initial vitamin content of the basic ration were not significant for the losses which occurred of niacin and riboflavin were of far greater magnitude than the variation in different samples. The analyses showed that more of the vitamins assayed were present than were required for proper nutrition of rats, even in samples stored for a period greater than six months. No lot of food was sufficiently large to last more than this period.

TABLE III.—VITAMIN A AND FAT CONTENT OF SUPPLEMENTED PURINA LABORATORY CHOW

Sample identification	Date of preparation of pellets	Moisture (in percent)	Fat content (dry basis) average (percent)	Vitamin A (USP units/gram) (dry basis) average
0.4 percent L–MSG	June 14, 1950	4.92	7.50	351
Do	Sept. 29, 1950	5.78	6.85	321
0.4 percent L–GA	Jan. 23, 1950	4.95	6.66	355
Do	June 14, 1950	4.94	7.50	217
Do	Sept. 29, 1950	6.62	6.79	279

TABLE IV.—NIACIN CONTENT OF SUPPLEMENTED PURINA LABORATORY CHOW

Sample identification	Date of preparation of pellets	Moisture (in percent)	Niacin content (wet basis) average	(γ/gm) (dry basis) average
0.4 percent L–MSG	June 14, 1950	4.92	30.6	32.2
Do	Sept. 29, 1950	5.78	32.9	35.0
0.4 percent L–GA	Jan. 23, 1950	4.95	26.2	27.5
Do	June 14, 1950	4.94	31.5	33.1
Do	Sept. 29, 1950	6.62	41.5	44.4

TABLE V.—RIBOFLAVIN CONTENT OF SUPPLEMENTED PURINA LABORATORY CHOW

Sample identification	Date of preparation of pellets	Moisture (in percent)	Riboflavin content (wet basis) average	(γ/gm) (dry basis) average
0.4 percent L–MSG	June 14, 1950	4.92	13.8	14.5
Do	Sept. 29, 1950	5.78	15.6	16.5
0.4 percent L–GA	Jan. 23, 1950	4.95	12.0	12.6
Do	June 14, 1950	4.94	14.1	14.8
Do	Sept. 29, 1950	6.62	16.5	17.6

TABLE VI.—THIAMINE CONTENT OF SUPPLEMENTED PURINA LABORATORY CHOW

Sample identification	Date of preparation of pellets	Moisture (in percent)	Thiamine content (wet basis) average	(γ/gm) (dry basis) average
0.4 percent L–MSG	June 14, 1950	4.92	2.98	3.14
Do	Sept. 29, 1950	5.78	3.38	3.59
0.4 percent L–GA	Jan. 23, 1950	4.95	3.28	3.45
Do	June 14, 1950	4.94	3.09	3.25
Do	Sept. 29, 1950	6.62	3.36	3.59

TABLE VII.—VITAMIN B_{12} CONTENT OF SUPPLEMENTED PURINA LABORATORY CHOW

Sample identification	Date of preparation of pellets	Moisture (in percent)	Vitamin B_{12} content (wet basis) average	(γ/gm) (dry basis) average
0.4 percent L–MSG	June 14, 1950	4.92	0.038	0.040
Do	Sept. 29, 1950	5.78	.054	.057
0.4 percent L–GA	Jan. 23, 1950	4.95	.038	.040
Do	June 14, 1950	4.94	.031	.033
Do	Sept. 29, 1950	6.62	.042	.045

TABLE VIII.—SUMMARY OF VITAMIN ASSAY DATA [1]

Description	Date of preparation	Vitamin A		Niacin		Riboflavin		Thiamine		Vitamin B_{12}	
		(γ/gm) (dry basis)	Percent loss or gain in storage	(γ/gm) (dry basis)	Percent loss or gain in storage	(γ/gm) (dry basis)	Percent loss or gain in storage	(γ/gm) (dry basis)	Percent loss or gain in storage	(γ/gm) (dry basis)	Percent loss or gain in storage
0.4 percent L-MSG	June 14, 1950	351	+9.3	32.2	−8.0	14.5	−12.1	3.14	−12.5	0.040	−29.8
Do	Sept. 29, 1950	321		35.0		16.5		3.59		.057	
0.4 percent L-GA	Jan. 23, 1950	355	27.1	27.5	−38.0	12.6	−28.4	3.45	3.9	.040	−11.2
Do	June 14, 1950	217	−22.2	33.1	−25.5	14.8	−15.9	3.25	9.5	.033	−26.6
Do	Sept. 29, 1950	279		44.4		17.6		3.59		.045	

[1] Comparison is between theoretical amount and amount actually found.

GROWTH AND DEVELOPMENT

The growth and development of all rats proceeded at a normal rate. At regular intervals all rats were weighed and the amount of weight gain or loss recorded. At first, the times of weighing all rats consecutively was scheduled as nearly as possible to be five or six weeks apart until the rats had reached their maximum growth. Data on weights from 0–106 test days was reported on March 27 and August 4, 1950. This will not be repeated here, but is summarized in Figures 1–3, which show that for both male and female rats on all supplemented diets, the absolute and per cent weight gain from 0–206 test days was greater than for control rats of both sexes.

Ten series of complete weighings were made including the weight at zero day and the final weight before autopsy. The ninth weighing was made when the feeding program had been in progress twenty months. The tenth was the weight taken at time of autopsy. The following table lists the intervals between weighing of all rats:

Weighing series	*Number test days*
1	0
2	29
3	71
4	106
5	144
6	206
7	254
8	309
9	606
10	(1)

[1] Terminal.

The per cent of weight gain and weight loss for a random selection of animals was calculated after each weighing series over a ten-month period. At that time, maximum growth had been obtained and the incidental factors affecting weight were not related to growth. Several animals failed to ingest their usual weight of food because of dental abnormalities, and this was soon reflected in their body weight. After 300 test days, the losses and gains in weight were irregularly distributed throughout all rat groups and does not seem to indicate any particular trend. We believe the most significant data regarding body weight is that covering 206 test days at which time the rats were aged approximately ten months. After that time, the weight curve leveled and was not significantly altered for any group as a whole. Certainly there was no marked adverse effect exerted on the early growth and development by the test supplements. The effect, if any, was a slightly favorable one in terms of weight gain especially in male rats on supplemented diets.

FIGURE 1

TOTAL PERCENT WEIGHT GAIN OF RATS ON CONTROL DIET
AND ON CONTROL DIET SUPPLEMENTED BY
L-MONOSODIUM GLUTAMATE

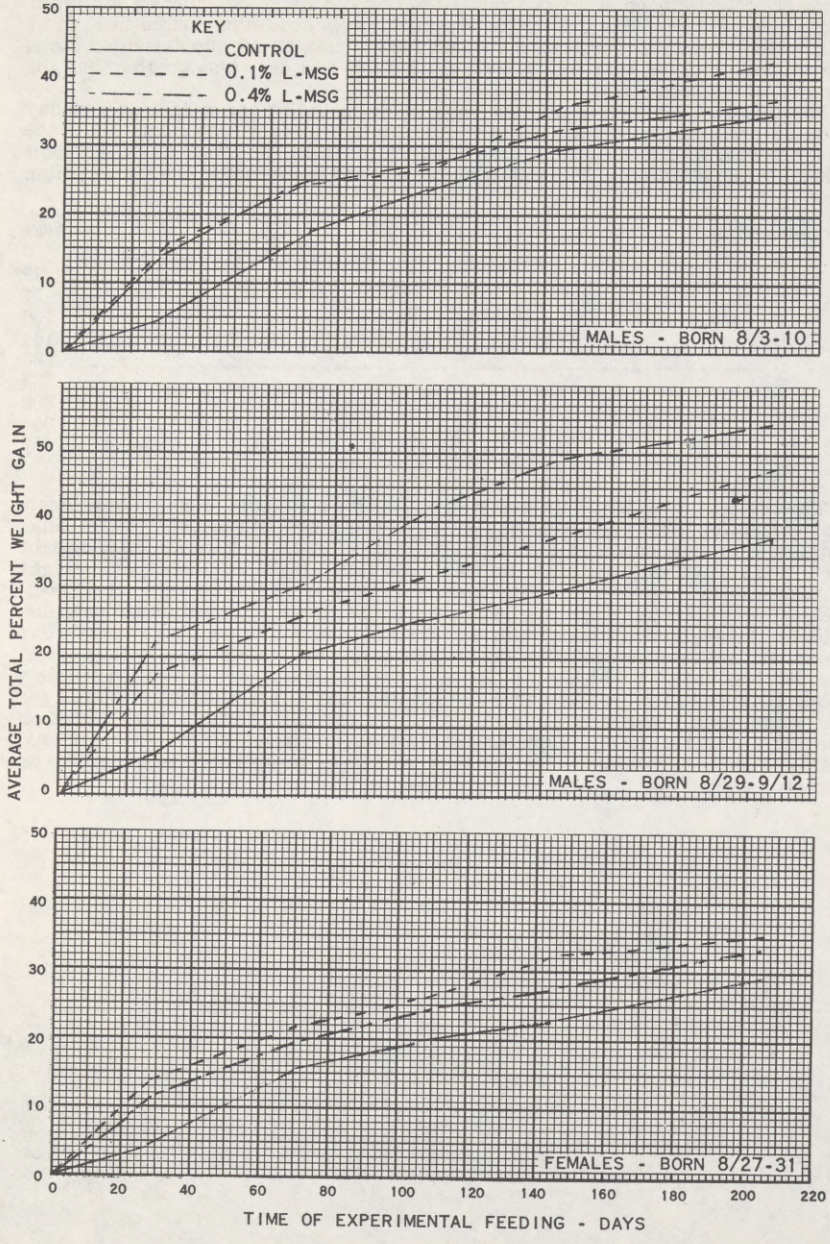

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FIGURE 2

TOTAL PERCENT WEIGHT GAIN OF RATS ON CONTROL DIET
AND ON CONTROL DIET SUPPLEMENTED BY
DL-MONOSODIUM GLUTAMATE

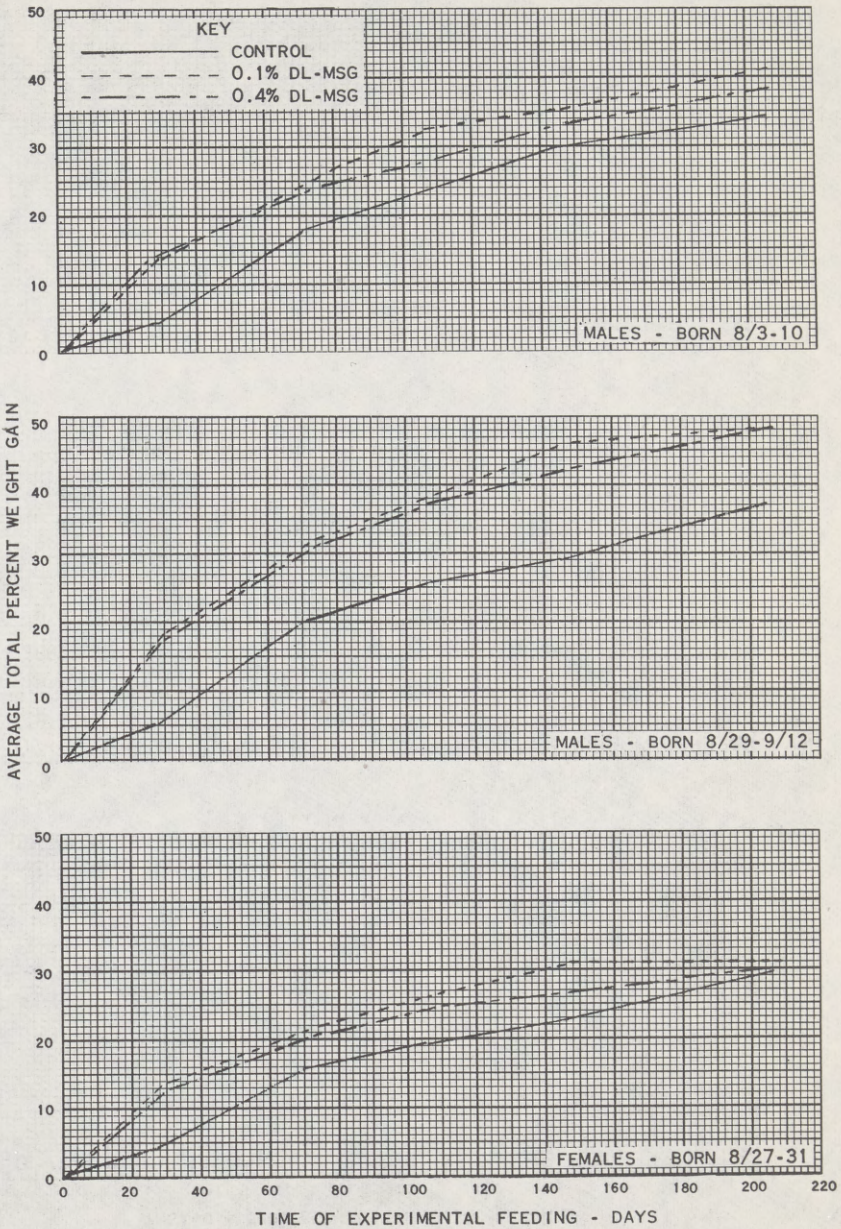

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FIGURE 3

TOTAL PERCENT WEIGHT GAIN OF RATS ON CONTROL DIET
AND ON CONTROL DIET SUPPLEMENTED BY
L-GLUTAMIC ACID

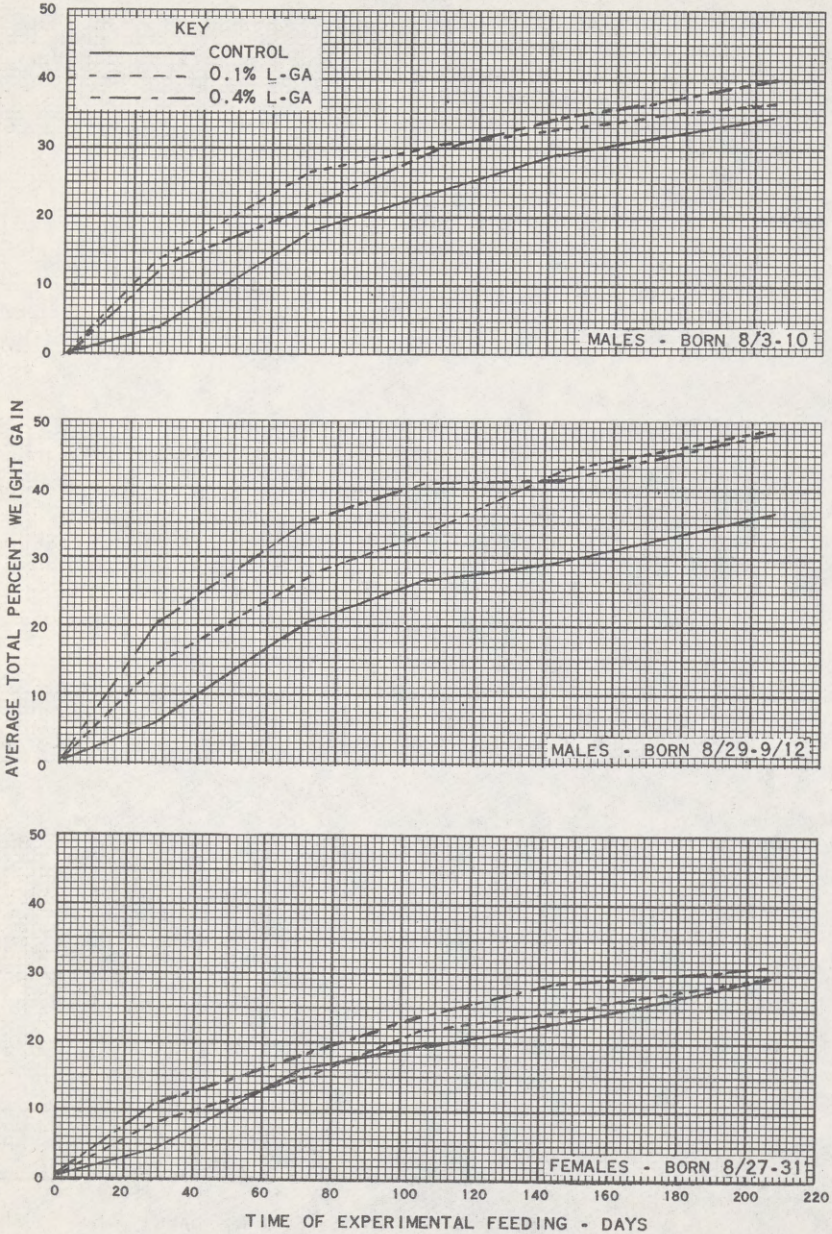

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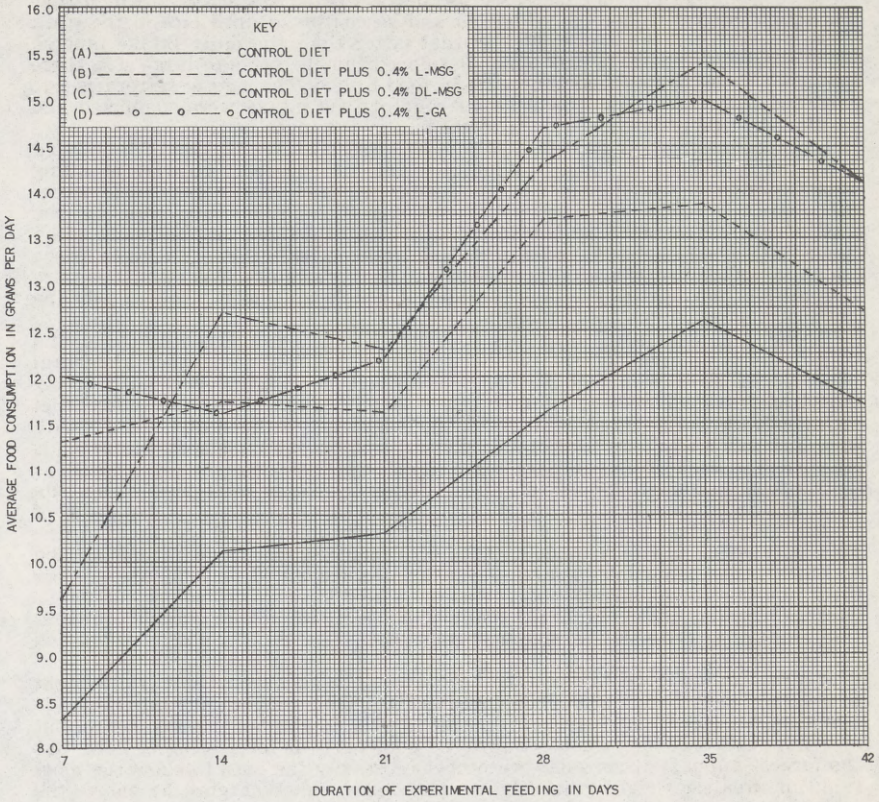
FIGURE 4

AVERAGE FOOD CONSUMPTION IN GRAMS PER DAY - FEMALE WEANLING RATS



FOOD INTAKE

The method of feeding from wire holders permitted the rats to eat *ad libitum*. While the net intake per rat varied from day to day, it was found to be remarkably constant throughout the investigation on the basis of average daily intake in grams per rat, measured over a period longer than two months. A controlled study was undertaken at 180 test days in which the amount of food offered and the amount consumed was weighed daily for selected rats from each feeding group. An effort was made to determine the water intake at the same time but this proved to be impractical since pressure from the animal's body against the glass nipple caused water to be released into the bottom of the cage introducing a large element of error. The information to be obtained did not warrant the time which would have been required to obtain accurate volume measurements; we estimate the average daily water intake for all rats to have been approximately 32 ml. per day.

When the work had been in progress for six months, food consumption measurements were made for all groups, test as well as control. The several age groups represented in the original stock, the different dietary groups and the two sexes were represented. Each rat used in the substudy was caged separately and was fed and watered independently. Animals were selected whose body weight and development at that time were representative of the entire group. Due measurement of spillage was made (averaging 10 grams per day). From the accumulated data, it was determined that for all animals, test and control, the average daily

intake of food was 21.4 grams. Some considerable variation was noted in a given rat from day to day, but the trends in all groups were consistent. Thus, if the intake was high on one day, it tended to be less on the subsequent day and vice versa. The intake per day increased as the rats reach maturity, at which time the intake tended to become stabilized and so continued until late in the work when the rats had become senile. At that latter time, the daily intake tapered off to a certain extent. In rats which developed tumors, often of large size, there appeared to be no significant increase in food intake. The rats were returned to their original cages after the measurements of food intake were completed and continued in their original groups to the end of the investigation.

At the request of Dr. Paul D. V. Manning a second investigation of individual food intake was made, but a new group of rats was used. These were weanling rats (Sprague-Dawley strain). It had been noted from data presented in a previous progress report submitted by us on August 4, 1950 that rats fed on supplemented diets showed a greater weight gain than did those on the control diet. Some relationship between amount of food intake, stimulation of appetite by the supplements and net weight gain appeared to be a possibility. Weanling rats were selected so that measurements of intake and weight gain might be made during the period of maximum normal weight gain.

Twenty-four female weanling rats (Sprague-Dawley) weighing between 35 and 50 grams were housed together as a group on control food for a week of general observation. As a period of further acclimatization each rat was individually caged for a second week and fed from a wire feeder containing the control diet of Ralston Purina Laboratory Chow. At the beginning of the study (0 day) with appropriate food, i.e., the control food plus 0.4 percent of supplement. Six animals were used in each of the four groups.

The food consumption was recorded daily by weighing each feeder and subtracting the spillage which was carefully collected on pieces of paper towel of known weight placed in the tray below the feeder for this purpose. Four successive daily weighings were made and the fifth included the weekend consumption so that whenever possible, a seven-day week was accounted for. The average per diem consumption on a week's basis was calculated for *each animal* as well as the average per diem consumption *per group* on a weekly basis. The graphic presentation (Figure 4) gives the average food consumption per day for a six-week period for each group.

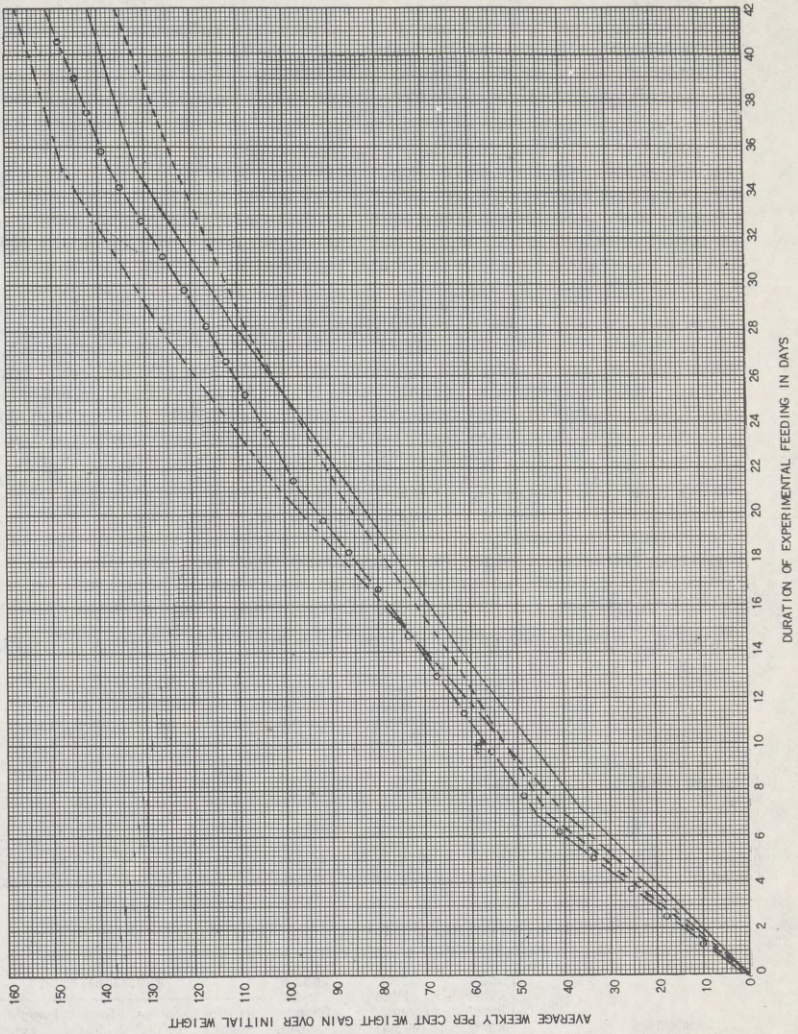
The rats weighed weekly and the percent weight gain over the initial weight calculated. An attempt was made to have the initial weight calculated. An attempt was made to have the initial animal weights similar in each group, but in a few instances compromises had to be made. It was interesting to note that the largest animals at zero day were not necessarily the ones to show the most rapid or greatest weight gain. The accompanying chart (Figure 5) shows the average percent weight gain per week over the initial weight for each group.

The per diem intake of food in grams increases with the growth of the rats. Although the difference between the intake of control food and that which had been supplemented was never great, it was always lower for control food. Similarly, the growth increase was faster for rats fed supplemented diets until the 26th day when the weight gain for rats fed a supplement of 0.4 percent L-monosodium glutamate fell below those rats fed on the control diet or on diets supplemented by 0.4 percent DL-monosodium glutamate or 0.4 percent L-glutamic acid, remaining lower until the end of the experiment. The greatest increase in weight was seen in rats fed on control diet plus 0.4 percent DL-monosodium glutamate which appears noteworthy because of the reported physiological inactivity of racemic isomers. In general, the differences in weight gain are not significant but demonstrate a small but favorable and consistent effect of the three supplements on food intake and weight gain.

Throughout the two-year period, male rats consumed more food than did females. This was uniformly true for control and supplemented diets at both concentrations. In the last few months of breeding when the age was about 2½ years or more, the daily intake dropped for all groups, an occurrence which is customary in all normal aged mammals for the metabolic requirements are decreased markedly in senility. Activity decreased in parallel manner. It appears, further, from a comparison of weight gain and food intake that rats fed on supplemented food gained more in terms of percentage increase over their initial weight in a shorter period than did the control animals. This may have been due to a specific stimulation of appetite by the supplement, to a higher specific dynamic action imparted to the ration by the supplement or to a different level of motor activity than was seen in control rats. It is our belief that a combination of factors operated to increase the daily weight of food consumed, and to stimulate weight gain.

FIGURE 5

AVERAGE WEEKLY PER CENT WEIGHT GAIN - FEMALE WEANLING RATS



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BLOOD EXAMINATIONS

At intervals, hematological examinations were made of random animals from each test group. Both male and female rats were represented. Representative findings are presented in a series of summary tables which are typical of the blood picture after 241, 567 and 681 test days. (a table showing normal values for the laboratory rat is also presented.) (Tables IX–XV).

Complete blood counts included the erythrocyte and leukocyte count, the hemoglobin concentration expressed in grams per 100 ml. blood, and a differential count of the leukocytes present. The method of counting erythrocytes and leukocytes followed standard procedures; Hayem's diluting fluid was used for red blood cells, and a three percent aqueous solution of glacial acetic acid was used as the diluting fluid for white blood cells. The hemoglobin determinations were based on the Sahli scale of 17 grams of hemoglobin per 100 ml. of blood. These values were then converted to a scale of 14.6 grams of hemoglobin per 100 ml. of blood which is the normal hemoglobin concentration in rat blood. The differential smear was stained with Wright's stain and the distribution in type of leukocytes expressed in percent.

The blood examinations showed the deviations from so-called normal blood values to be minimal. There was a slight tendency in all groups to monocytosis and in female rats when examined at 681 test days a slight eosinophilia was found. An average hemoglobin figure of 12.4 grams per 100 ml. blood was found which is slightly below the normal value cited in the pertinent literature, but is within the range of normal hemoglobin values. A similarly low value for hemoglobin was found in control rats which minimizes the significance of the finding. The increase in monocytic cells, especially when it occurs later in the course of the study, may be related in some manner to the evidences of a low-grade infectious process seen in post-mortem microscopic examination of the viscera. (These cells are importantly concerned with phagocytosis and immunity.)

In general, the blood picture of these rats was not seriously altered at any time from the normal range of values found elsewhere. The deviation from the values for the control group found by us was slight. There appeared to be no evidence of pathological changes in physical condition reflected in the blood.

TABLE IX.—AVERAGE BLOOD COUNTS OF FEMALE RATS (355 DAYS OF AGE) AFTER 241 TEST DAYS

Supplement	Erythrocytes (millions/mm³)	Hemoglobin (grams/100 ml)	Leukocytes (count/mm³)	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
0.1 percent L–MSG	9,240,000	11.9	13,050	6	2	1	88	3
0.4 percent L–MSG	8,590,000	12.2	11,750	16	2	0	76	6
0.1 percent DL–MSG	8,255,000	12.1	14,030	8	1	0	84	7
0.4 percent DL–MSG	8,325,000	12.3	15,850	12	0	0	79	9
0.1 percent L–GA	8,680,000	12.4	14,750	4	0	0	89	7
0.4 percent L–GA	8,350,000	12.6	12,300	17	0	0	75	8
Control	7,245,000	12.1	12,350	8	0	0	80	12

TABLE X.—AVERAGE BLOOD COUNTS OF MALE RATS (339 TO 353 DAYS AGE) AFTER 241 TEST DAYS

Supplement	Erythrocytes (millions/mm³)	Hemoglobin (grams/100 ml)	Leukocytes (count/mm³)	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
0.1 percent L–MSG	9,355,000	12.9	13,150	12	0	0	83	5
0.4 percent L–MSG	10,955,000	13.3	8,050	20	0	0	79	1
0.1 percent DL–MSG	8,745,000	12.9	16,075	28	0	0	71	1
0.4 percent DL–MSG	8,750,000	12.6	14,450	18	1	0	72	9
0.1 percent L–GA	8,705,000	12.9	13,600	21	0	0	75	4
0.4 percent L–GA	8,015,000	12.3	13,925	18	0	0	76	6
Control	9,055,000	12.8	12,550	16	0	0	75	9

TABLE XI.—AVERAGE BLOOD COUNTS OF MALE RATS (373 TO 380 DAYS OF AGE) AFTER 241 TEST DAYS

Supplement	Erythrocytes (millions/mm³)	Hemoglobin (grams/100 ml)	Leukocytes (count/mm³)	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
0.1 percent L–MSG	9,325,000	12.3	11,550	21	1	0	75	3
0.4 percent L–MSG	8,700,000	11.8	11,575	21	1	1	74	3
0.1 percent DL–MSG	8,840,000	12.0	10,225	22	1	1	71	5
0.4 percent DL–MSG	8,905,000	12.2	12,750	9	1	0	84	6
0.1 percent L–GA	9,400,000	12.8	13,250	11	1	0	84	4
0.4 percent L–GA	8,360,000	13.1	17,700	15	1	0	77	8
Control	8,845,000	13.4	11,300	8	0	0	84	7

TABLE XII.—AVERAGE BLOOD COUNTS OF RATS (BOTH SEXES) AFTER 567 TEST DAYS

Supplement	Erythrocytes (millions/mm³)	Hemoglobin (grams/100 ml)	Leukocytes (count/mm³)	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
0.1 percent L–MSG	8,030,000	12.6	7,800	28	1	0	68	3
0.4 percent L–MSG	10,340,000	12.9	8,940	20	1	0	72	7
0.1 percent DL–MSG	7,740,000	13.8	11,030	28	1	0	64	7
0.4 percent DL–MSG	8,800,000	13.1	13,275	20	1	1	72	6
0.1 percent L–GA	8,490,000	12.8	11,850	24	2	0	69	5
0.4 percent L–GA	8,405,000	13.0	13,175	19	2	0	75	4

Note: Control: No control values done at this time.

TABLE XIII.—AVERAGE BLOOD COUNTS OF FEMALE RATS AFTER 681 TEST DAYS

Supplement	Erythrocytes (millions/mm³)	Hemoglobin (grams/100 ml)	Leukocytes (count/mm³)	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
0.1 percent L–MSG	6,990,000	11.6	13.225	27	1	1	57	14
0.4 percent L–MSG	7,610,000	11.7	10,675	32	1	0	63	4
0.1 percent DL–MSG	9,485,000	12.4	11,800	25	2	1	65	7
0.4 percent DL–MSG	7,675,000	9.7	22,225	38	1	0	49	12
0.1 percent L–GA	7,530,000	11.2	24,580	23	4	1	65	7
0.4 percent L–GA	8,155,000	10.9	13,125	37	1	1	54	7
Control	8,190,000	11.6	11,625	33	1	0	61	5

TABLE XIV.—AVERAGE BLOOD COUNTS OF MALE RATS AFTER 681 TEST DAYS

Supplement	Erythrocytes (millions/mm³)	Hemoglobin (grams/100 ml)	Leukocytes (count/mm³)	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
0.1 percent L–MSG	6,865,000	11.6	17,525	36	3	1	55	5
0.4 percent L–MSG	7,210,000	9.5	25,250	27	1	0	61	11
0.1 percent DL–MSG	8,945,000	12.2	14,200	19	3	0	70	8
0.4 percent DL–MSG	9,111,000	12.7	15,550	24	1	0	67	8
0.1 percent L–GA	9,280,000	12.4	14,725	21	0	1	72	6
0.4 percent L–GA	8,970,000	11.9	20,175	36	1	0	56	7
Control	9,090,000	11.7	21,750	27	3	1	54	15

TABLE XV.—NORMAL RANGE OF BLOOD VALUES IN THE LABORATORY RAT [1] [2]

	Average	Range
Erythrocytes (millions/mm³ blood)	8, 900, 000	7, 200, 000–9, 600, 000
Blood hemaglobin concentration (grams per 100 ml.)	14. 8	12–17. 5
Leukocytes (count/mm³)	14, 000	5, 000–25, 000
Differential count (distribution per 100 cells):		
Neutrophils	22. 0	9–34
Eosinophils	2. 2	0–6
Basophils	0. 5	0–1. 5
Lymphocytes	7. 3	65–84
Monocytes	2. 3	0–5

[1] Air Force Technical Report No. 6039, "Standard Values in Blood," July 1951.
[2] Gardner, Mary V., "Blood Picture of Normal Laboratory Animals," J. Franklin Inst. 243, 77, 1947.

GENERAL BEHAVIOR

Throughout the course of the investigation, the behavior of all rats was normal and typical for their age and sex. During the day, activity was limited as it tends to be for most laboratory rodents. In the early evening and at night, motor activity increased to a great extent. This was noted for all groups, test and control. As the rats aged, motor activity decreased. No differences in general behavior were seen in rats fed on a diet supplemented by L-glutamic acid although there may have been a tendency for their offspring to mature earlier than did the offspring of rats fed on other supplemented diets.

The rats, when first received, were normally aggressive when handled, but soon became oriented to their surroundings and much gentler when picked up. Except in rats who developed tumors which prevented ambulation because of the location, all rats surviving over 730 days were normal in activity up to the time when sacrificed.

As the experimental work progressed, it appeared that rats fed on glutamate supplemented diets seemed to be in better condition than were the control rats. Their coats seemed sleeker, their general alertness seemed notably greater. As both groups aged and approached senility, the differences grew less. All rats surviving 730 + days appeared to be aged and to have suffered considerable loss of vigor. It would have been difficult at 730 days to have distinguished test and control rats by their external appearance alone.

FERTILITY OF TEST ANIMALS

One of the phenomena which is importantly stressed in long term toxicity studies is the effect of the material under test on fertility. To determine the anatomical changes which may have occurred in the sex organs after prolonged feeding is insufficient; in those animals of our series which survived over two years, there were observed in some rats both gross and microscopic anatomical changes. These were for the most part, changes which may be categorized as "senile", but gave no indication of the integrity of function of the reproductive organs during the phase of the study when the rats were vigorous and mature. An effort was made to learn the effect of the test supplements on reproduction in all groups, including controls, during the first year. Lehman [1] suggested the breeding of subject animals for two generations. In some groups, we were able to continue to the fifth generation. Our original stock is referred to as F_0 and subsequent generations as F_1, F_2, etc. The diet of the young was the same as that fed the parents as soon as they were weaned.

The breeding study was initiated with the original group of animals (F_0) when they had been on the feeding program approximately seven months. Four females and one male were selected from each of the six test groups and the control group and caged together. The females were examined periodically until pregnancy was apparent, at which time they were removed to individual whelping cages. For each litter, the following data was recorded: identity of mother, date of weaning, number in litter and distribution by sex. The litter identity could be retraced at any time by a system of notching the ears like that used on the F_0 rats.

The females quickly became pregnant, when opportunity was presented, but many neglected their litters immediately after they were born. In the group fed

[1] Lehman, A. J.; *Proof of Safety*, J. Am. Pharm. Assoc., 40, 305, 1951.

on a diet supplemented with 0.1 per cent L-monosodium plutamate, one female was replaced because a tumor became apparent during pregnancy. It was estimated that 15 to 20 percent of all the pups survived. It was difficult to determine the survival rate of rat pups accurately, since some rats after delivery destroyed and ate part or all of their litters, in some cases before they were observed by attendants.

A second and third study was initiated at nine and eleven months, using four different males and females from each group. The same difficulty was encountered in determining the survival rate. It was not surprising that more litters did not survive since the rats were nine months of age when first bred. Although this is not old for breeding, it is an advanced age for delivering a first litter, since fertility is at its maximum when rats are from 100-300 days of age.

Two females of the F_1 generation in the 0.1 percent L-glutamic acid group, and one of the three control females became pregnant before they were separated from their male litter mates. One delivered a litter of eight males and two females at approximately 61 days of age. The second female delivered a litter of 4 males and 6 females at approximately 69 days. One of the three females from the control group delivered a healthy litter of six males at approximately seventy-nine days of age.

The successful delivery of an F_2 litter, albeit unplanned, by females so young in age is not common but has been reported. The age at which fecundation and pregnancy is possible is controversial. In a personal communication by Shay to Griffith and Farris[1] observations on 250 male and 262 female Wistar rats demonstrated the vagina to be patent in about 60 percent of the females between 35-50 days of age (range 15-67 days) and that the testes had descended in 85 percent between 18-31 days of age, (range 15-51 days). Regarding an especially well-fed and tended group of rats, Donaldson[2] cites observations made by Greenman and Duhring[3] that exceptional females in such a group case their litters at 55 and 57 days of age. These rats therefore became pregnant at 33 and 35 days.

When the F_1 generation of our rats had reached ten months of age, the breeding study was resumed. Since the surviving F_2 generation of controls at that time was all male, a second attempt was made to produce an F_2 control generation. The F_1 and F_2 generations of the 0.1 percent L-glutamic acid group were also successfully bred. One female of the F_1 generation in the 0.1 percent DL-monosodium glutamate group became pregnant and was isolated. Before delivery, she died from an unknown cause, leaving no female with which to reproduce this generation. Several females of the F_0 generation (approximately 21 months of age) were caged with males with the hope that one of them might still be fertile, but no pregnancies ensued.

Since the breeding program at its inception was planned solely to observe fertility, its course was interrupted. In the later stages of the breeding program emphasis was concentrated on the dietary groups and generations of particular interest, namely, the 0.1 per cent L-glutamic acid group, the 0.4 percent L-glutamic acid group, and the control group.

Fairly large populations of F_3 and F_4 rats from these three groups were bred. Partial data on the number of rats of each generation in each group are presented on the following pages. (Tables XVI and XVII).

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[1] Griffith, J. Q. and Farris, E. J.; *The Rat in Laboratory Investigation.* J. B. Lippincott, 1942, p. 3.

[2] Donaldson, H. H.; *The Rat: Data and Reference Tables.* Memoirs of the Wistar Institute of Anatomy and Biology, No. 6, Philadelphia, 1924.

[3] Greenman, M. J. and Duhring, F. L.; *Breedings and Care of the Albino Rat for Research Purposes.* Published by the Wistar Institute of Anatomy and Biology, Philadelphia, 1931. Second edition.

TABLE XVI.—NUMBER AND SIZE OF LITTERS BY GENERATION

Group	Generation	Number litters	Total number of individuals	Average per litter	Males	Average per litter	Females	Average per litter
0.1 percent L-MSG	F_1	3	13	4.3	10	3.3	3	1.0
	F_2	5	20	4.0	9	1.8	11	2.2
	F_3	23	65	2.8	32	1.4	33	1.4
0.4 percent L-MSG	F_1	3	13	4.3	10	3.3	3	1.0
	F_2	1	3	3.0	1	1.0	2	2.0
	F_3	3	14	3.6	4	1.3	10	3.3
	F_4	2	12	6.0	4	2.0	8	4.0
0.1 percent DL-MSG	F_1	2	6	3.0	5	2.5	1	.5
0.4 percent DL-MSG	F_1	1	6	6.0	4	4.0	2	2.0
	F_2	4	17	4.2	6	1.5	11	2.9
	F_3	8	50	6.3	28	3.5	22	2.7
	F_4	2	9	4.5	5	2.5	4	2.0
0.1 percent L-GA	F_1	2	7	3.5	5	2.5	2	1.0
	F_2	3	34	1.3	19	6.3	15	5.0
	F_3	18	133	7.4	61	3.3	72	4.1
	F_4	11	51	4.6	27	2.6	24	2.0
	F_5	4	24	6.0	11	2.8	13	3.2
0.4 percent L-GA	F_1	1	8	8.0	5	5.0	3	3.0
	F_2	2	11	5.5	6	3.0	5	2.5
	F_3	6	49	8.1	23	3.9	26	4.3
	F_4	2	10	5.0	5	2.5	5	2.5
Control	F_1	1	7	7.0	3	3.0	4	4.0
	F_2	3	16	5.3	7	2.3	9	3.0
	F_3	10	56	5.6	24	2.4	32	3.2
	F_4	12	48	4.0	25	2.0	23	1.9

TABLE XVII.—AVERAGE NUMBER AND SIZE OF LITTERS PRODUCED BY RATS (F_0–F_4) ON SUPPLEMENTED DIETS

Group	Total number of successful matings represented	Average number litters/ generation	Average number per litter	Average per litter (males)	Average per litter (females)
0.1 percent L-MSG	31	10.3	2.9	1.6	1.3
0.4 percent L-MSG	9	10.5	4.7	2.1	2.6
0.1 percent DL-MSG	2	2.0	3.0	2.5	.5
0.4 percent DL-MSG	15	3.7	5.5	2.9	2.6
0.1 percent L-GA	38	7.2	6.6	3.5	3.0
0.4 percent L-GA	11	2.8	7.0	3.4	3.6
Controls	26	6.5	4.7	2.1	2.6

The data is probably of low statistical significance since maximum opportunity for breeding was not presented to all groups. The distribution between male and female offspring is approximately equal, discounting statistical differences resulting from the small number of rat matings represented. There appears to be a trend toward smaller litters in the F_4 generation, but before this point could be established, breeding under more exactly controlled conditions would be necessary.

It is a reasonable conclusion that there was no impairment to fertility in the F_0 generation rats which had been on a supplemented diet for seven to nine months before breeding. The successive generation (F_1–F_5 bred from the initial group (F_0) and which were also fed the corresponding supplemented diet as the parent stock were capable of producing healthy, normal offspring.

GENERAL PHYSICAL CONDITION

Throughout the first year, the general physical condition of all rats was good. Their growth and development was satisfactory and only a few died from natural causes or were sacrificed because of some specific abnormal condition. At approximately 368 test days, a number of animals had developed tumors and a few had begun to show eye changes involving the cornea. This abnormality was distributed throughout the test and control groups but at 368 days was not seen in the 0.1 per cent L-monosodium glutamate or the 0.1 per cent DL-monosodium glutamate groups. The eyes showed a white film covering the cornea with some enlargement. Both eyes were never involved in one animal. Soon after its first appearance the whiteness disappeared, and in the more seriously affected rats, the eye developed a condition of keratoconus with

areas of vascularization. The less seriously involved cases developed corneal opacities. In a few rats, congenital anomalies interfered with normal eye development. Paralyses were seen in a few rats late in the feeding period and could usually be related to tumors involving the legs or adjacent mammae.

Dental anomalies were seen of various types and were often so marked or advanced as to interfere with eating. A common type was that in which one or more teeth in the upper or lower jaw were missing. In some rats the teeth required regular clipping because of spiral elongation of the incisors due to the failure of attrition. This condition was most common in a group of male control rats. According to Griffith and Farris[1] "when by accident one of the incisors is broken or when malocclusion occurs, the non-attrition of the opposing incisor and its continuous growth results in an elongation or so-called overgrowth. The term 'overgrowth' is misleading. In reality this elongation is not related to the rate of growth of the tooth, but is the result of the lack of wear, just as long hair can be the result not of overgrowth, but of lack of trimming."

As the rats aged, their fur tended to become yellow, but no group was affected in this respect more than another.

In the early days of this investigation, it appeared that animals fed on glutamate-supplemented diets grew more rapidly, were more alert and generally were superior to the control animals. This impression continued until approximately one year after the beginning of our observations. At that time, and subsequently up to the termination of the experimental observations, there appeared to be a lesser difference between test and control animals. At 730 experimental days, all surviving animals, whether test or control were approximately equal in general condition but there remains some reason to believe that glutamate-fortified diets may cause earlier physical and sexual maturation in rats.

SURVIVAL DATA

The rats were counted daily at the time of feeding and cleaning cages. At least twice a week, each rat was carefully examined and his general condition described and recorded in individual histories. Deaths were recorded in terms of elapsed test days and whenever the post-mortem condition permitted, an examination was made. The cannibalistic tendencies of rats limited the observations unless the body was discovered immediately after death. For this reason, rats who were in severe distress or obviously moribund were often sacrificed to permit an autopsy to be made. Thus, the figures on mortality (or survival) are not exact. Such errors as exist are conservative for the survival rate may have been higher and the number of rats sacrificed might have been reduced but the survival rate would not have been lower. An additional reduction in the colony occurred as a result of two series of autopsies in which 71 animals were intentionally sacrificed at 63 or 548 test days. Due allowance is made for the deliberately sacrificed animals in computing percentage of surviving rats.

A series of tables is presented showing survival data and general clinical condition at 182, 368, 548 and 730 test days (Tables XVIII–XXI).

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[1] Griffith, J. Q. and Farris, E. J.; *The Rat in Laboratory Investigation.* J. B. Lippincott, 1952, p. 114.

TABLE XVIII.—CLINICAL CONDITION AND SURVIVAL RATES OF RATS FED SUPPLEMENTED DIETS FOR 182 TEST DAYS

Supplement	Number in original group	Number sacrificed	Percentage natural deaths	Percentage survival	Percentage abnormal conditions [1]			
					Tumors	Dental anomalies	Eye condition	Miscellaneous
0.1 percent L–MSG	75	7	0	100	1.5	0	0	0
0.4 percent L–MSG	75	7	1.5	98.5	1.5	0	0	1.5
0.4 percent L–MSG	75	6	0	100	0	0	0	0
0.4 percent DL–MSG	75	6	1.5	98.5	0	1.5	0	0
0.1 percent L–GA	75	6	0	100	0	0	1.5	0
0.4 percent L–GA	75	6	1.5	98.5	0	1.5	0	1.
Control	150	15	.7	99.3	.7	6.7	0	.7

[1] Computed with allowance for (a) animals who died as a result of existing conditions; (b) animals sacrificed because of existing conditions; (c) animals surviving with existing condition.

TABLE XIX.—CLINICAL CONDITION AND SURVIVAL RATES OF ANIMALS FED SUPPLEMENTED DIETS FOR 368 DAYS

Supplement	Number in original group	Number sacrificed	Percentage natural deaths	Percentage survival	Percentage abnormal conditions [1]				
					Tumors	Dental anomalies	Eye conditions	General debility	Miscel-laneous
0.1 percent L–MSG	75	9	3.0	97.0	6.0	1.5	0	0	1.5
0.4 percent L–MSG	75	8	1.5	98.5	2.9	0	2.9	0	0
0.1 percent DL–MSG	75	6	1.4	98.5	1.4	0	0	0	1.5
0.4 percent DL–MSG	75	6	4.3	95.7	0	2.9	1.5	0	2.9
0.1 percent L–GA	75	7	2.9	97.0	1.5	1.5	2.9	0	2.0
0.4 percent L–GA	75	7	2.9	97.0	2.9	0	2.9	0	2.9
Control	150	16	6.8	93.3	4.5	7.4	2.8	0.7	4.5

TABLE XX.—CLINICAL CONDITION AND SURVIVAL RATES OF RATS FED ON SUPPLEMENTED DIETS FOR 547 DAYS

Supplement	Number in original group	Number sacrificed	Percentage natural deaths	Percentage survival	Percentage abnormal conditions [1]				
					Tumors	Dental anomalies	Eye conditions	General debility	Miscellaneous
0.1 percent L–MSG	75	13	8.0	92.0	14.5	3.2	1.6	3.2	1.5
0.4 percent L–MSG	75	10	7.7	92.4	6.1	0	3.8	0	9.2
0.1 percent DL–MSG	75	6	14.5	85.5	4.3	0	0	0	13.0
0.4 percent DL–MSG	75	7	11.8	88.4	5.9	4.4	1.4	1.4	8.8
0.1 percent L–GA	75	9	10.7	89.4	10.6	3.0	4.5	3.0	12.1
0.4 percent L–GA	75	7	8.8	91.2	5.9	0	1.5	0	4.4
Control	150	18	12.1	87.9	9.0	7.0	3.8	.8	9.8

[1] Computed with allowance for (a) animals who died as a result of existing condition; (b) animals sacrificed because of existing condition; (c) animals surviving with existing condition.

TABLE XXI.—CLINICAL CONDITION AND SURVIVAL RATES OF RATS FED SUPPLEMENTED DIETS FOR 730-PLUS DAYS

Supplement	Number in original group	Number sacrificed	Percentage natural deaths	Percentage survival	Percentage abnormal conditions [1]				
					Tumors	Dental anomalies	Abnormal eye conditions	Paralyses	Miscellaneous
0.1 percent L–MSG	75	22	45.3	54.7	54.7	5.6	5.6	----------	28.3
0.4 percent L–MSG	75	21	37.6	62.4	39.6	1.8	7.5	0	33.9
0.1 percent DL–MSG	75	13	41.9	58.1	29.0	0	1.6	0	27.4
0.4 percent DL–MSG	75	17	41.5	58.5	34.4	6.9	6.9	----------	32.7
0.1 percent L–GA	75	18	42.2	57.8	40.3	3.5	3.5	----------	29.8
0.4 percent L–GA	75	14	47.5	52.5	42.6	3.2	4.9	----------	36.0
Control	150	32	40.7	59.3	42.4	16.9	7.6	0	21.2

[1] Computed with allowance for (a) animals who died as a result of existing condition; (b) animals sacrificed because of existing condition; (c) animals surviving with existing condition.

At 730+test days, the animals were aged approximately 2⅓ years. Donaldson [1] has stated that survival of the albino laboratory rat to three years represents an age equivalent to 90 years in man. On that basis, each of these rats at 730 days was at an age equivalent in human terms to 70 years of age and could be expected to show senile changes. It was a matter of some surprise to us that only a few showed general debility at this time. The survival rate in no group, either test or control was less than 52.5 per cent ranging up to 62.4 per cent (0.4 per cent L-monosodium glutamate). The percentage survival for all test rats was 58.8 per cent. (Sherman has stated that 33⅓ per cent survival after two years is a very acceptable rate for nutritional studies.)

PATHOLOGICAL EXAMINATIONS

It had originally been planned that the colony would be progressively reduced to watch the development of pathological processes, if any. A group of 48 rats, representing 12 from the control group and 6 from each of the test groups was sacrificed after 63 test days by intraperitoneal injection of nembutal. Since neither gross nor microscopic findings showed abnormal changes, the initial plan was modified. Another factor influencing this decision was a conference held with Dr. Arnold J. Lehman and associates of the Division of Pharmacology, U.S. Food and Drug Administration. It was emphasized in discussion that if the colony was progressively reduced, adequate data on survival could not be accumulated. The risk of missing reversible pathological lesions which do not apparently affect the clinical condition of the animals was present but the best evidence of the non-toxic nature of the materials under test are living animals in good clinical condition.[2]

As the project progressed, each animal was examined regularly, and those with any indication of abnormalities such as tumors, dental anomalies, paralyses, pneumonia, atypical eye conditions, or general debility were sacrificed whenever the condition had progressed to the point where it was obvious that the rat would not survive. As the colony aged, spontaneous deaths due to unknown causes increased. Whenever possible, post-mortem examinations were made, but in animals whose deaths occurred at night or during a weekend period, decomposition had progressed too far before the body could be examined.

After 548 test days, (1½ years), a group of 23 animals was sacrificed and autopsy performed. Gross examinations revealed no evidence of toxic effects from the supplements under test. When a two year test period had elapsed the remaining animals were autopsied.

The method of sacrifice was by an intraperitoneal injection of veterinary nembutal. Pieces of tissue were reserved from the lungs, heart, thyroid, trachea, esophagus, stomach, intestine, kidneys, liver, spleen, gonads, and any other tissue warranting special attention. If a tumor presented a heterogeneous structure, several pieces of tissue were taken. The tissues were fixed in a 10 per cent formalin solution in preparation for histological treatment. The body weight, tumor weight, (if present), and principal organ weights were recorded. The organs from over 300 rats were examined.

The gross post-mortem findings are described in Part II in tabular form divided according to supplement and giving a description of each organ showing gross pathology, indicating number of test days, method of sacrifice, and other pertinent data. Those organs which were normal are not described. The animals whose tissues were completely normal and not remarkable in any respect are also omitted from these tables.

The 48 rats autopsied on the 63rd test day showed no apparent pathology on gross inspection. No evidence of gastrointestinal irritation was seen, and the heart, kidneys (with one exception), lungs, spleen, pancreas and reproductive organs were entirely normal. One animal fed on the 0.4 per cent DL-monosodium glutamate diet showed an abnormality of both kidneys resembling, if not identical with hydronephrosis. The kidneys seemed shrunken and on longitudinal section, the pelves were seen to be dilated, with wasting of the renal tissue. The thinning of the renal substance was more marked in the left kidney than in the right. No gross evidence of obstruction of the ureters was seen. The bladder was normal in appearance, not distended, and there was no apparent blocking of the urethra. Adjacent organs were normal and did not appear to be pressing on the kidneys.

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[1] Donaldson, H. H.; *The Rat*, Memoirs of Wistar Inst. of Anat. and Biol., No. 6, Philadelphia, 1924.

[2] Lehman, A. J.; *Proof of Safety*. J. Amer. Pharm. Assoc. 40 :305, 1951.

The liver weights were recorded of the first group of animals autopsied and the ratios of liver weight to total body weight were presented in a progress report dated March 27, 1950.

Twenty-three rats were sacrificed in a second autopsy group with three rats from each test group and from the control group (with one extra rat from the 0.4 percent monosodium glutamate and 0.4 percent L-glutamatic acid groups). The organs of the extra animals at these two levels were photographed *in situ* when the abdominal cavity was exposed. The pictures demonstrate the generally good physical and nutritional status of these animals after an 18 month period on supplemented diets. The animals were sacrificed as before with an intraperitoneal injection of nembutal. (Occasionally, other anaesthetics were used in this study.) When the body cavity was opened, all the viscera were of good color and consistency. The final body weight and the principal organ weights were recorded, but on analysis of the data no specific trends could be observed. The gross post-mortem observations were not remarkable except in a few rats which are described in a table which follows. The findings do not suggest toxic effects of the supplements because they are not confined to a single group and are varied in type.

The incidence of gross abnormalities in 284 animals surviving two years or longer was higher in the control group (82.1)[1] than in all test animals (58.3) or in any test group. The highest incidence in the test group was in the 0.4 per cent L-monosodium glutamate group (75.6) and the lowest in the 0.4 per cent DL-monosodium glutamate group (29.6). The mean incidence was 70.2.

TABLE XXII.—POST-MORTEM EXAMINATIONS

Test group	Final examinations[1]		Earlier examinations	Total examinations
	Complete	Partial		
0.1 percent L-MSG	31	10	22	63
0.4 percent L-MSG	37	19	19	75
0.1 percent DL-MSG	41	11	13	65
0.4 percent DL-MSG	44	8	17	69
0.1 percent L-GA	36	19	18	73
0.4 percent L-GA	39	20	14	73
Control	56	14	32	102
Total	284	101	135	520

[1] At 730 test days or later.

TABLE XXIII.—GROSS POST-MORTEM FINDINGS IN RATS SACRIFICED AT 548 TEST DAYS

Identification and sex	Supplement	Description of abnormal organ
8 30, female	0.1 percent L-monosodium glutamate.	Lung: Small cystic area on surface.
23 11, male	0.1 percent DL-monosodium glutamate.	Skin: Small hardened area ½ inch below right axillary margin.
28 01, female	0.1 percent DL-monosodium glutamate.	Lung: Very small cystic area on surface.
36 03, male	0.4 percent DL-monosodium glutamate.	Kidney: Small, collagenous tumor adjacent to left kidney.
50 01, female	0.1 percent L-glutamic acid	Lung: 2 small cystic areas on surface.
61 10, female	Control	Fibrous mass present in right axillary region, firmly adherent to skin but loosely attached to ribs. On section, appeared to be fibrous connective tissue; convoluted but not vascularized.

[1] This figure refers to average number of gross lesions per animal × 100.

TABLE XXIV.—DISTRIBUTION OF GROSS ABNORMALITIES [1]

Test group	Number animals represented	Number showing pathology	Organs involved														Total
			Lungs	Liver	Kidneys	Spleen	GI tract	Seminal vesicles	Uterus	Testes	Ovary	Trachea	Preputial gland	Heart	Adrenal	Bladder	
0.1 percent L–GA	31	13	8	2	5	2	2	2									21
0.4 percent L–GA	37	20	15	2	8				1	1		1					28
0.1 percent DL–MSG	41	16	9	5	5	4			2		1		1				27
0.4 percent DL–MSG	44	8	3		6	2			1					1			13
0.1 percent L–GA	36	14	12	4	3	4									1		24
0.4 percent L–GA	39	13	9	2	3	1			2	1				1		1	20
Control	56	33	21	8	6	3		1	4	1	2						46
Total	284	117	77	23	36	16	2	3	10	3	3	1	1	2	1	1	179

[1] Exclusive of tumors and based on post mortem observation of animals surviving 730+ test days.

TABLE XXV.—LOCATION GROSS ABNORMALITIES

Supplement	Number animals represented	External abnormalities	Number	Tumors	Disease	Number	Tissues showing gross changes	Number
0.1 percent L–MSG	18	Anemia	1	16	Lungs	8	Liver	2
		Paralysis	1		Kidneys	5	G.I. tract	2
		Corneal opacity	1		Spleen	2	Seminal vesicles	2
		Dental anomaly	1					
0.4 percent L–MSG	25	Corneal opacity	1	17	Lungs	15	Trachea	1
		Debility	2		Kidneys	8	Uterus	1
					Liver	2	Testes	1
0.1 percent DL–MSG	20	Corneal opacity	2	10	Lungs	9	Uterus	2
		Keratoconus	2		Kidneys	5	Preputial gland	1
		Paralysis	2		Liver	5	Ovary	1
					Spleen	4		
0.4 percent DL–MSG	16	Keratoconus	1	10	Kidneys	6	Heart	1
		Paralysis	1		Lungs	3	Uterus	1
		Corneal opacity	1		Spleen	2		
		Corneal vascularity	1					
0.1 percent L–GA	18	Paralysis	2	16	Lungs	12	Kidneys	3
		Debility	2		Spleen	4	Adrenal	1
		Keratoconus	2		Liver	4		
0.4 percent L–GA	18	Paralysis	1	12	Lungs	9	Testes	1
					Kidneys	3	Spleen	1
					Liver	2	Heart	1
					Uterus	2	Bladder	1
Controls	40	Anemia	2	26	Lungs	21	Spleen	3
		Dental anomaly	1		Liver	8	Ovary	2
		Paralysis	1		Kidneys	6	Testes	1
		Corneal vascularity	1		Uterus	4	Seminal vesicles	1

Occurrence of Spontaneous Tumors

At the end of one year of observation, a number of rats showed swellings which were presumed to be spontaneous tumors. These findings are described in detail in Part II of this report. The incidence of tumors in the various groups at 182, 368, 547 and 730 days is shown in Table XXVI. Microscopic sections were made of a representative number of tumor specimens and they were found to be chiefly adenomatous in type and with no exception, benign in type.

The comment of Dr. Lloyd C. Fogg, our consultant in pathology, regarding these tumors (based on microscopic examination) follows:

"None of the external outgrowths suggest any positive etiological relation to the dietary supplements.

"The tumors, both in the test animals and the controls, show a general pattern sharply divided between sexes. The tumors of the females resemble adenomas of sweat glands or of the breast, some of which are actively secreting and some that show extensive fibrosis.

"The outgrowths in the male are associated with skin lesions, some of which are metaplastic, or cystic, or fibrotic.

"A striking observation is the frequency and the uniformity in the type of outgrowth in the female. With no exception, all the outgrowths were probably associated with mammary gland proliferation. It is suggestive that this represents a predilection in the females of the Sprague-Dawley strain for this type of growth."

TABLE XXVI.—PRESUMPTIVE PERCENTAGE INCIDENCE OF TUMORS [1]

Test days	182	368	547	730
0.1 percent L-MSG	1.5	6.0	14.5	54.7
0.4 percent L-MSG	1.5	2.9	6.1	39.6
0.1 percent DL-MSG	0	1.5	4.3	29.0
0.4 percent DL-MSG	0	0	5.9	34.4
0.1 percent L-GA	0	1.5	10.6	40.3
0.4 percent L-GA	0	2.9	5.9	42.6
Control	.7	4.5	9.0	42.0

[1] Based on observations during life.

A summary comparison of all groups of rats, i.e., test with control rats, at 730+ days is shown in Table XXVII. It can be seen that there is no significant difference in the incidence, severity, extent or character of tumors in all test rats, all control rats and all rats. The incidence of tumors in control rats is 1.7 percent higher than in all rats surviving for two years.

The abnormalities perceptible on gross inspection were chiefly seen in lungs, liver and kidney, but were not in every case verified as serious pathological changes by microscopic examinations (Table XXV). In many cases, microscopic examination revealed lesions which were not apparent to gross inspection. However, gross and microscopic examinations confirmed each other on two points:

1. The most numerous abnormalities occurred in lungs, kidneys and spleen in both test and control groups.
2. The abnormalities were those associated with age.

TABLE XXVII.—SUMMARY, COMPARISON OF ALL TEST RATS WITH CONTROL RATS AT 730-PLUS TEST DAYS

		Percentage abnormal conditions		
	Percentage survival	Tumors	Dental anomalies	Miscellaneous [1]
Average all test rats	57.3	40.1	3.5	31.3
Average all rats	57.6	40.7	5.4	29.8
Control rats	59.3	42.4	16.9	21.2

[1] This category includes conditions of such diversity that further classification would require extensive subgrouping. See pt. II for tabulation of miscellaneous abnormalities.

MICROSCOPIC EXAMINATIONS

The tissue specimens taken at autopsy were prepared for microscopic examination by standard techniques and stained with hematoxylin and eosin. They were examined and screened by Dr. M. G. Gray and reviewed by Dr. Lloyd C. Fogg, our consultant in pathology. Approximately 1400 sections were prepared from tissue material resulting from 520 post-mortem examinations. Of these 960 sections were reviewed by Dr. Fogg. A description of abnormal sections will be found in Part II. Sections not described in that place can be assumed to have shown no abnormalities or to have been entirely consistent with the age of the animal represented.

In summary, it can be said that the chief microscopic changes were an increase in connective tissue elements and the general shrinkage of organic structures which characterize the elderly animal. No evidence was found that could be directly or indirectly related to toxic activity on the part of the supplements fed. The low-grade inflammatory process seen in lungs and kidneys of control animals and in the kidneys of test animals is very similar to that seen in a group of senile C–57 mice maintained to a comparable age and used in a correlative study. It is probably the result of a low-grade infection but the causative organism is not known to us.

The incidence of benign tumors appears to be related to the highly inbred strain of rats used (Sprague-Dawley) and is discussed in Part II. There was no essential difference in the type of pathological changes seen in control and test rats. The characteristics which were sought for in particular were those of chronic toxic character. Occasionally an acute lesion was found but these were not confined to any group. It is to be expected in a group of the size with which we were concerned that occasional lesions would be found. The variety and random distribution leads us to conclude that they should not be ascribed to the effect of the supplementary compounds.

Control Group

There was no obvious pathology in the liver, genital glands, spleen, or heart. The lungs show foci of alveolar fibrosis and pinpoint accumulations of lymphocytes around the bronchi or bronchioles which can be related to a low-grade infection.

The kidneys showed evidence of low-grade, chronic infection expressed by foci of inflamatory reaction such as dilated tubules, concretions and an occasional fibrotic glomerulus.

L-Monosodium Glutamate Group

No clear-cut difference from the control group was seen nor did any significant difference appear on later examination of the DL-monosodium glutamate or L-glutamate acid groups. The kidneys of animals fed at both levels showed a more extensive chronic nephritis but this appearance did not approach acute intensity in any section.

DL–Monosodium Glutamate Group

There was no distinctive difference between this group and the controls. There was a suggestion that the low-grade infection noted in the controls showed a marginal intensification in these animals.

L–Glutamic Acid Group

There was seen in this group a suggestion of irritation in the gastro-intestinal mucosa. However, the observation was not peculiar to this group but appeared slightly intensified. No correlative changes in accessory organs was seen.

For a detailed description of the microscopic abnormalities, the reader's attention is directed to Part II. For convenience, a summary and comparison of the findings for all groups is presented here. Animals are represented who were sacrificed at 63, 548, 745, 752, 759 and 830 test days; animals showing no lesions are not included. When the lesions were seen, they were of the type described below.

Control Group

Liver.—Essentially normal. Only one case of focal hepatitis was noted in an aged animal.

Kidney.—Foci of cortical and medullary inflammation which are highly variable in intensity from small infrequent foci of congestion to numerous dilated tubules with concretions and fibrotic glomeruli. The inflammation was universal in the older animals.

Lungs.—In the 14 animals studied, all sections showed accumulations of lymphocytes around bronchioles with some fibrosis.

Spleen.—In the younger animals, the tissue was normal. Characteristics of age such as mild congestion and disorganized red and white pump appeared in the older groups.

Heart.—Normal. No pathology.

Intestine.—Of four animals, 745 and 752 days old, two had an abscess, one showed worms in the lumen, and one, corroded epithelium. Other sections normal.

Genital glands.—Normal.

L-MONOSODIUM GLUTAMATE GROUP

	0.1 percent	0.4 percent
Liver	Of 18 rats. 15 were normal. 3 had traces of inflammation as shown by pinpoint foci of lymphocytic infiltration around blood vessels.	3 rats showed mild lymphocytic infiltration as in 0.1 percent group.
Lungs	Foci of fibrosis and areas of inflammation around bronchi or bronchioles, varying from a trace to extensive involvement. There were 2 lung abscesses.	Mild chronic irritation. 2 with marked congestion and edema. 1 with possibility of lobar pneumonia.
Kidney	In general, there were foci of inflammation around blood vessels, sometimes only in cortex but occasionally extending to renal pelvis. In extreme cases, expressed as dilated tubules with concretions. Diagnosed as mild, chronic interstitial nephritis.	Similar to appearance seen in 0.1 percent group but not more severe.
Intestines	Chronic irritation as evidenced by presence of sterile abscesses, eroded epithelium or polyposis.	No abscesses seen but otherwise as seen in 0.1 percent group.
Ovary	Several corpora lutea seen but no obvious pathology. No primary follicles. Senile ovaries.	No pathology seen.
Trachea and esophagus	No pathology	1 section showed disorganized epithelium.
Spleen	In older animals, there was some congestion and disorganization, typical for senility. No obvious pathology.	As seen in 0.1 percent group.
Heart	No pathology	No pathology.
Genital glands	do	Do.
Aorta	1 section sclerotic	
Salivary glands	No pathology	Do.
Testis	do	Practically depopulated of germinal cells; senile. No obvious pathology.

DL-MONOSODIUM GLUTAMATE GROUP

Liver	In 2 rats (777 and 779 test days old) there was evidence of focal lobular necrosis and suggestion of portal cirrhosis.	1 section showed hypertrophied epithelium in gall bladder. Not diagnosed as malignant, but probably indicates irritation. All other sections normal.
Kidney	Changes varying from normal to evidence of mild chronic interstitial nephritis.	Appearance as in 0.1 percent group but somewhat intensified.
Lung	Changes varied from normal to foci of fibrosis with pinpoints of inflammatory areas around bronchi and bronchioles. 2 cases showed edema and minute hemorrhagic areas in aged animals.	Same appearance as in 0.1 percent group.
Spleen	In young animals, no change from normal. In older animals, senile appearance as shown by disorganization and mild congestion.	Same appearance as in 0.1 percent group.
Heart	No pathology	No pathology.
Trachea and esophagus	2 sections show mild, chronic irritation in glandular epithelium, nonmalignant.	No section showed disorganization of tracheal epithelium but could be an artefact.
Adrenal	No obvious pathology	
Ovary	Senile appearance but no obvious pathology	
Intestine	In 1 case (779 test days), chronic enteritis. No evidence of malignancy.	1 section shows extensive papillary-type folds in epithelial layer extending into lumen suggesting partial obstruction. No evidence of malignancy.

L-GLUTAMIC ACID GROUP

	0.1 percent	0.4 percent
Liver	Essentially normal in all animals represented	2 animals over 700 days old showed foci of necrotic tubules.
Kidney	Mild chronic, interstitial nephritis evidenced by foci of dilated tubules with concretions, thickened vascular walls and areas of lymphocytic infiltration.	Same as 0.1 percent animals.
Lungs	Varying degrees of inflammation around bronchioles and fibrosis. No obvious edema or congestion.	Do.
Spleen	All sacrificed at 63 and 548 days were normal. Those at 688 days or later showed disorganization characteristic of senility. No obvious pathology.	Do.
Intestine	Alterations in epithelium in animals sacrificed at 740 test days or later ranging from sterile abscesses to fibrotic villi with eroded mucosae.	Do.
Esophagus and trachea	No pathology	Do.
Testis	Typical of senility; sparsely populated with germ cells. No obvious pathology.	
Heart	No pathology	No pathology.
Ovary	Normal except for involutional changes	Do.
Stomach	No pathology	Do.
Adrenal	1 section somewhat disorganized but no obvious pathology seen.	Do.
Genital glands	No pathology	Do.
Skin	No sections	Keratinous cyst, not malignant, in 1 rat.

TABLE XXVIII.—DISTRIBUTION OF MICROSCOPIC ABNORMALITIES EXCLUSIVE OF TUMORS

Test group	Number animals represented	Number sections examined	Lungs	Kidneys	Spleen	G.I. tract	Liver	Trachea	Testes	Ovary	Aorta	Esophagus	Bronchus	Adrenal	Total number abnormalities
0.1 percent L–MSG	63	154	18.0	13.0	12.0	3.0	4.0				1				52.0
0.4 percent L–MSG	75	162	9.0	11.0	8.0	6.0	2.0	1	1	1					38.0
0.1 percent DL–MSG	65	190	7.0	7.0	7.0	1.0	3.0	1		1		1			28.0
0.4 percent DL–MSG	69	173	10.0	13.0	9.0	1.0	4.0	1					1		39.0
0.1 percent L–GA	73	236	10.0	7.0	8.0	8.0	0		1					1	35.0
0.4 percent L–GA	73	163	14.0	9.0	12.0	6.0	3.0		1						45.0
Average for test animals			11.3	13.3	9.7	4.1	2.6	(1)	(1)	(1)	(1)	(1)	(1)	(1)	39.5
Controls	102	305	14.0	10.0	5.0	4.0	1.0	1							35.0
Total	520	1,383	82.0	70.0	63.0	29.0	17.0	4	3	1	1	1	1	1	272.0

[1] Less than 1.0.

TABLE XXIX.—STATISTICAL DISTRIBUTION OF ABNORMALITIES

	Gross [1]	Microscopic [2]
Incidence (average number lesions per animal times 100):		
Controls	82.1	34.3
All animals	63.0	52.3
All test animals	58.3	56.6
0.1 percent L–MSG	67.7	82.5
0.4 percent L–MSG	75.6	50.7
0.1 percent DL–MSG	65.8	43.0
0.4 percent DL–MSG	29.6	56.5
0.1 percent L–GA	66.6	47.9
0.4 percent L–GA	51.4	61.8
Mean incidence	70.2	45.4
Deviation from mean incidence:		
All animals	−7.2	+6.9
All test animals	−11.9	+11.2
All controls	+11.9	−11.2

[1] 284 animals surviving 730-plus test days.
[2] 1383 sections from 520 rats coming to autopsy.

An examination of Table XXIX shows a statistical comparison of the incidence of gross and microscopic abnormalities. We do not believe that the volume of data available is adequate for further statistical analysis but the trends are worthy of comment. It is noteworthy that the data for gross and microscopic abnormalities are derived from groups of animals of different sizes. The criteria for indicating severity of abnormality was the same (so far as possible) for both observations, and was based on a scale ranging from 0–4. Thus

0 = Essentially negative, no pathology
1 = Trace
2 = Apparent
3 = Obvious
4 = Severe

Only changes rated two or higher are included in the statistical analysis. However, many gross abnormalities consisted solely of departures from normal color and consistency, while the microscopic examinations represent only verifiable anatomical alterations.

Although the incidence of microscopic abnormalities is higher in test animals than in controls, the data presented above regarding percentage survival in control and test animals suggests that for all animals represented, the microscopic lesions seen among test animals were not of such severity that they contributed significantly to mortality. In all categories represented in TABLE XXVIII, the abnormalities represented are, with few exceptions, consistent with senility. The figures for incidence of microscopic abnormalities do include tissues from rats dying earlier in the experiment, while the figures for gross abnormalities include only those surviving 730 days or longer.

GLUTAMIC ACID CONTENT OF BLOOD AND ITS RELATIONSHIP TO TUMORS

The claims [1] of relationship between the glutamic acid level of blood and the presence of malignant tumors led us to have analyses made of rat blood from animals fed on diets containing added 0.4 per cent L-monosodium glutamate, 0.1 and 0.4 per cent L-glutamic acid and from others fed on the control diet. Rats with obvious tumors and others without tumors were selected, the latter to be used as a secondary control. Blood samples were taken between 754 and 759 days by decapitation.

The blood was collected in beakers which had been coated with 0.1 ml. of a dilute solution of Heparin. The beakers were roated while drying over an electric plate to spread the Heparin uniformly. Since the female rats had the largest numbers of tumors, male rats with tumors were selected whenever possible to make as even a division by sex as possible. An autopsy was then performed on those animals sacrificed for blood and observations made of the gross appearance of organs and tumors. Pieces of tissue were saved from each organ and tumor for histological preparation.

[1] Beaton, J. R., McGanity, W. J., and McHenry, E. W.; *Plasma Glutamic Acid Levels in Malignancy*. Canad. M. Ass. J. 65, 219, 1951.

The quantity of blood plasma required was 10 ml. per test, but this provided two 5 ml. samples for duplicate determinations. Approximately 6–8 ml. could be obtained from the female rat and 10–15 ml. from the male rat.

Arrangements were made for Dr. Samuel P. Bessman of the Children's Hospital Research Foundation of Washington, D.C., to make determinations of glutamic acid content on plasma filtrates sent him by us. Dr. Bernard Gould, of the Massachusetts Institute of Technology prepared the filtrates. Each filtrate represented a pooling of the blood of four animals from each group according to Dr. Bessman's directions.

The general procedure for preparing filtrates required the centrifugation of heparinized blood to separate the red cells from the plasma. A protein-free filtrate was then prepared by treating 2 ml. plasma with 1 ml. of fresh, cold 15 per cent trichloracetic acid. The precipitated protein was then separated by centrifugation as rapidly as possible. The supernatant fluid was poured off and frozen as quickly as possible and stored in a "deep-freeze" cabinet. The prepared filtrates were sealed in glass vessels and shipped to Dr. Bessman by Air Express.

The glutamic acid content of the blood filtrates as determined by Dr. Bessman is presented on the following page, (TABLE XXX).

TABLE XXX.—GLUTAMIC ACID CONTENT OF BLOOD FILTRATES[1]

	Animals without tumors		Animals with tumors	
	mg. percent glutamic acid	mg. percent glutamine	mg. percent glutamic acid	mg. percent glutamine
Control	2.75	10.38	2.62	9.75
	2.42	9.06	2.42	9.06
	3.25	10.25	2.91	10.69
0.1 percent L-GA	2.32	10.39	2.12	9.02
	3.32	10.35	2.66	11.01
0.4 percent L-GA	2.24	11.20	2.18	8.62
	2.40	9.55	1.52	11.98
0.4 percent L-MSG	2.12	10.35	3.11	9.68
	2.58	10.92	2.59	10.58

[1] Each value represents a filtrate prepared by pooling the blood samples of 4 rats.

From the values obtained there is no difference in glutamic acid content of the blood between animals in this series with tumor development and those without. There are no significant differences among the three dietary groups or in comparison with the control group. Later microscopic examination showed all the tumor specimens to have been benign.

Because of the non-malignant character of the tumors represented the preceding data neither substantiates nor disproves the contention of McHenry and his associates that the plasma glutamic acid content is elevated in animals which are hosts to malignant tumors.

DISCUSSION

For adequate evaluation, any toxicological investigation must be considered in light of the use which will be made of the test materials or the conditions under which human subjects will be exposed. To say categorically that a substance is or is not toxic would savor of the dogmatic. All chemical substances have a toxic level, although for one reason or another, (such as low solubility and other physico-chemical characteristics) it may be impossible to expose a human to that concentration. We might expect that a large proportion of the subject animals would develop pathological lesions or show metabolic, cardiac, renal or hepatic insufficiency if under the experimental conditions obtaining, the test material exhibited chronic toxic activity. We would further expect that under the stress of special situations such as pregnancy, lactation, fatigue or tumor formation that the signs of chronic toxicity would become increasingly manifest, if potentially present. Ultimately, we might expect that an effect would be exerted on survival rates in comparison to those of control animals.

The development of abnormal changes resulting from the chronic toxic effects of chemical substances under investigation would vary in severity and in the time required for their maximum development. Regression in a pathological process might occur and if so, a lesion might not come to observation. If this were true, the lesion would in all probability be so minor in significance that its total effect on the living subject animal would be negligible. We might also expect to see some effect on the fertility of test animals and their ability to beget, con-

ceive, deliver and rear another generation. Nutritional deficiencies might be observed due to primary toxic interference with absorption or metabolism or to a secondary effect on an organ concerned with metabolism, storage or excretion.

None of these changes were consistently seen in test animals of any group or in control animals. Those pathological changes observed in tissues and organs were of the type commonly associated with the natural operation of the aging process. In general, all our test animals coming to autopsy were found to have muscles of good consistency, size and firmness and in all but a few animals the distribution of fat was normal for their age. Hemorrhage from body orifices was not seen. Fever was observed only in a few animals moribund from traumatic wounds inflicted by their cage mates. Commonly, animals (and humans) bearing tumors show febrile reactions to proteins liberated from tumor tissue and absorbed into the blood stream. Such proteins may also affect the red blood cells and blood forming organs. Changes of this type were entirely lacking in both control and test animals. The mild inflammatory changes observed at autopsy were distributed through test and control groups and are considered to be a senile phenomenon. Senility can be expressed in several other forms in laboratory animals. The microscopic changes which are commonly seen in the elderly rat are chiefly in the sex organs. The senile ovary fails to show any primary follicles and the sterile testis becomes depopulated of germ cells. The lung of the aged animal shows fibrosis and focal edema with thickening of the connective tissue walls. The kidneys show mild but chronic inflammation which may proceed to a frank glomerulonephritis with varying degrees of fibrosis while the senile spleen shows diffuse disorganization of the red and white pulp. The gastro-intestinal tract is not regularly affected in the aging process although there is a loss of muscle tone without necessarily accompanying microanatomical changes.

The dental anomalies and corneal changes upon which comment has been made are not apparently related to diet. Overgrowth of teeth in rats has been reported by other investigators and a number of publications have appeared dealing with eye changes in the inbred albino rat. The incidence of tumors and survival rate is approximately the same for control rats, all test rats and all rats which suggests that no lethal or toxic factors acted upon one group which did not act to the same extent on the others.

CONCLUSION

In consideration of the observations made during life and the post-mortem findings both gross and microscopic, and with due evaluation of the type of abnormalities and their distribution between test and control groups, it is our conclusion that no evidence of chronic toxicity was seen in this investigation to be exerted by L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid.

SUMMARY

An investigation of the acute and chronic toxicity of L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid is reported. The study was carried out over two years during which albino rats (Sprague-Dawley strain) were fed on a standard diet appropriate to their nutritional needs to which had been added the test materials to the extent of 0.1 or 0.4 percent. A control group of animals was maintained on the standard diet without supplement under identical conditions. The age of rats at the beginning of the feeding period was approximately three months, and the division by sex was approximately equal. Each test group for each supplemented diet was comprised of 75 rats and the control group numbered 150, a total of 600 rats.

The single lethal dose (LD_{50}) was determined for these compounds and found in rats to be: for L-monosodium glutamate, 19.9 grams per kilogram; for DL-monosodium glutamate, 10.3 grams per kilogram; and for L-glutamic acid, more than 30 grams per kilogram. The LD_{50} was determined also in rabbits for L-glutamic acid and found to be more than 23 grams per kilogram.

Assays were made of the standard ration for vitamin content and found to be adequate. Although the content of the supplements was not exact, it was found on assay to be slightly higher than intended so that all animals received more than the minimal amount. Observations were made of general physical condition, behavior, activity and fertility of all test animals during the feeding period of two years, and little difference was seen between the control and test groups. The per cent of survivors among test rats, control rats and all rats was found to vary not more than ± 1.0 percent from a median value of 58.3 percent at 730 test days. For animals of this age (approximately 2⅓ years) this survival rate is about 25 per cent higher than the expected survival rate, according to Sherman.

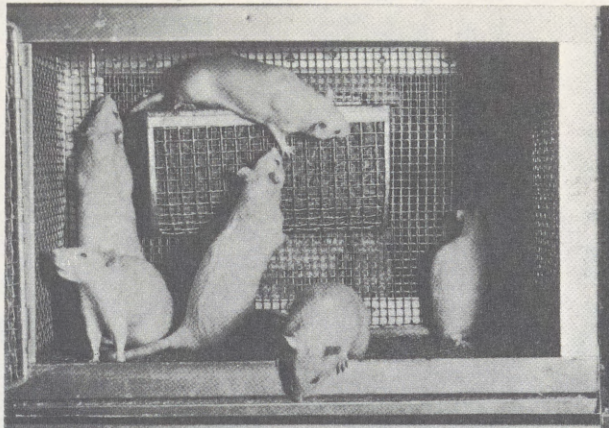
A number of spontaneous tumors, all of them benign, developed in both test and control rats. The incidence was approximately the same for all test rats, all control rats and all rats; the variation from the median incidence of 41.1 percent was not greater than ±1.3 percent for test rats, control rats or all rats. We believe that the high incidence of tumors in the strain of rats used is due to close inbreeding.

Pathological examinations, either complete or partial by gross and microscopic inspection were made of 520 rats. The abnormalities seen varied from test group to test group and from control to test group. In general, the type of lesions seen were consistent with the age of the rat at time of death and in most rats were associated with the aging process. The most common type of lesion in rats surviving to 730 days or longer was a low-grade inflammatory process involving lungs, kidneys, spleen and occasionally other organs. Other abnormalities varied so greatly in type or were so random in their distribution in both test and control groups that they do not appear to be associated with chronic toxic characteristics of any of the supplements fed.

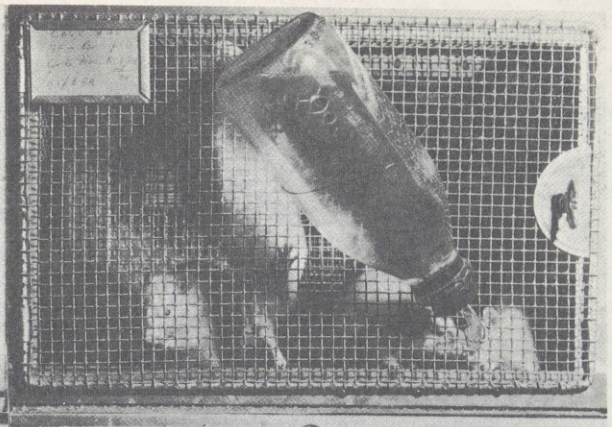
On the basis of our observations made in living animals and at post-mortem examination, it is our conclusion that we have seen no evidence of chronic toxicity to be exerted by L-monosodium glutamate, DL-monosodium glutamate or L-glutamic acid.

ANIMAL ROOM SHOWING CAGING FACILITIES
Windows have been made opaque to regulate lighting intensity.

EQUIPMENT FOR WEIGHING RATS



Food was furnished in containers designed to prevent wastage and favor good dental condition.

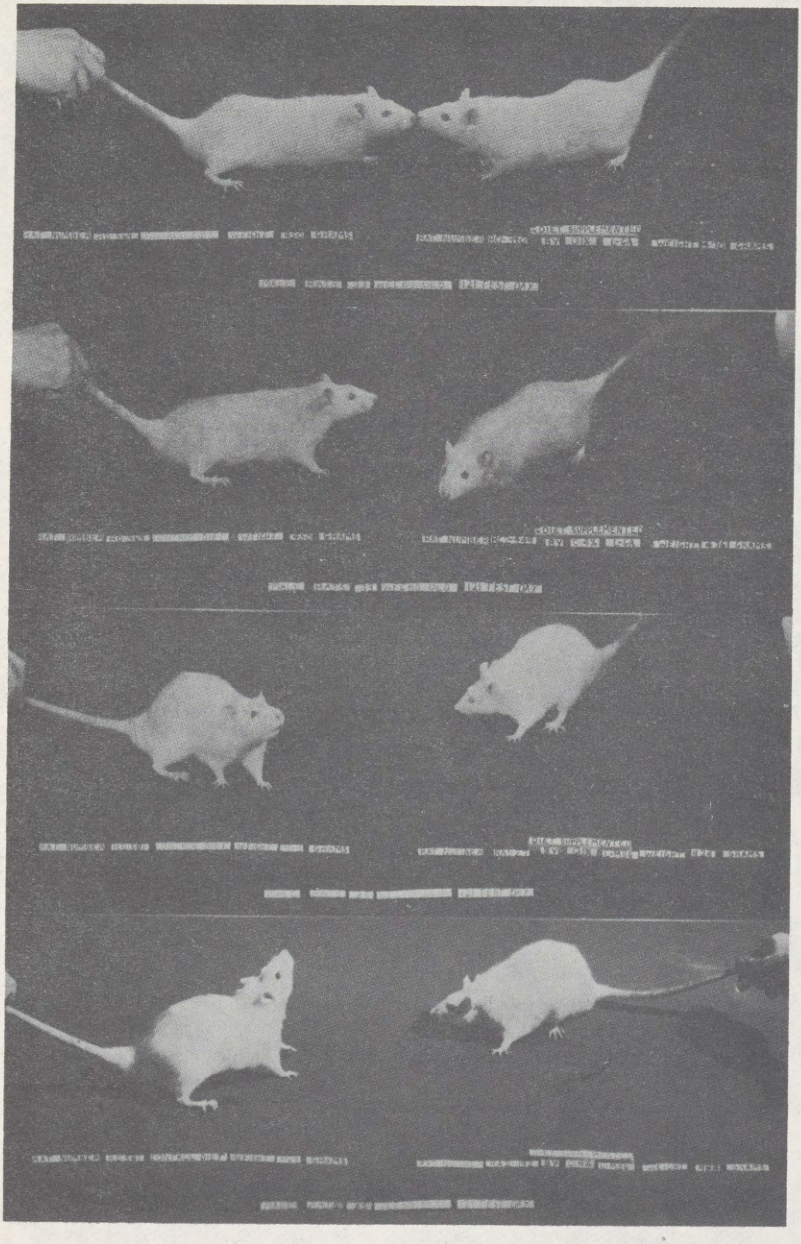


To show "demand" constant water supply.

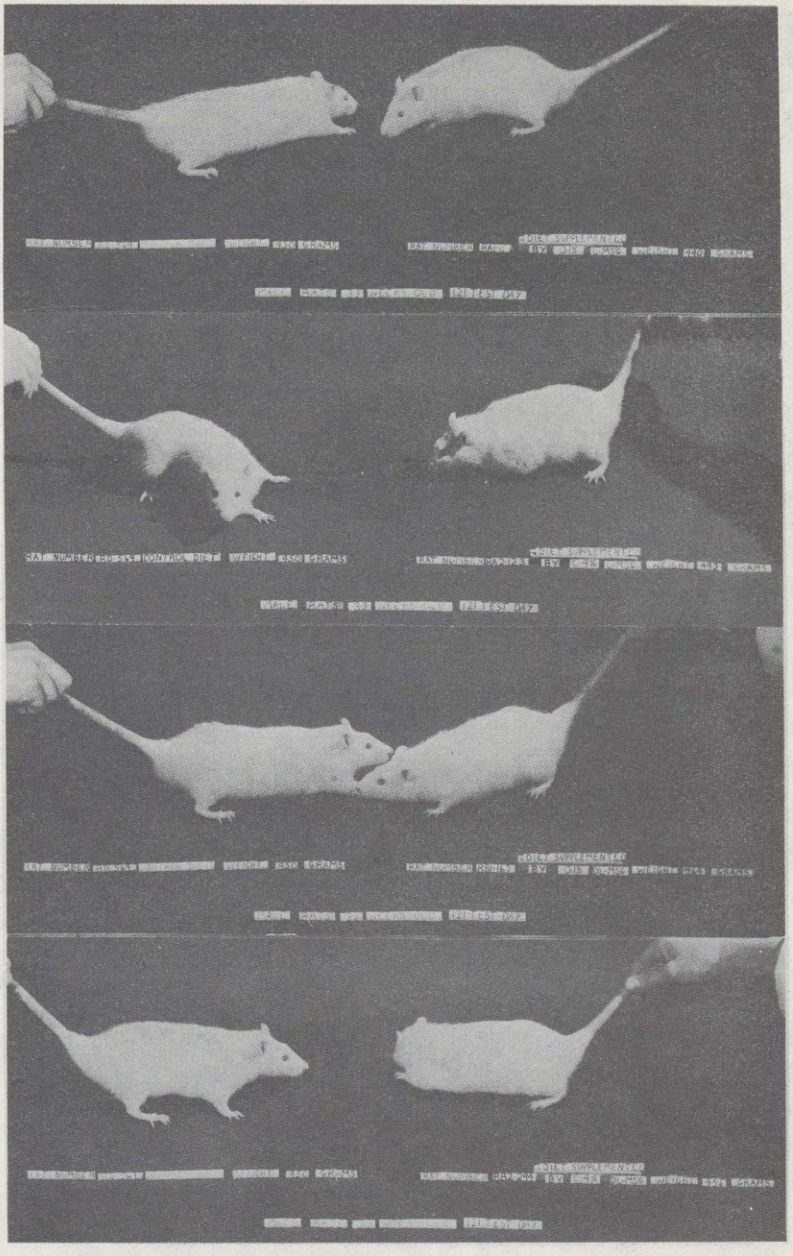
PHOTOGRAPHS SHOWING CONDITION OF RATS

AT 121, 595, AND 826 TEST DAYS

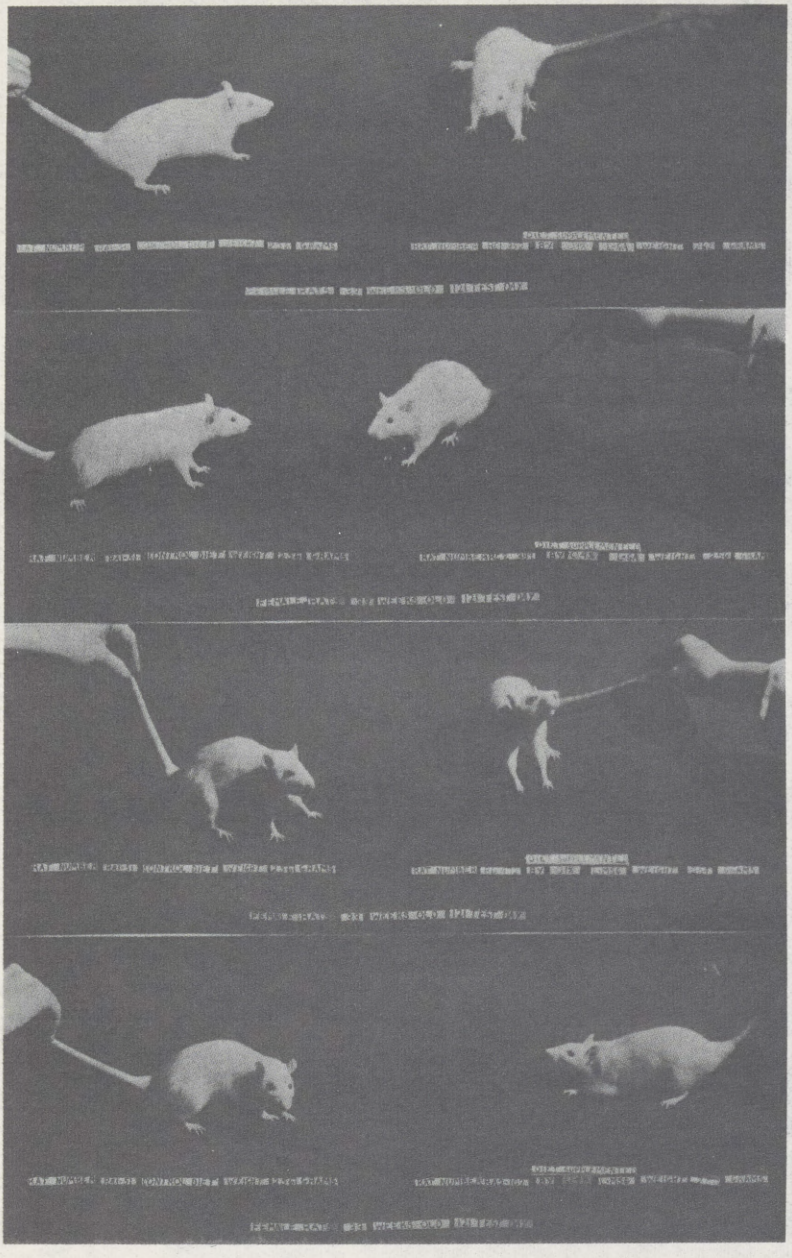
(All rats from original stock. Rats kept on test for 826 days had been reserved for a special project.)



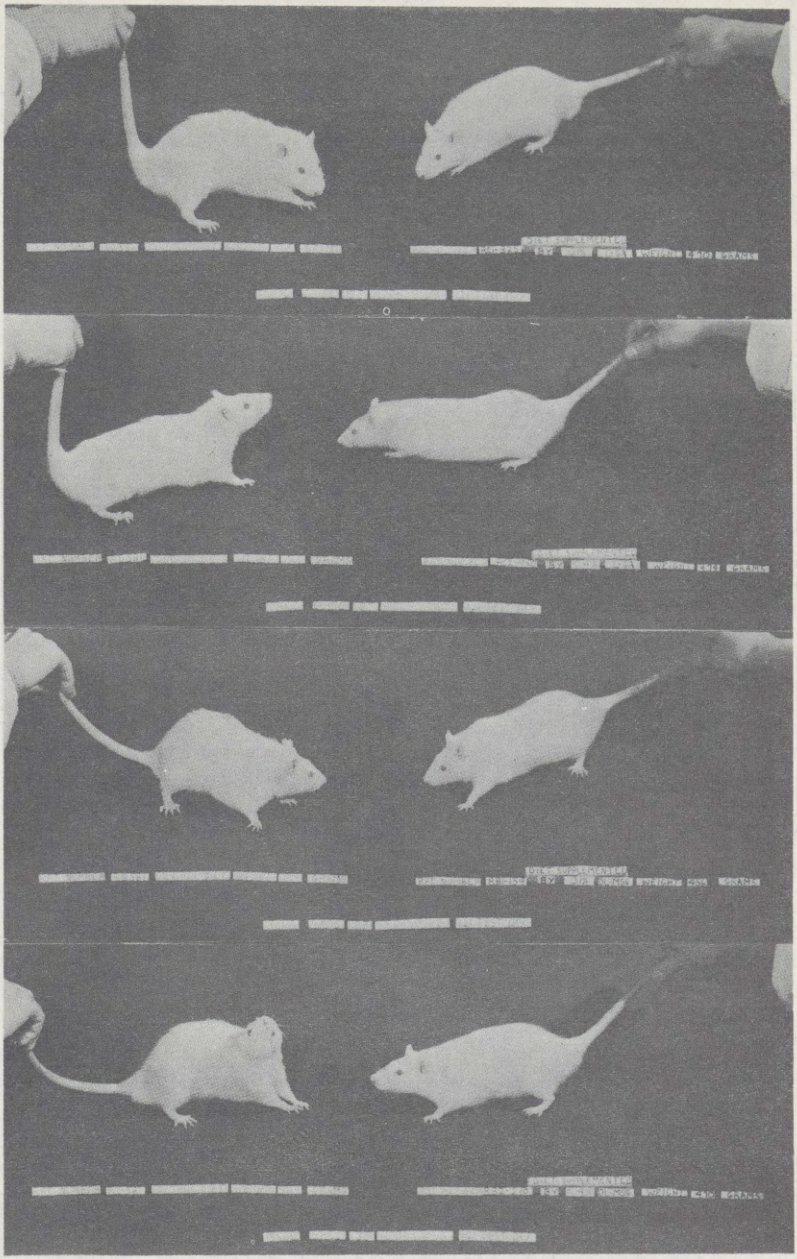
Illustrates condition of male test and control rats after 121 test days.
Age 33 weeks - 35 weeks.



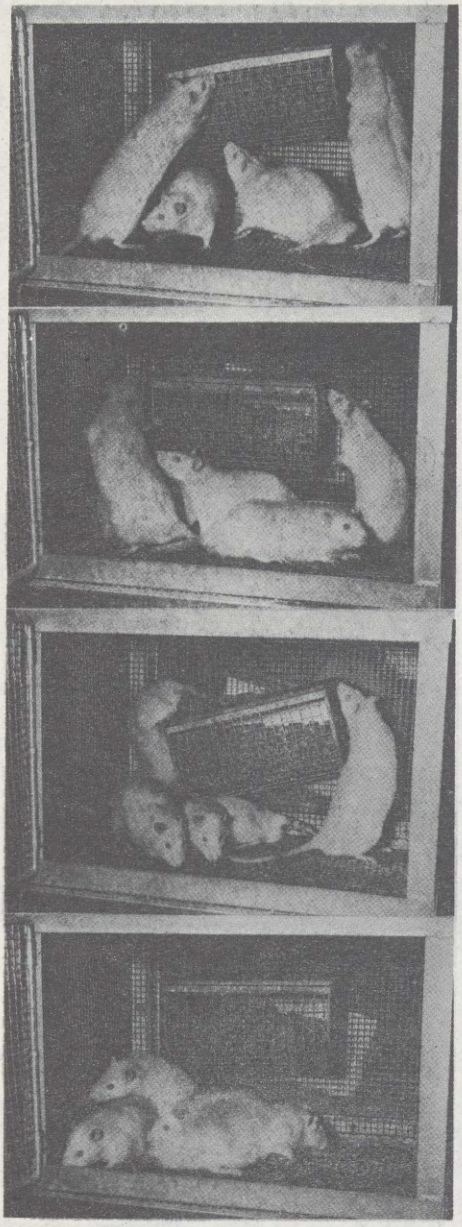
Illustrates condition of male control and test rats after 121 days.
Age 33 weeks.



Illustrates condition of female control and test rats after 121 test days. Age 33 weeks.



Illustrates condition of male control and test rats after 121 test days. Age 35 weeks.

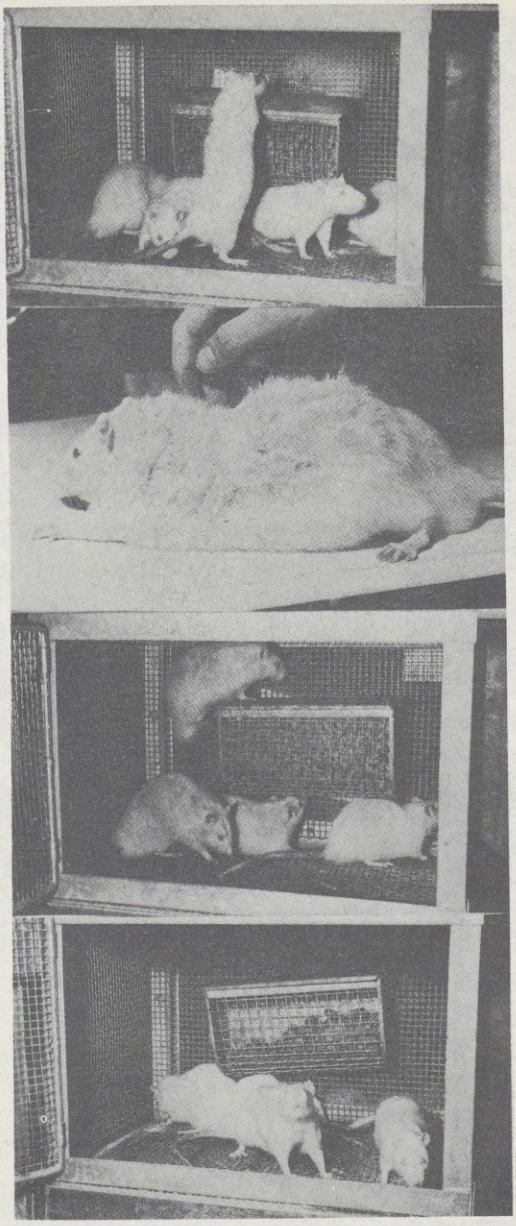


Rats fed on a diet supplemented with 0.4 percent L-monosodium glutamate after 587 test days.

Rats fed on a diet supplemented with 0.1 percent L-monosodium glutamate after 585 test days.

Rats fed on a diet supplemented with 0.1 percent DL monosodium glutamate after 587 test days.

Rats fed on a diet supplemented with 0.4 percent DL-monosodium glutamate after 591 test days.

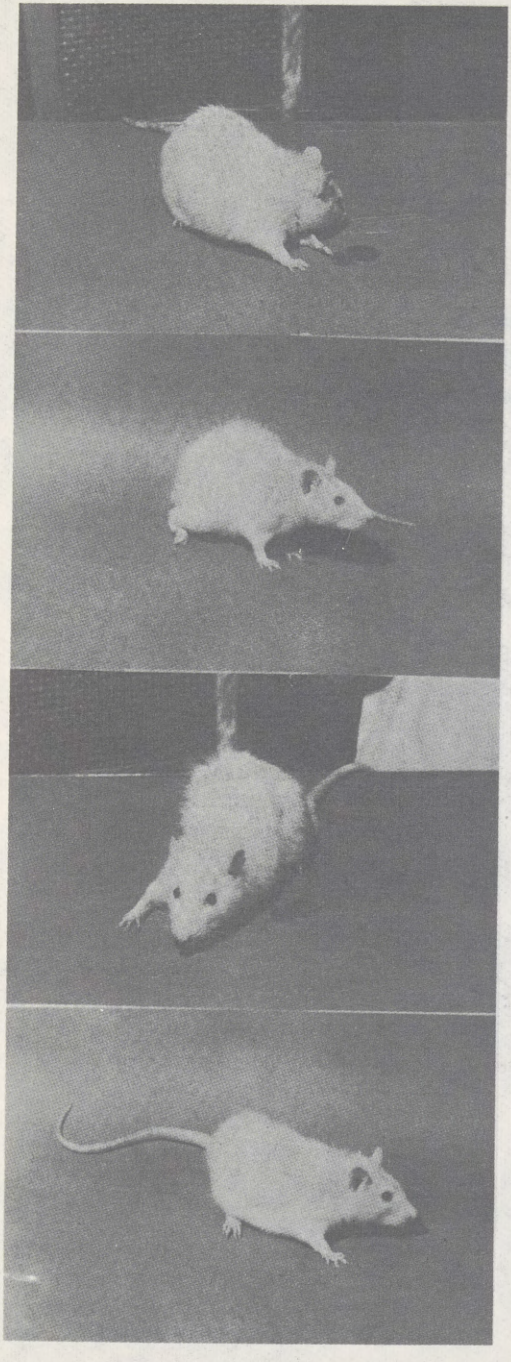


Rats fed on a diet supplemented with 0.4 percent L-glutamic acid after 596 test days.

Typical male rat fed on a diet supplemented with 0.1 percent L-glutamic acid for approximately nineteen months (573 days).

Rats fed on a diet supplemented with 0.1 percent L-glutamic acid after 594 test days.

Rats fed on a control or unsupplemented diet after 605 test days.

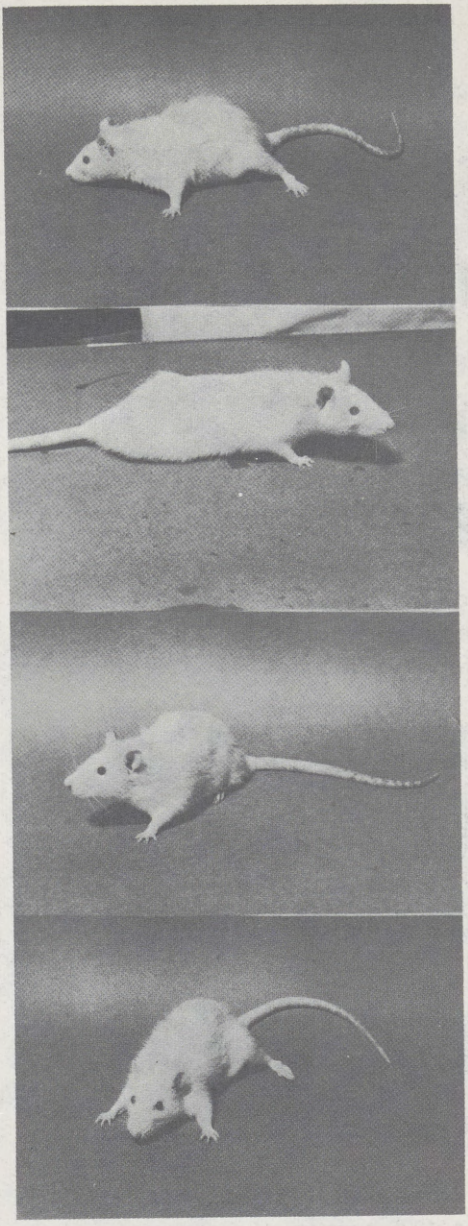


Female rat fed on a control or unsupplemented diet for 826 test days.

Female rat fed on a diet supplemented with 0.1 percent L-glutamic acid for 826 test days.

Male rat fed on a diet supplemented with 0.4 percent L-glutamic acid for 826 test days.

Female rat fed on a diet supplemented with 0.4 percent L-glutamic acid for 826 test days.



Female rat fed a diet supplemented with 0.1 percent DL-monosodium glutamate for 826 test days.

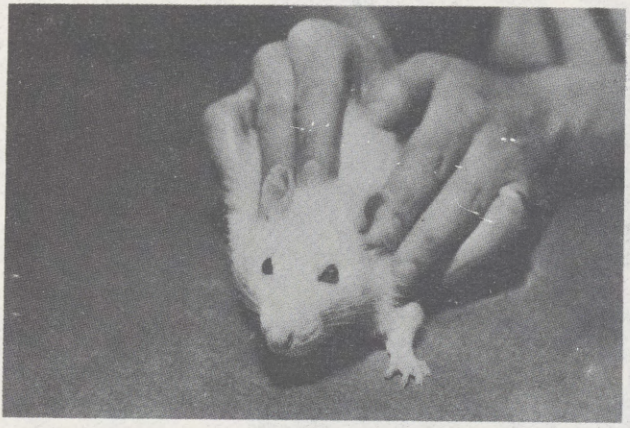
Female rat fed a diet supplemented with 0.4 percent DL-monosodium glutamate for 826 test days.

Female rat fed a diet supplemented with 0.4 percent L-monosodium glutamate for 826 test days.

Female rat fed a diet supplemented with 0.1 percent L-monosodium glutamate for 826 test days.

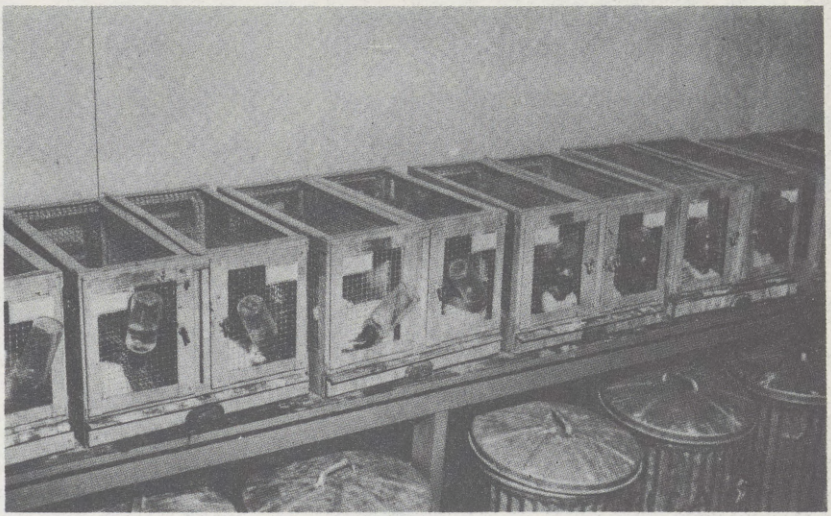
PHOTOGRAPHS ILLUSTRATING ABNORMAL EYE CONDITIONS DISCUSSED IN REPORT

Female rat fed control diet for 826 test days. Right eye enlarged and colorless with areas of vascularization.

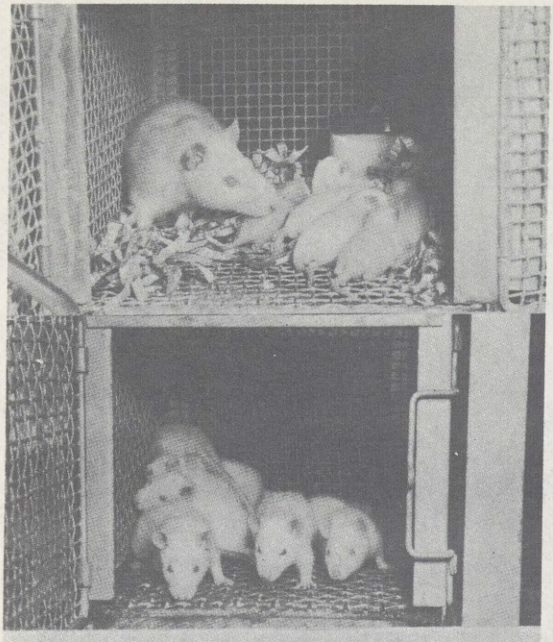


Female rat on 0.4 percent L-glutamic acid supplemented diet (826 test days). Shows keratoconus of the left eye with area of vascularization. Remainder of eye is colorless.

PHOTOGRAPHS SHOWING SUBSTOCK BRED FROM ORIGINAL RAT COLONY (F_O)



CAGING FACILITIES FOR SUBSTOCK

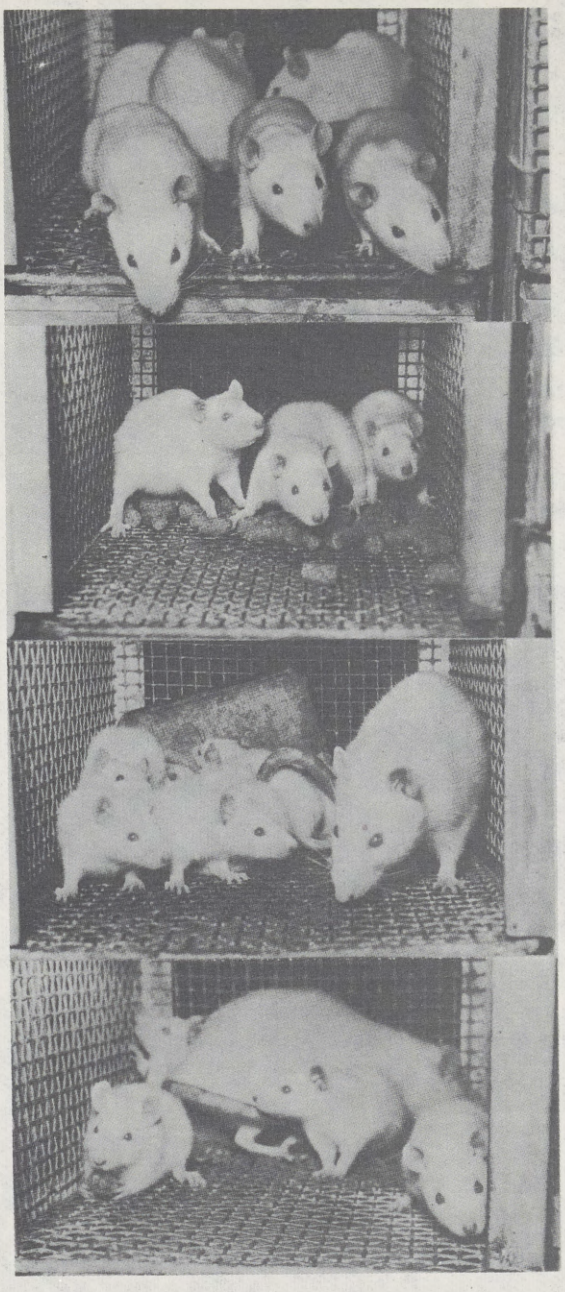


F_1 rats fed on a diet supplemented with 0.4 percent L-glutamic acid at 11 days of age.

F_1 rats fed on a control diet at 21 days of age.

F_1 female fed on 0.1 percent L-monosodium glutamate for 570 days. Small tumor present in left pectoral mammary region.

Typical F_1 male fed on 0.1 percent L-glutamic acid supplemented diet for 570 days.

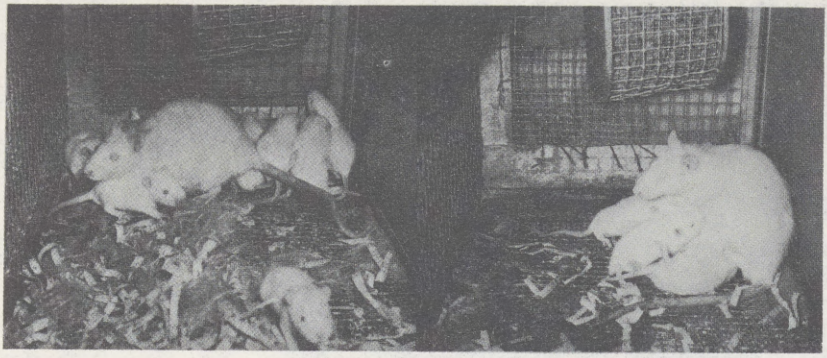


Male rats (F_2) fed on a diet supplemented with 0.4 percent DL-monosodium glutamate. Seven weeks of age.

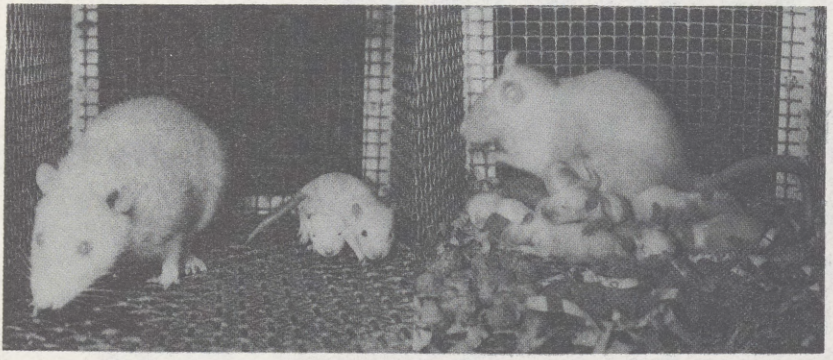
F_2 males fed on 0.4 percent DL-monosodium glutamate supplemented diet at seven weeks of age.

F_2 rats fed on 0.1 percent L-glutamic acid supplemented diet at three and a half weeks of age.

F_2 rats fed on control diet at three and a half weeks of age.



F_2 rats fed on a diet supplemented with 0.1 percent L-glutamic acid at nineteen days of age. The mother became pregnant by a litter mate and delivered when 61 days of age.



F_2 rats fed on a diet supplemented with 0.1 percent L-monosodium glutamate diet at four weeks of age.

F_2 rats fed on a diet supplemented with L-glutamic acid at eleven days of age. Mother impregnated by litter mate and delivered when 69 days old.

F_2 rats fed on control diet at twelve days of age. Mother became pregnant by litter mate and delivered when 79 days old.

F_2 rats fed on a diet supplemented with 0.1 percent L-glutamic acid at approximately three and a half weeks of age.

F_2 rats fed on control diet at three and a half weeks of age.

F_2 females fed on 0.4 percent DL monosodium glutamate supplemented diet at seven weeks of age.

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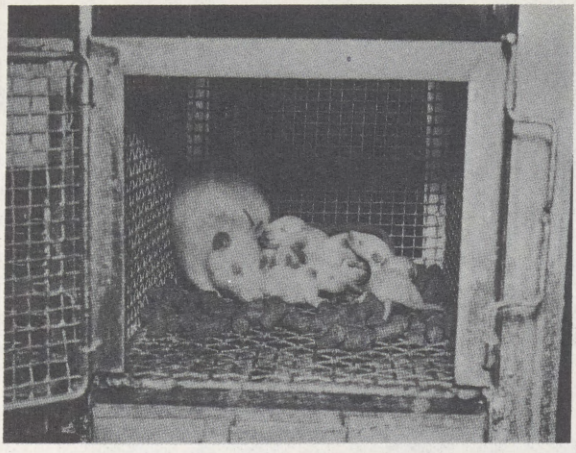
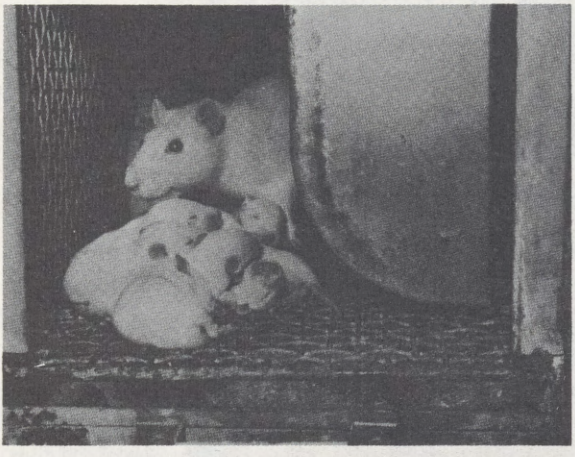
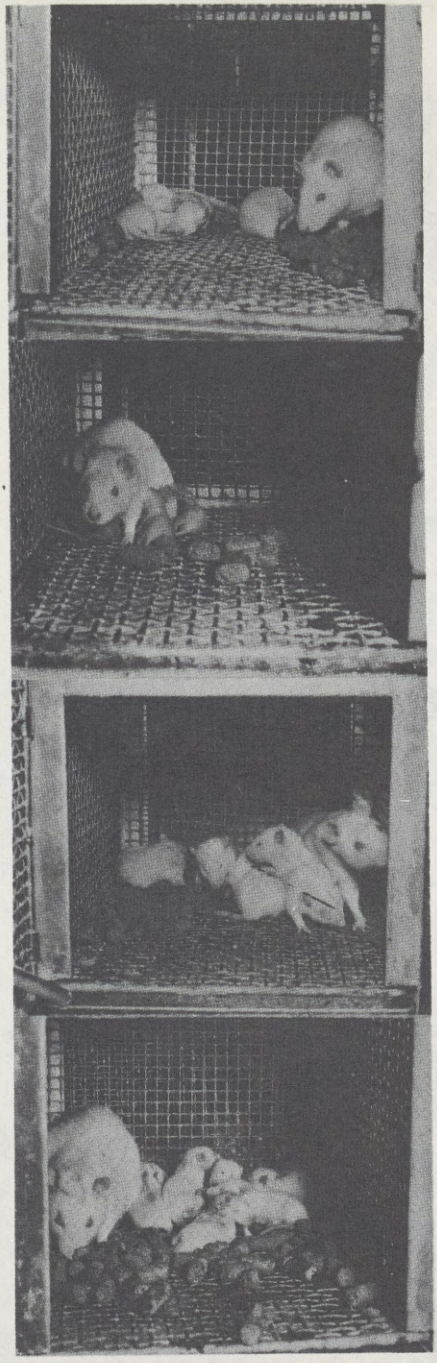


F_3 rats fed on a diet supplemented with 0.1 percent L-monosodium glutamate at fifteen days of age.



F_3 rats fed on a diet supplemented with 0.1 percent L-glutamic acid at approximately four weeks of age.



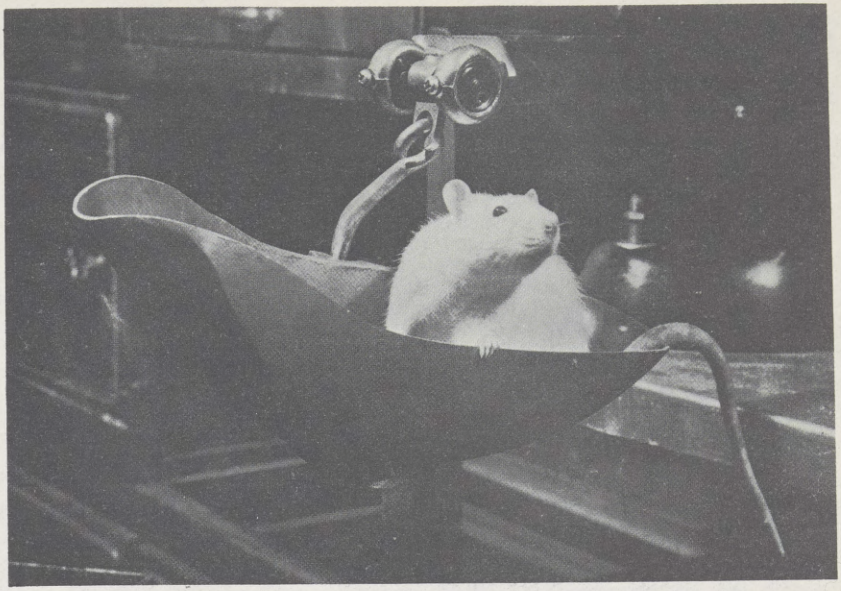
F_4 rats fed on a diet supplemented with 0.4 percent L-glutamic acid at eleven days of age.

F_4 rats on control diet at eight days of age.

F_4 rats fed on a diet supplemented with 0.4 percent DL-monosodium glutamate at twenty days of age.

F_4 rats fed on a diet supplemented with 0.4 percent L-monosodium glutamate at thirteen days of age.

F_5 rats fed on a diet supplemented with 0.1 percent L-glutamic acid at 31 days of age.



PART II

For purposes of reference, detailed data concerned with gross and microscopic appearance of rat tissues are presented in Part II, together with data on spontaneous tumors. Although of interest to a limited group of readers, the findings are chiefly important as matters of record for it is largely upon post-mortem findings in laboratory animals that the essential conclusions are based. In effect, the material in Part II of this report is an appendix.

OCCURRENCE OF SPONTANEOUS TUMORS

At the end of one year of observation, a number of rats showed swellings which were presumed to be spontaneous tumors. Previous to 368 test days, tumors had been seen in one control rat and in one rat from each of the groups fed on L-monosodium gultamate. At 368 test days, the number had increased so that rats from all groups except that fed on 0.4 percent DL-monosodium glutamate showed tumor growth. The percentage incidence at that time in the 0.1 percent L-monosodium glutamate group was 6.0 percent and in the control group, was 5.4 percent. The incidence for all rats at this time was 2.7 percent, and for all test rats was 2.5 percent which is significantly lower than for the control group.

At one and a half years (547 test days) the percentage incidence ranged from 4.3 percent in the group fed a supplement of 0.1 percent DL-monosodium glutamate to 14.5 percent for the group fed a supplement of 0.1 percent L-monosodium glutamate. Making a similar comparison to that above, the percentage incidence for all test rats was 7.9 percent, for all rats was 8.0 percent and for controls was 9.0 percent.

Between one and a half and two years, the incidence of presumptive tumors increased very greatly. At 730+ days, the incidence varied from 29.0 percent in the group fed a supplement of 0.1 percent DL-monosodium glutamate to 54.7 percent in the 0.1 percent L-monosodium glutamate group. However, rats fed on a supplement of 0.4 percent L-monosodium glutamate showed an incidence of 39.6 percent which was next to the lowest for all groups. At two years (730 + days) the average percentage incidence for all rats was 40.7 percent, for all test rats 40.1 percent and for control rats was 42.4 percent. From these data it appears that although the rate of development of tumors varies between test and control rats, the presumptive[1] incidence at two years is approximately the

[1] The term "presumptive" is used in discussing tumor growth when the data is based on observations made during life. At autopsy, a number of suspected tumors were found to be swelling, cysts, etc., but not verified tumors. Thus, the verified incidence of tumors is slightly lower than the presumptive incidence.

same. The male rats were more resistant to spontaneous tumor formation than females, but this is not peculiar to the Sprague-Dawley strain.

The incidence among female rats was approximately three and a half times that seen in male rats. One of four female rats with tumor showed multiple tumor sites. Since these were chiefly mammary adenomas, it is probable that they did not represent true metastases but were continuous along the course of the interconnecting mammary tissue. Ten times as many tumors in female rats were found on the ventral surface as on the dorsal surface or on mixed body surfaces. In male rats, only one showed multiple tumors. The tumor sites among male rats were equally divided between the dorsal and ventral surfaces. The comparative absence of internal tumors in both sexes is noteworthy.

The typical tumor in male rats appeared on either dorsal or lateral body surfaces and was horny or wart-like. It was invariably external to the body wall and on section often contained a granular material or milky secretion which may have represented cystic regression.

Of 90 tumors carefully examined microscopically, more than one-half were purely adenomatous in type. The next highest category was that of fibrosarcoma represented by 11 tumors. Mixed types of tumors were seen in 10 specimens. The origin was not conclusively established for 46 tumors but because of the sites involved, they probably originated in mammary tissue or in connective tissue adjacent to mammary tissue. It was possible to verify mammary origin in 33 tumors.

The appearance of tumors is described in tabular form below. In referring to mammary tumors, the mammae are designated as pectoral, abdominal or inguinal according to the nomenclature used by Greene.[1]

TABLE I.—INCIDENCE OF TUMORS [1]

Test group	Original number of rats	Number with tumors	Percentage incidence
0.1 percent L–MSG	75	41	54.7
0.4 percent L–MSG	75	30	39.6
0.1 percent DL–MSG	75	22	29.0
0.4 percent DL–MSG	75	26	34.4
0.1 percent L–GA	75	31	40.3
0.4 percent L–GA	75	32	42.6
Control	150	64	42.4
Total	600	246	41.0
Average percentage incidence:			
All test rats			40.1
All rats			40.7
Control rats			42.4

[1] Based on observations during life up to 730 test days.

TABLE II.—PRESUMPTIVE PERCENTAGE INCIDENCE OF TUMORS [1]

Test days	182	368	547	730
0.1 percent L–MSG	1.5	6.0	14.5	54.7
0.4 percent L–MSG	1.5	2.9	6.1	39.6
0.1 percent DL–MSG	0	1.4	4.3	29.0
0.4 percent DL–MSG	0	0	5.9	34.4
0.1 percent L–GA	0	1.5	10.6	40.3
0.4 percent L–GA	0	2.9	5.9	42.6
Control	.7	4.5	9.0	42.4

[1] Based on observations during life.

[1] Greene, E. C.; *Anatomy of the Rat.* Trans. Am. Phil. Soc., 27, Philadelphia, 1935.

TABLE III.—DATA ON TUMORS[1] (SUMMARY)

Test group	Number of rats with tumors			Number of rats with multiple tumors			Location on body surface					
							Dorsal		Ventral		Mixed	
	Male	Female	Total	Male	Female	Total	Male	Female	Male	Female	Male	Femael
0.1 percent L–MSG	3	12	15	0	4	4	1	1	1	11	1	0
0.4 percent L–MSG	3	12	15	0	3	3	1	0	2	11	0	1
0.1 percent DL–MSG	4	7	11	0	3	3	0	0	3	7	1	0
0.4 percent DL–MSG	2	6	8	0	3	3	0	0	0	6	2	0
0.1 percent L–GA	4	11	15	0	1	1	4	2	0	9	0	0
0.4 percent L–GA	1	12	13	0	1	1	0	0	0	11	1	1
Control	5	17	22	1	4	5	2	1	2	15	1	1
Total	22	77	99	1	19	20	8	4	8	70	6	3

[1] Based on gross autopsy findings in animals surviving 730-plus test days.

All tumors were benign (by microscopic examination), most were encapsulated and external to the body wall. The consistency was usually fibrous and firm. A few had ulcerated and become cystic and some showed regression. A table is presented showing the relation of tumor weight to total body weight:

$$\text{i.e. } \frac{\text{body weight}}{\text{tumor weight}}.$$

Thus, the smaller the ratio, the larger was the tumor. This data shows little more than trends and is not considered to be significant or to warrant firm conclusions since the size of the tumor was a function of its age which in turn is related to whether the animal was sacrificed soon after the tumor became apparent or whether it was allowed to live. In only a few cases did the size or condition of the tumor require the sacrifice of the animal. Determination of the functional body weight was rendered difficult in rats bearing large tumors. No marked losses of body tissue were seen except in animals with tumors which had grown to large size. This may have been due to the utilization of food by the tumor substance resulting in deprivation of normal tissues and subsequent shrinkage. (Emaciation is a concomitant of tumor growth, when uninterrupted and in general, the effect is greater at first on muscular than on predominantly fatty structures.)

TABLE IV.—CLASSIFICATION OF TUMORS

Test group	Type										Origin						
	Adenoma	Fibro-sarcoma	Mixed	Fibro-adenoma	Fibroma	Carci-noma	Adenocar-cinoma	Sarcoma	Unclas-sifiable	Total	Unknown	Mammary	Epithelial	Sweat gland	Uterine	Epider-moid	Total
0.1 percent L–MSG	5	3	3							11	8	3					10
0.4 percent L–MSG	10	2	1	2	1					16	6	6	2	1	1		16
0.1 percent DL–MSG	3		1	1	2		2	1		10	6	4					11
0.4 percent DL–MSG	5		1		1	1				8	5	3					1
0.1 percent L–GA	5	3	3							11	8	3					18
0.4 percent L–GA	10	2	1	2	1				2	18	7	6	2	2	1		18
Control	11	1		1		2		1		16	6	8					16
Total	49	11	10	6	5	3	2	2	2	90	46	33	4	3	2	2	90

TABLE V.—RATIO OF TOTAL BODY WEIGHT TO TUMOR WEIGHTS OF MALE AND FEMALE RATS

0.1 percent L–MSG		0.4 percent L–MSG		0.1 percent DL–MSG		0.4 percent DL–MSG		0.1 percent L–GA		0.4 percent L–GA		Control	
M	F	M	F	M	F	M	F	M	F	M	F	M	F
4.6	4.4	3.5	2.2	2.1	2.2	8.2	1.8	2.3	2.2	118.7	2.3	68.9	1.6
19.6	1.6	75.7	2.8	20.0	4.3	------	2.0	2.3	3.1	-------	21.0	172.6	1.3
2.6	3.0	------	3.4	3.2	5.4	------	2.7	118.7	9.6	-------	3.2	8.7	2.7
	2.5	------	6.5	------	40.9	------	4.0	-------	11.8	-------	5.3	483.0	4.6
	5.9	------	4.9	------	3.2	------	3.7	-------	11.0	-------	9.8	-------	47.4
	30.3	------	3.4	------	3.3	------	1.9	-------	170.1	-------	9.4	-------	12.8
	4.9	------	4.2	------	2.2	------	139.3	-------	4.0	-------	2.4	-------	9.4
	13.0	------	15.3	----------	----------	----------	1.9	-------	3.2	----------	----------	----------	2.2
	9.2	------	3.9	----------	----------	----------	----------	----------	----------	----------	----------	----------	6.8
	4.4	------	1.9	----------	----------	----------	----------	----------	----------	----------	----------	----------	8.9
	2.9	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	3.2
Average; 8.9	7.5	39.6	4.85	8.4	8.8	8.2	19.7	41.1	26.8	118.7	7.6	183.3	9.2

TABLE VI.—INCIDENCE TUMORS BY SEX[1]

Supplement	Number animals represented	Number with tumors			Percentage incidence		
		Male	Female	Total	Male	Female	Total
0.1 percent L–MSG	31	3	12	15	9.7	38.7	48.4
0.4 percent L–MSG	37	3	12	15	8.1	32.4	40.5
0.1 percent DL–MSG	41	4	7	11	9.8	17.1	26.9
0.4 percent DL–MSG	44	2	4	8	4.5	13.5	18.0
0.1 percent L–GA	36	4	11	15	11.1	29.2	40.3
0.4 percent L–GA	39	1	12	13	2.6	30.7	33.3
Control	56	5	17	22	8.8	30.4	39.2
Total	284	22	77	99	7.7	27.7	35.4

[1] Based on gross autopsy findings in animals surviving 730+ test days.

TABLE VII.—TUMOR CHARACTERISTICS[1] (GROSS OBSERVATIONS)

LOCATION ACCORDING TO BODY QUADRANT

Test group	Right anterior		Right posterior		Left anterior		Left posterior		More than 1 quadrant	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0.1 percent L–MSG	0	4	1	2	2	4	0	1	0	1
0.4 percent L–MSG	1	3	0	2	--------	2	0	3	2	2
0.1 percent DL–MSG	3	0	1	1	0	0	0	1	0	5
0.4 percent DL–MSG	0	0	0	1	0	0	0	1	2	4
0.1 percent L–GA	0	1	0	3	2	2	1	4	1	1
0.4 percent L–GA	1	1	0	1	0	4	0	2	0	4
Controls	4	3	0	2	2	2	0	4	0	5
Total	9	12	2	12	6	14	1	16	5	22

Test group	External to body wall		Encapsulated		Firm		Soft		Consistency mixed or unspecified)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0.1 percent L–MSG	2	10	2	10	2	9	1	2	0	2
0.4 percent L–MSG	3	11	1	10	1	9	3	2	0	0
0.1 percent DL–MSG	3	8	2	8	2	6	1	0	1	1
0.4 percent DL–MSG	0	6	0	6	0	5	2	0	0	1
0.1 percent L–GA	3	10	2	10	3	6	0	5	1	0
0.4 percent L–GA	1	12	1	11	1	9	0	3	0	0
Controls	5	16	1	16	0	13	5	3	0	1

[1] Based on gross autopsy findings in animals surviving 730-plus test days.

The mechanism leading to death in tumor-bearing animals is commonly a progression from ulceration to infection, then resulting in general sepsis, exhaustion and death. Death, when it occurred naturally in our rats, whether tumor-bearing or tumor-free did not follow such a sequence.

When the high incidence of tumors in all groups became apparent, we wrote to the Sprague-Dawley, Inc., requesting any available data regarding the incidence of tumors in this strain of rats. Our letter in part follows:

November 6, 1951

"We have found an excessively high incidence of tumors in this group of animals. They vary in size and rate of growth within wide limits. That the tumors result from factors other than those intrinsic to the experiment is fairly obvious, for control rats show a slightly higher incidence than do the test rats. We have removed tumors surgically with complete success and there has been no evidence of recurrence at the primary site or elsewhere in operated rats. Tumor transplants in rats previously free from tumors show no evidence of viability in the new sites. There are a few animals which show multiple tumors, but since they are breast tumors, we can not fairly draw any inferences as to metastasis.

"Our question is, therefore, have you any data derived under control conditions as to the incidence of tumors in Sprague-Dawley rats? Has it been obtained in your own laboratory or elsewhere? What types have predominated and have you any evidence of malignancy?"

A reply dated November 8, 1951 and signed by Mr. E. R. Dawley suggests that no exact information as to the incidence of spontaneous tumors exists for this strain. It must be considered, however, that the maintenance of rats to the age represented by our group is unusual and that no previous investigation may have been carried on sufficiently long to permit this data to be accumulated. Mr. Dawley's letter (in part) follows:

"We have no quantitative data on the incidence of tumors in our rats. We usually can find a few old discarded female breeders which have tumors. Last May we sent five of these animals to our consultants at the University of Wisconsin. They reported as follows:

'The diagnosis is based on the histological and gross lesions. Histologically, the tissue sections revealed a well lined glandular arrangement with epithelial cells of normal appearance. Though several mitotic figures were seen in the epithelial cells, such figures were hardly characteristic. There was a certain degree of sclerosis. Since the tumors were well localized subcutaneously without any effect on general condition, the diagnosis is adenoma with sclerosing features.'

"All of our present production is derived from an original 15 rats taken by Caesarian in 1940. Since that time we have never found a malignant tumor in any animal."

In light of the similarity of figures for incidence of tumors at 730 + days, i.e.

	Percent
All rats	40.7
All test rats	40.1
Control rats	42.4

we are unable to relate the development of tumors conclusively to the supplementary materials fed over the two-year period.[1]

SURGICAL REMOVAL OF TUMORS

When the feeding program had been in progress approximately 20 months the tumor growths present in four test and two control animals, all females, were removed in an effort to determine whether they would recur. A transplant of a tumor from one animal on the 0.1 percent DL-monosodium glutamate dietary level was made to the corresponding position in a male rat of the F_1 generation on the 0.4 per cent DL-monosodium glutamate dietary supplement to see whether the tumor would grow in a new host. (Transplantability is an important criterion of malignancy in tumors.) The tumors were removed with aseptic technique, with the animal under light nembutal anesthesia, fortified later by ether. In all animals used, the tumors were located on the ventral surface in the mammary region and were fibro-adenomas in type. They were external to the body wall, encapsulated and easily removed.

[1] In the tables referring to tumors some variation in the totals may be observed. This results from differences in the criteria used for establishing tumor growth. For example, in living rats, all persistent swellings were assumed to be tumors. Post-mortem examination of several suspected tumors showed them to be non-neoplastic. Not all tumors could be examined microscopically because of their grossly disorganized condition when autopsy was done.

Four of the animals died within two days of the operation, probably from the asphyxiant effect of excessive anesthesia since their respiration continued to be shallow until death and complete consciousness was never restored. A fourth animal from the 0.1 L-monosodium glutamate dietary group, who pulled out the operative sutures with his teeth on three occasions in a period of eight days, lived 104 days with no tumor recurrence. The tumor transplanted into a non-tumor-bearing rat showed no evidence of tumor growth 174 days after transplantation.

Caesarian section was performed on a female rat of the F_1 generation on the control diet who had been unable to deliver and was in distress for a period of several days. Five very large fetuses were removed. The rat recovered from the operation and was still surviving 174 days later. These three rats, although few in number, attest the good physical condition and ability to withstand surgery.

TABLE VIII.—EFFECT OF SURGICAL REMOVAL OR TRANSPLANTATION OF TUMORS

Supplement	Sex	Tumor description	Result
0.1 percent L-MSG	Female	Large tumor on right ventral surface in pectoral mammary region.	Died 1 day postoperative.
Do	Female	Small tumor on right ventral surface in inguinal mammary region.	Resutured 3 times after animal pulled out stitches; sacrificed 104 days postoperative with no regrowth of tumor in that time.
0.1 percent DL-MSG	Female	Transplant made of tumor which was removed from the left ventral surface, inguinal mammary region.	Died 2 days postoperative.
0.4 percent DL-MSG	Male (F_1 generation)	Transplant made of tumor in the same site as in host, i.e., inguinal mammary region.	No growth from tumor transplant after 174 days.
Control	Female	Small tumor on right ventral surface in mammary region removed.	Died 2 days postoperative from asphyxia.
Do	Female	Small tumor on left ventral surface in mammary region removed.	Succumbed to operation.

APPENDIX

Section 1

Gross Pathological Findings In Rats Fed On Supplemented And A Control Diet

In the following section, pathological changes perceptible at autopsy by gross inspection are presented. Only rats showing anatomical alterations are described. The location and external appearance of tumors, if present, are described.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON DIET SUPPLEMENTED WITH 0.1 PERCENT L–MSG

Identification and sex	Nature of death	Number of test days	External appearance	Tumor	Organs showing gross pathology
3 0–1, male	Ether inhalation	176	Normal except for tumor	Involved right gluteal region. Measured 8 by 9 cm. Encapsulated and firm to touch. On dissection, mass extended from crest of ilium to patella. Femur appeared to be involved.	None.
7 0–2, female	Chloroform vapor	270	Animal appeared sickly and anemic.	Left ventral surface attached to body wall and extending posteriorly to left limb. External to body wall and encapsulated. Tumor surface ulcerated and bleeding.	Spleen: Greatly enlarged.
2 0–2, mile	Intraperitoneal injection of nembutal.	716	Very thin paralysis of both legs	None	Lungs: Very dark, many mottled areas on surface. Kidneys: Both kidneys enlarged.
7 1–1, female	do	772	Normal except for tumors	2 medium-sized tumors on ventral surface. 1 involved left side from submaxillary to mammary region; on section was hard and white. Tumor on right side between hind legs. Bilobate, soft, gray in color.	Lungs: Gray patches; 1 lobe brown in color. Liver: Spotted area on 1 lobe. Kidneys: Deep crater near anterior tip of the right kidney.
7 0–1, female	do	772	do	Tumor tissue was hard with light and dark areas	Lungs: Many gray patches.
8 1–0, female	do	772	do	2 tumors on ventral surface extending dorsally; 1 over forelimb and one over hind limb.	None.
10 0–1, female	Chloroform vapor	347	Normal	Right ventral surface involving mammary region and forelimb.	Do.
6 3–0, female	do	518	Very thin; teeth had grown through tongue. Roof of mouth was pierced.	Ventral surface in region of left forelimb	Kidneys: Extremely dark, almost black.
8 0–2, female	do	632	Enlarged abdominal area	Internal mass. Gelatinous material filled abdominal cavity under which a large round mass of tissue was lying. Appeared to be in position of uterus.	Gonads: Fallopian tubes were attached to large round mass which appeared to be the uterus.
7 1–0, female	Intraperitoneal injection of nembutal.	641	Normal	Ventral surface near vaginal region involving left leg. Pressure sore on tumor surface.	Lungs: Mottled.
2 1–0, male	do	666	do	Nonencapsulated tumor attached to mesentery in abdominal cavity. On section, tumor was lobed, hard and pink-brown.	Liver: Granular, orange-brown color. Digestive System: One part of intestine and mesentery attached to tumor. Intestines appeared shrunken.
6 1–1, female	do	666	Tumor was so large animal unable to walk; legs suspended in air.	Very large tumor on ventral surface involving right leg and vaginal region.	Lungs: Mottled.
2 0–3, male	do	772	Normal except for tumor	Tumor on dorsal surface at base of spine, external to body wall. On section, very hard with white and yellow areas.	Lungs: Mottled. Digestive system: Small mass beside intestine in mesentery.
10 3–0, female	do	773	do	Tumor on ventral surface between forelimbs from midline of body to chin. On section, tumor had three lobes composed of yellowish-white tissue.	Lungs: Pinpoint gray areas on surface:
8 0–3, female	do	773	do	Three small tumors; one under right leg on ventral surface. Second tumor on ventral surface on right side of chest. Third tumor was forming under left forelimb.	Lungs: Large gray patches. Kidneys: Right kidney enlarged and contained a small liquid-filled bleb on outer surface. Spleen: Mottled.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON DIET SUPPLEMENTED WITH 0.1 PERCENT L–MSG—Continued

Identification and sex	Nature of death	Number of test days	External appearance	Tumor	Organs showing gross pathology
8 1–1, females	Intraperitoneal injection of nembutal.	773	Normal except for tumor	3 tumors; 2 were on left ventral surface near forelimb. 3d tumor on right side under forelimb.	None.
6 0–2, female	do	773	do	Small tumor on left side under hind leg. On section showed both hard and soft tissue.	
5 1–0, male	do	773	Animal was thin	None	Kidneys: Enlarged, grainy. Gonads: Hemorrhagic area in seminal vesicles.
			WITH 0.4 PERCENT L–MSG		
12 1–2, female	Chloroform vapor	347	Normal	Right ventral surface, mammary region	None.
15 0–2, female	do	374	do	Mammary region, scabbed on external surface	Do.
16 12–0, male	do	635	do	Very large external tumor on right side of body. Skin around tumor was spotted.	Lungs: Mottled and hemorrhagic. Kidneys: Pale.
12 0–3, female	do	641	do	2 tumors external to body. 1 very large, on left ventral surface lower mammary region. 1, smaller in size, on right ventral surface, upper mammary region.	Lungs: Mottled.
18 0–1, male	Intraperitoneal injection of nembutal.	641	Opacity of both eyes, pressure sore on right heel. Animal very thin.	None	Lungs: Mottled, gray in color. Kidneys: Enlarged, dark in color with dark spotted areas.
12 2–0, female	do	667	Normal	External tumor on upper left ventral surface. Small tumor on lower left ventral region.	None.
17 0–2, male	do	667	Very thin, debilitated. Infection in ear, opacity of both eyes.	Scabbed area on back	Lungs: Mottled.
19 2–0, male	do	667	Very thin, unable to use hind legs.	Yellow lump on skin near penis. When sectioned was filled with green pasty material.	Kidneys: Dark and mottled.
13 0–3, female	Ether inhalation	176	Normal except for tumor	External, encapsulated, measuring 6–1/2x6 cm. Right ventral surface from submaxillary region to middle of chest. On section, lobulated. Possible involvement of thyroid.	Thyroid: Normal to gross inspection.
16 1–0, male	Intraperitoneal injection of nembutal.	731	do	Enlargement on ventral surface involving neck and chin on both sides of head and extending to and including forelimbs. On section, jellylike material and a large amount of light amber fluid escaped.	Lungs: Granular. Trachea: Small, white, grapelike clusters lying against trachea, probably enlarged galnds.
11 1–2, female	Decapitated	750	Body very thin	Right ventral surface between forelimb and hindleg. On section, areas were white, some containing blood.	Lungs: Mottled.
12 1–0, female	do	750	Normal except for tumor	Ventral surface in mammary region and under left forelimb. On section, tissue was tan and red in color. Small tumor under left leg.	Do.

16	3–1, male	do	757	do	Tumor mass on left lateral aspect of body. On section, tumor was filled with yellow granular material.	Do.
14	3–0, female	do	757	do	Left mammary region above hindlimb. On section tumor tissue soft.	Do.
16	1–1, male	do	757	Normal	None	Liver: Occasional white mottled areas.
15	2–0, female	do	757	Opacity of 1 eye. White area under skin filled with a material resembling pus.	do	Lungs: Creamy in color with brown areas. Kidneys: Shrunken. Miscellaneous: Pleural cavity filled with watery, blood-tinged fluid.
15	1–0, female	do	757	Normal	do	Gonads: Left horn of uterus enlarged and filled with solid material.
20	0–1, male	Intraperitoneal injection of nembutal.	773	Animal very thin, paralyzed in hind legs. Both eyes had corneal opacities.	do	Lungs: Tan in color with dark brown spots; 1 lobe had gray patches. Gonads: Testes very small.
14	2–0, female	do	773	Animal had a dried bloody discharge around nose. 1 eye was convex with an opaque area at point.	Large ball-like mass in abdominal cavity which appears to be a uterine tumor. On section the mass of tissue was filled with a thick yellow gray material and a spongy soft tissue.	None.
17	2–0, male	do	750	Normal except for tumor. Pressure sores on feet.	2 small tumorlike masses on dorsal surface over spine. On section, lumps were cavities under skin filled with granular material.	Lungs: Mottled.
14	0–1, female	Decapitated	750	Normal except for tumor	3 external tumors. 2 were on lower left and right mammaries. Third on right side near forelimb but in a lateral position. 2 posterior tumors showed pressure sores; 1 contained a material resembling pus.	Kidneys: Brown and mottled; granular.
17	1–1, male	do	750	Hindquarters very thin. Fur over back, yellow-orange in color. Pressure sores on hindlegs.	None	Lungs: Pinpoint gray spots over lobes of lungs. Kidneys: granular.
20	1–1, male	do	750	Animal thin and emaciated. Paralyzed in hindlegs. Fur discolored.	do	Lungs: Pinpoint white spots over lobes. Kidneys: Both kidneys enlarged, grainy. Gonads: 1 lobe of preputial gland was filled with a green material resembling pus.
13	1–2, female	do	757	Opacity in 1 eye	Lagre tumor on right side extending from thigh to ribs in midline of ventral surface. On section tumor filled with a milky material. Tumor tissue firm to touch.	Liver: Spotted areas on liver. Lungs: Mottled; dark green pinpoint areas over surface.
13	2–0, female	do	757	Normal except for tumor	Ventral surface between hind legs, involving anus and genital region. Tumor was external but lying against abdominal wall. Part of tumor fibrous, part was yellow, filled with viscous material.	Lungs: Mottled.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON DIET SUPPLEMENTED WITH 0.1 PERCENT L–MSG—Continued

WITH 0.1 PERCENT DL–MSG

Identification and sex	Nature of death	Number of test days	External appearance	Tumor	Organs showing gross pathology
26 3–0, female	Intraperitoneal injection of nembutal.	772	Good except for tumor	3 tumors on right in mammary region, of medium size	Gonads: A large bleb on left horn of uterus.
22 3–0, male	do	772	Coat was discolored (yellow)	Large tumor external to body wall on lateral dorsal and ventral surface which involved right posterior quadrant. On section, tissue was hard and white.	Lungs: Black pinpoint areas over surface. Kidneys: Left kidney was mottled, granular, and enlarged.
30 0–3, female	do	773	Good except for tumor	Large tumor on ventral surface extending from submaxillary to abdominal region from right forelimb to left. A second tumor under right forelimb on left side. The larger tumor on section was hard, white, and bilobate.	None.
21 1–2, male	do	777	Normal	Palpable mass near genitals	Gonads: On dissection, preputial gland was filled with a green, pasty material.
28 0–3, male	do	777	do	None	Liver: White areas on surface. Kidneys: Both kidneys were mottled and grainy.
29 1–1, female	do	777	do	do	Lungs: Gray patches on surface. Spleen: Small in size and irregularly shaped. Gonads: Small, hard lumps present in the horns of the uterus.
28 2–0, female	do	777	Good condition except for 2 small tumors.	1 tumor had formed in the genital region and was pushing against the anus and vagina on left ventral side. On section, tissue was hard and white. Second tumor on right ventral surface in region of hindlimb. On section, tissue was soft and orange in color.	Lungs: Very pale and with gray patches over lobes.
28 1–1, female	do	777	Normal	None	Lungs: Black pinpoint areas along the periphery of 1 lobe. Liver: Liver was small and lumpy, irregularly lobed, and very friable. Spleen: Greatly enlarged.
23 1–1, male	do	548	do	Small hardened area of skin on right side near axillary margin.	None.
28 0–1, female	do	548	do	None	Lungs: One area appeared cystic.
21 0–2, male	Chloroform vapor	610	Opacities of both eyes	External tumor extremely large and soft to touch. Extended from right forearm to forelimb on ventral region. Very soft when cut into; appeared to be connective tissue.	None.
23 3–0, male	Intraperitoneal injection of nembutal.	641	Animal appeared sickly, wheezing heavily.	None	Lungs: Mottled and hemorrhagic, deep brown color. Kidneys: Enlarged. Spleen: Small in size.
29 1–0, female	do	772	Normal	A large tumor covered the entire ventral surface from neck to abdominal region. On section, a milky secretion escaped. Tumor was tough and fibrous.	Lungs: One lobe of lung had many gray patches on its dorsal aspect.

30	0–1, female	do	772	Enlarged left eye which was devoid of color.
23	0–1, male	do	780	Paralysis of hind legs
23	1–0, male	do	780	do
23	2–0, male	do	780	Normal
24	0–3, male	do	780	do
26	1–1, female	do	780	Left eye enlarged, with corneal opacity.
26	0–2, female	do	780	Normal

Very large tumor on ventral surface from neck to abdominal region and attached to both front limbs. Pressure sore on tumor which on secretion was lobed, hard, white.	Lungs: Pinpoint, gray areas scattered over all lobes.
None	Kidneys: Both kidneys were slightly mottled. Digestive system: Colon was very inflamed.
Tumor below the chin on the ventral surface, appeared to be attached to the thyroid. On secretion, a blood-tinged fluid escaped. Tissue was soft, gelatinous, with clotted blood in some areas.	Spleen: Enlarged, mottled, and cystic.
None	Lungs: Mottled. Liver: Enlarged. Kidneys: Enlarged, mottled and granular. Tissue soft and friable. Stomach: A hard white mass about 1 inch in diameter was present in the greater curvature.
do	Kidneys: Left and right kidneys were mottled. Areas of clear fluid within tissue of right kidney. Spleen: Irregularly shaped. Constriction in middle gave appearance of 2 lobes. Thyroid: Gelatinous material around the gland (colloid).
A large tumor present on ventral surface from submaxillary to abdominal region between both forelimbs measuring 4½ inches by 3 inches. On section tissue very hard.	Liver: Occasional, white mottled areas on dorsal and ventral aspects. Gonads: Clear, cystic area on one ovary. Adrenal: Adrenal appeared atrophied, gray in color.
Large external tumor on left side beneath hindlimb	Liver: Small cyst on one lobe.

WITH 0.4 PERCENT DL–MSG

31	3–0, female	Intraperitoneal injection of nembutal.	64	Normal
36	0–3, male	do	548	do
40	1–1, male	Chloroform vapor	610	Normal, hair over back was discolored. Left eye was enlarged and misshapen.
38	2–0, male	do	610	Very thin and sickly over a long period of time.

None	Kidney: Pelves of both kidneys caseated pulp missing, more marked in left than right. Clear watery fluid, escaped from kidneys on section.
Internal mass in vicinity of kidneys which was collagenous in type.	None.
Large protursion on left side of face above the eye the size of a walnut, soft to touch and scabbed. When pressure was applied, yellowish material resembling pus oozed out.	Do.
Small sac below costal region just over the heart which was filled with a watery fluid.	Lungs: Lumps on lobes filled with yellow pasty material. Very little sound lung tissue. Heart: Lump over base of heart size of a dime filled with thick yellow, pasty material. Kidneys: Both kidneys very dark in color, left kidney slightly mottled. Spleen: Brown in color.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON DIET SUPPLEMENTED WITH 0.1 PERCENT L–MSG—Continued

Identification and sex	Nature of death	Number of test days	External appearance	Tumor	Organs showing gross pathology
37 3–0, male	Intraperitoneal injection of nembutal.	675	Very thin, paralysis of both legs. Discharge from anus.	Internal, attached to intestines, and laced in and around large intestine. Tumor composed of many small lobes and balls.	Kidneys: Both kidneys were enlarged and dark in color. Digestive System: Intestines attached to tumor. Large intestines matted together in areas and laced around tumor mass.
39 0–1, male	do	675	Animal very thin	None	Lungs: Few dark spots. Kidneys: Enlarged dark in color, granular. Spleen: Small in size.
31 1–1, female	do	688	Normal	2 large tumors, 1 on upper, right mammary region. 1 on lower right mammary region.	None.
32 0–2, female	do	689	Normal except for tumor	1 large tumor between legs on ventral surface. Encapsulated, external. Stripped easily from surrounding skin.	Do.
31 1–2, female	do	772	do	3 separate tumors. 1 on right lateral aspect extending from forelimbs to abdominal region. On left side, a similar tumor present but more dorsal in position.	Do.
35 0–2, female	do	772	do	Large tumor on right side which extended from right forelimb to midsection of body. Hard in consistency.	Do.
33 2–0, female	do	773	do	Tumor on ventral surface which extended from below midline of body to the left front limb. Appeared to have some dark necrotic areas.	Gonads: Uterus filled with a thick yellow fluid, both horns enlarged.
33 1–2, female	do	773	do	2 mammary tumors, 1 on left side under forelimb. On section, was lobed, hard and white, 2d tumor on left side beside hind leg. Tissue purplish.	None.
31 0–1, female	do	777	do	None	Lungs: Gray patches on surface. Kidneys: Left kidney mottled.
35 1–2, female	do	780	Very good except for tumor	Small tumor on left ventral side between neck and forelimb.	Gonads: Uterus inflamed.
36 2–1	do	780	Both eyes showed vascularized areas across cornea. Corneal opacity of left eye. Fur over dorsal surface discolored and yellow.	None	Kidneys: Both mottled. White bleb on surface filled with a clear fluid.
WITH 0.1 PERCENT L–GA					
47 1–0, female	Chloroform vapor	281	Emaciated	Tumor from neck to midline on left ventral surface encircling forelimb. When sectioned, a milky-gray fluid escaped.	None.

46	0–3, female	Intraperitoneal injection of nembutal.	696	Animal very thin and paralyzed in both hind legs.	None	Lungs: Mottled, gray spotted areas. Spleen Small.
47	1–1, female	do	696	Pressure sores on both legs, one leg swollen.	External, encapsulated tumor between hind limbs, ventral surface. On section, outer layer of tumor was dark. Part of tumor filled with yellow material resembling pus.	Liver: Granular, orange in color.
42	1–2, male	Decapitated	745	Thin, emaciated	Dorsal surface over left shoulder. On section encapsulated, white and very hard.	Lungs: Mottled. Liver: Whitened areas over surface. Gelatinous material contained within liver tissue. Kidneys: Brown in color and mottled.
46	3–0, female	do	745	Normal except for tumor	Small tumor ventral surface near left forelimb	Lungs: Mottled.
46	1–1, female	do	745	do	Tumor on ventral surface below right hind leg. External to body wall, encapsulated.	Lungs: Mottled. Gonads: Small cyst on left ovary.
50	0–3, female	do	745	do	Large tumor on right ventral surface. On section, tissue spongy in consistency, white and brown in color.	Lungs: Mottled.
49	2–0, female	Ether inhalation	375	Normal	Left anterior ventral surface which interfered with locomotion. Internal tumor in abdominal cavity appears to be uterine.	Lungs: Pale. Liver: Small in size, pale. Kidneys: Both attached to tumor, 1 on ventral aspect of tumor, 1 on dorsal. Both kidneys misshapen at ureters. Spleen: Enlarged, red in color. Gonads: 1 ovary attached to body wall and tumor.
50	0–1	Intraperitoneal injection of nembutal.	548	do	None	Lungs: 2 areas appeared to be cystic. Gonads: Slight inflammation of uterus.
45	1–1, male	Chloroform vapor	640	do	Large tumor on ventral surface between the hindlimbs. On section, tumor was 2 distinct masses but encapsulated together.	Lungs: Mottled.
42	0–1, male	do	640	do	Left ventral surface in hind region	Do.
47	0–2, female	Intraperitoneal injection of nembutal.	645	Eyes enlarged and very pale	Ventral surface on lower right mammary region	None.
46	2–0, female	do	688	No color in left eye, smaller than right eye, congenital condition.	Large external tumor, right ventral surface. 2 small abscesses opened as tumor was excised. Tumor was hard, white in color.	Lungs: Slightly mottled. Spleen: Very small
45	2–0, male	Spontaneous death	719	On center of dorsal surface, a large cavity about ¾ in. × ½ in.	Description under external appearance, may be residue of a tumor.	None.
49	0–3, female	Decapitated	759	Normal except for tumor	Right anterior ventral surface. An area between the right hind leg and midline of the body involving a nipple contained a yellow-white fluid, quite viscous. On section, tumor was hard.	Do.
47	0–1, female	do	759	do	Small tumor on right side anterior to hind leg	Lungs: Mottled and hemorrhagic. Spleen: Enlarged to almost 3 times the norma size. Digestive System: Thickened mesentery. Adhesion of 2 loops of intestine suggestive of old peritonitis.
46	0–2	do	759	Very good except for tumor	Small tumor on ventral surface which involved left nipple near hind leg.	None.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON DIET SUPPLEMENTED WITH 0.1 PERCENT L–MSG—Continued

Identification and sex	Nature of death	Number of test days	External appearance	Tumor	Organs showing gross pathology
45 3–1, male	Decapitated	759	Paralyzed	Small wartlike area on ventral surface	Lungs: Gray mottling over surface. Spongy in consistency. Heart: Acutely distended. Fluid in pleural cavity. Trachea: Small mass attached to trachea. Liver: Mottled. Kidneys: Enlarged, granular, and with white and red spotted areas. Adrenal: Left adrenal greatly enlarged, 3 red lumps on surface.
56, 2–0, male	Spontaneous	30	Normal	None	Lungs: Dark, postmortem changes. Liver: Very dark, postmortem change. Spleen: Very dark, postmortem change. Digestive system: Small reddened area on intestine, appearance of hemorrhage.
51, 0–3, female	Chloroform vapor	347	Normal	Left ventral mammary region	None.
51, 0–3, female	do	347	Normal	Left ventral mammary region near hind limb	None.
57, 3–0, male	do	632	Very thin, blood-tinged discharge from nose.	None	Heart: Enlarged. Gonads: Right testes enlarged. Capsule thin and transparent showing tubules to be encased in watery fluid. Bladder: Very distended containing a dark concentrated urine.
51 0–1, female	Intraperitoneal injection of nembutal.	696	Normal except for tumor	Large tumor on left ventral surface, mammary region	Lungs: Very pale, numerou gray areas over surface. Abscess on one lobe.
51 1–1, female	Decapitated	746	do	2 large tumors on ventral surface. 1 on neck between forelimbs, 1 on left side under forelimb.	Lungs: Mottled.
51 2–0, female	do	746	do	Large tumor over right ventral surface. Ulcerated pressure sore on tumor.	Lungs: Hemorrhagic.
55 3–0, female	do	746	do	Tumor on left ventral side. On section, tissue was yellow, contained some blood.	Do.
57 0–1, male	do	746	do	Under right forelimb, lateral and external to body wall	Lungs: Mottled. Liver: One lobe greatly enlarged. A second lobe showed hemorrhagic areas. Spleen: Granular. Kidneys: Both kidneys enlarged; brown in color and granular. Gonads: One lobe of tissue near penis (preputial gland) was discolored and one lobe filled with a dark fluid.
59 3–0, male	do	746	Animal had difficulty in moving hind legs. Of good size but very thin; hair was discolored.	None	None.
54 2–0, female	do	746	Normal except for pressure sores on hind feet.	do	Lungs: Dark pinpoint areas on surface.

52	0–3, female	do	750	Normal except for tumor	2 tumors on right ventral surface anterior to forelimbs. Larger tumor firm but not hard in consistency. Smaller tumor soft.	None.
52	3–0, female	do	750	do	Left ventral surface near forelimb	Lungs: Hermorrhagic. Kidneys: 1 kidney very small.
53	1–2, female	do	750	do	Left mammary tumor proximal to hind limb	None.
54	1–1, female	do	750	do	Small tumor on left side, lateral aspect, under forelimb. Tumor soft to touch but on section was hard and coarse. White in color.	Lungs: Gray in color with mottled areas over surface. Gonads: 1 section of uterus had a small bleb on surface.
52	2–0, female	do	752	Normal	None	Gonads: 1 horn of uterus enlarged and kinked. A very firm blood clot contained within the enlarged horn.
55	2–0, female	do	752	do	do	Liver: Whitened area on liver surface.
58	0–3, male	Intraperitoneal injection of nembutal.	794	do	Swellings on both sides of the neck. On section, involved the thyroid gland. Consistency soft.	None.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON CONTROL DIET, NO SUPPLEMENT

64	3–0, female	Chloroform vapor	274	Animal bloated in abdominal region. Probably post-mortem change.	Large internal tumor in abdominal cavity, adjacent to liver. Possible uterine tumor because of position and attachment of fallopian tubes to the tumor mass. On section composed of spongy tissue.	Lungs: Reduced in size. Liver: Reduced in size. Kidneys: Reduced in size. Spleen: Imbedded in a reddish mass of tissue attached to tumor. Digestive system: Stomach reduced in size. Intestines enmeshed in tissue growth attached to tumor. Gonads: Tumor mass appeared to be uterus with fallopian tubes attached to external surface.
65	0–1 female	Unknown cause	273	Normal other than tumor. Organs not examined since decomposition had progressed too far.	Left ventral surface from forelimb to middle of body. Approximately 2 inches horizontally, 6 inches length. Encapsulated, external to body cavity and very hard. Almost 10 cc. of orange fluid poured out of orifice in center of tumor.	Lungs: Pale. Liver: Pale. Spleen: Very enlarged, spongy and rubbery in consistency.
80	0–1, female	do	731	Animal was bloated in abdominal region.	None, bloated appearance was from a large amount of blood stained fluid which was released on section. Stringy gelatinous material in abdominal cavity.	None.
75	3–0, male	Decapitated	738	Normal	None	Liver: Yellow mottled areas. Kidneys: Right kidney appeared enlarged. Cyst on surface of kidney contained light amber fluid. Gonads: Seminal vesicles shrunken.
66	2–0, female	Air injection into heart	738	Normal	do	Lungs: Pale areas over surface.
61	1–0, female	Intraperitoneal injection of nembutal.	548	do	Mass on right axillary region firmly adherent to skin but loosely attached to ribs. Very fibrous and convoluted on section.	Gonads: Uterus inflamed.
69	3–0, female	Chloroform vapor	640	do	Left ventral surface mammary region, external to body wall.	Lungs: Gray in color and mottled.
68	3–0, female	Intraperitoneal injection of nembutal.	688	do	2 external tumors on left ventral surface. Large tumor located in lower mammary region. Smaller tumor near chest area. Very tough in consistency.	Lungs: Mottled. Scattered, dark pinpoint spots on peripheral surface. Spleen: Small.

GROSS PATHOLOGICAL FINDINGS IN RATS FED ON CONTROL DIET, NO SUPPLEMENT—Continued

Identification and sex	Nature of death	Number of test days	External appearance	Tumor	Organs showing gross pathology
80 1–1, female	Intraperitoneal injection of nembutal.	688	Normal	2 external tumors on lower ventral mammary region. Larger on left side, smaller on right. Both tumors lobed.	Lungs: Very pale in color. Gray-white spots on surface.
80 0–3, female	do	688	do	4 external tumors on ventral surface, involving both upper and lower mammary regions bilaterally.	Liver: Granular and friable.
79 3–0, female	Decapitated	757	Normal except for tumor	Three small tumors; 1 on side of head from ear to forelimb on right side. 1 on right side from forelimb to midline on chest. 3 tumor, smallest, posterior to the 2d.	None.
73 0–3, male	Decapitated. Blood was very thick.	759	Fur yellow in color. Ventral surface discolored.	The peritoneal and pleural cavities were filled with a foul fluid, apparently a tumor residue.	Digestive System: Bloody fluid in intestines.
76 1–0, male	Decapitated	759	Good except for discoration of for over dorsal surface.	None	Lungs: A few gray, pinpoint areas scattered over surface. Kidneys: Enlarged, pale, and granular.
79 1–0, female	Intraperitoneal injection of nembutal.	773	Animal anemic, eyes had no color.	Small tumor on side of vagina, external to body wall. Internal uterine tumor.	Liver: Mottled and granular A small pale cyst on one lobe. Spleen: Very large and irregular in shape.
79 1–1, female	do	773	Animal was extremely large and in good condition.	Large mass in abdominal cavity encased in fat above, but not attached to left ovary. One part of mass was filled with clear fluid, another part contained blood-tinged fluid.	None.
80 2–0, female	do	774	Animal was anemic, very little color in eyes.	None	Digestive System: 2 yellow lumps on intestines about the size of peas.

80 0–2, female	do	774	Normal	do	Lungs: Mottled, 1 lobe attached to dorsa wall of pleural cavity. Gonads: Uterus hemorrhagic. A solid material was enclosed in enlarged area of left uterine horn.
75 1–1, male	Decapitated	738	do	do	Lungs: Mottled. Kidneys: Enlarged, gray-brown color.
75 0–3, male	do	738	do	do	Gonads: Preputial glands contained fluid.
61 0–1, female	do	745	do	Left ventral surface mammary region posterior to hind leg.	None.
61 1–1, female	do	745	do	Ventral mammary region posterior to right leg. External and encapsulated. On section, white and red areas of hard consistency. 1 part of tumor contained a pasty, yellow material.	Lungs: Hemorrhagic areas. Kidneys: White nodule on right.
63 0–1, female	do	745	do	Small mammary tumor under right forelimb. On section, soft and lobate.	Lungs: Hemorrhagic areas. Liver: White area on one lobe.
65 0–2, female	do	745	do	Large mammary tumor posterior right hindleg, external to body wall, encapsulated. On section, hard in consistency, lobed, white and deep red in color.	Lungs: Mottled.
64 1–1, female	do	752	Normal except for tumor	Small mammary tumor posterior to right forelimb. On section, soft and cheesy.	Lungs: Hemorrhagic. Gonads: One horn of uterus enlarged and cystic; contained a pink-tinged fluid.
64 0–3, female	do	752	do	3 small tumors, 2 on lower mammary region beside the hind legs, 1 on the mammary region anterior to right hind legs.	Lungs: Hemorrhagic. Liver: Raised area on one lobe of liver.
78 3–0, male	do	752	Normal	Small wart-like tumor on dorsal surface under skin. On section, filled with granular material. Small mass at neck may be an enlarged thyroid. A fatty, gelatinuous mass of tissue also present.	Lungs: Mottled.
70 0–3, female	do	752	do	Large external tumor on left mammary region between hind legs. On section, tussue deep purple in center. There was a white milky secretion from part of tumor.	Lungs: Hemorrhagic.

Section 2.—Description of Microscopic Pathology

The following tables indicate the types of lesions found by microscopic examination of tissues obtained at autopsy. The numerals preceding an entry indicate the number of elapsed test days at time of death. This data represents abnormal sections from 520 animals who were subjected to post-mortem examination, either partial or complete. Approximately 1400 microscopic sections were prepared but only those showing pathology are described here.

When numbers followed by a dash and a subsequent number (1—4) occur, they refer to the descriptions immediately preceding. The first number indicates the number of elapsed test days at time of death and the second number to the severity of the abnormality, which for that section is identical in type with the last previous description. For example, 543—4 can be interpreted thus: an animal sacrificed or dying after 543 elapsed test days shows in the organ in question, the same abnormality as in the last previous description. The intensity, or degree of involvement is 4 (severe) on the following scale:

Graduation of microscopic lesions

0 essentially negative, no pathology
1 trace
2 apparent
3 obvious
4 severe

0.1 PER CENT L-MONOSODIUM GLUTAMATE GROUP

Liver

63-Parenchyma rarely binucleate or hyperchromatic.
773-Pinpoints of inflammation around central veins.

Kidney

63-Foci of concretions in tubules in pelvis. Mild congestion of blood vessels in cortex.
347-Foci showing mild chronic nephritis.
548-Foci of inflammation around blood vessels in cortex. In rare foci this is expressed as dilated tubules containing concretions. Mild chronic interstitial nephritis.
548-As above, slightly increased.
548-One small focus of necrotic tubules. Thickened connective tissue around small blood vessels.
632-Mild chronic interstitial nephritis as shown by fibrosis, dilated tubules and pinpoint hemorrhages
641-Mild chronic interstitial nephritis in cortex as shown by foci of dilated tubules containing concretions. Thickened blood vessel walls.
641-3
650-2
716-4
772-1
773-2
773-4

Lungs

63-Foci of alveolar fibrosis.
63-As above.
63-Slight focal fibrosis. In one focus, lymphocytic nodular area has penetrated wall of bronchus.
347-Extensive foci of hemmorrhage. Dilated cystic areas. Thickened walls around terminal bronchioles. Probable abscess. (2 rats)
650-3
716-1
772-2
772-1
773-1 (2 rats)
548-Foci of fibrosis. Foci of inflammation around bronchioles.
548-Extensive areas of collapsed alveoli. Dilated blood vessels. Pinpoints of inflammation around bronchioles. Some Fibrosis. (2 rats)
641-Focal fibrosis and inflammation.
666-Edema in foci. Some fibrosis. Foci of inflammation around bronchioles.
772-Focal fibrosis, inflammation and edema. Hyperplasia of epithelium and bronchioles.
773-Foci of fibrosis. Foci of inflammation around bronchioles.

Intestines

666-Some necrosis of connective tissue in villi. Excessive number of plasma cells between villi. Suggests mild irritation in lamina propria and foci of traumatization in epithelium.
772-Focal abscesses. Lymphatic nodules perforate epithelium.
773-Colitis with polyposis.

Ovary

772-Several corpora lutea. No obvious primary follicles. Suggests senile type.

Lymph Node

632-Enlarged

Spleen

63-Trace of congestion. Slight increase in amount of white pulp.
63-Slight disorganization of pulp. Trace of congestion.
347-Disorganized senile spleen.
548-Uniformly disorganized. No sharp demarcation between red and white pulp. Mild congestion
548-As above.
632-Disorganized senile spleen.
650-Congested.
666-Uniformly disorganized. No sharp demarcation between red and white pulp. Mild congestion.
772-Congested.
772-Uniformly disorganized. No sharp demarcation between red and white pulp. Mild congestion.
773-Mildly congested, senile.

Aorta

773-Sclerotic.

0.4 PER CENT L-MONOSODIUM GLUTAMATE GROUP

Lung

63-Focal fibrosis in lung parenchyma. Foci of lymphocytic infiltrations around bronchi and bronchibles. In one area, the inflammation has penetrated a bronchus. (3 rats)
347-Focal fibrosis. Pinpoints of inflammatory areas around bronchioles. (2 rats)
374-Focal fibrosis and edema.
667-Extensive foci of fibrosis.
750-Focal fibrosis and edema, plus marked congestion.
750-Marked congestion. Bronchioles full of exudate.
773-Lobe showing marked leucocytic infiltration. Pneumonitis, possibly lobar pneumonia, acute stage.
641-1
757-3

Kidney

63-Small, infrequent foci of congestion. Rare dilated tubules with concretions. (2 rats)
63-Rare foci of fibrosis in medullary area.
750-Foci of cortical interstitial interstitial inflammation extending to tubular and glomerular fibrosis.
750-Extensive foci of marked nephri tis. Suggestion of small kidney stone.
750-Foci of degeneration of proximal convoluted tubules.
750-Cortex negative. Some necrosis in renal tubules.
641-4
667-4
757-3

Liver

757-Mild pinpoint areas of inflammation, dilated blood vessels. Pinpoints of hemorrhage. Disorganization of parenchyma indicative of mild chronic irritation.
757-2
757-1

Colon

63-Foci of erosion of epithelium with well-developed fibrosis. No active ulceration.

757-Erosion of mucous epithelium with extensive polyp formation to extent where it obstructs the lumen.

Spleen

347-Somewhat disorganized red and white pulp. Characteristic of normal senile spleen. (7 rats, 374-750 test days)

Testes

773-Practically depopulated of germ cells. Sterile.

Intestine

750-Marked necrosis of epithelial lining. Lymphocytic nodules extensive. Lumen full of amorphous masses suggesting obstruction.

750-Foci of partial obstruction in small intestine caused by excessive folds. (2 rats)

Trachea

750-Epithelial lining of trachea disorganized. Possibly an artefact.

0.1 PER CENT DL-MONOSODIUM GLUTAMATE GROUP

Liver

610-Parenchyma normal. One pinpoint focus of hemorrhage.

777-Portal cirrhosis.

779-Beginning hepatic necrosis on one lobule. Chronic suppurative hepatitis.

Kidney

548-Foci showing evidence of mild chronic interstitial nephritis, expressed by appearance of concretions in tubules or cortex.

548-Mostly normal. Rare pinpoint foci showing tubules with concretions.

610-Foci of mild chronic interstitial nephritis expressed by inflammation, tubular dilation and lumen concretions.

558-2
779-4
779-4

777-Mostly normal. Rare pinpoint foci showing tubules with concretions.

548-1

Lungs

548-Foci of fibrosis. No edema or congestion. No evidence of inflammation.

548-Extensive fibrosis in parenchyma. Thickened connective tissue around bronchi and bronchioles. Blood vessels dilated. An extensive area of lymphocytic nodule penetrating epithelial lining. Fibrotic type lung with bronchiolar irritation.

558-Some exudate in alveolar sacs. Otherwise normal.

610-Foci of fibrosis. Foci of hemorrhage. Thickened bronchiole walls.

610-Focal fibrosis and areas of inflammation around bronchioles.

772-Foci of edema with exudate in sacs. Frequent foci of fibrosis. Some lymphocytic accumulation around bronchi and bronchioles.

772-Some dilated alveolar sacs. Several areas of fibrosis. One point of hemorrhage. Small edematous areas show exudate. Lymphocytic accumulation around bronchi.

777-Foci of fibrosis.

Spleen

548-Disorganized white pulp. Mild congestion.
548-Generally disorganized spleen. Marked congestion. White pulp limited
772-Generally disorganized spleen. Marked congestion. White pulp limited. (2 rats)
777-Senile.
777-Congested.
779-Senile, congested.
779-Senile, congested.

Trachea

777-Markedly dilated ducts in epithelial lining.

Ovary

772-Mostly depopulated of follicles as in senile type.

Intestine

779-Chronic enteritis. General loss of villi and eroded mucous epithelium. No evidence of malignancy.

Esophagus

779-Glandular proliferation in lower part of esophagus. Cell perforation without malignancy.

0.4 PER CENT DL-MONOSODIUM GLUTAMATE GROUP

Liver

779-Hypertrophy of the epithelium of the gall bladder to form interlocking meshworks in dilated cavities. No evidence of calculi. Hypertrophic.
548-1
610-1
777-1

Kidney

772-Foci of cloudy swelling in cortical epithelium. Marked dilation of tubules in renal section and some fatty degeneration of parenchyma.
772-One pinpoint focus of dilated tubules and thickened blood vessels.
548-4
675-4
772-Focus of hemorrhage in cortex. Thickened blood vessel walls. Pinpoint areas of inflammation. Foci in pelvis show dilated tubules with hyalin deposits. Mild chronic nephritis.
548-2
610-4
675-3
710-3
777-2
777-3
779-4
778-Small lymph nodule on wall of cortex. Pinpoint areas of accumulation of lymphocytes around renal arteries. Rare tubules with concretions. Renal pelvis normal. Cortical infection.

Lungs

63-Infrequent small foci of fibrosis.
772-1 plus a focus of edema.
778-1
610-Abscess of bronchus.
620-Marked fibrosis. Thickened bronchiolar walls.
620-Focal hemorrhage. Foci with edema.
548-1
548-2
710-2
777-2
777-3.5
779-Frequent foci of fibrosis. Lymphocytic accumulation around bronchi, in one area penetrating epithelial lining.

Spleen	Intestines	Trachea
548-Senile and congested.	772-Extensive papillary type folding in epithelium extending into lumen indicating partial obstruction. Non-malignant.	772-One focus of cartilaginous breakdown
548-Mildly congested.		772-Inner lining disorganized. This could be fixation. (2 rats)
675-Mildly congested.		
688-Senile.		
710-Congested and senile.		
772-Senile. (3 rats)		
779-Red and white pulp disorganized. Mild congestion. Minimal white pulp. Suggests senile type.		

0.1 PER CENT L-GLUTAMIC ACID GROUP

Kidney

548-Glomeruli, tubules and blood vessels mostly normal. Renal pelvis normal. One small focus indicated infection by presence of tubular concretions.

558-Mild, chronic, interstitial nephritis evidenced by foci of dilated tubules with concretions, thickened walls of blood vessels and lymphocytic inflammatory areas.

746-Concretions in renal pelvis. Cortex normal.

746-2
759-3
759-4

759-Numerous areas or foci showing infection as seen by tubules with concretion and lymphocytic masses around blood vessels.

Lungs

558-Extensive fibrosis. Foci of edema. Pinpoints of inflammatory areas around terminal bronchioles.

688-1
745-2
746-1
759-1
759-2
759-2.5
759-3

746-Frequent foci of fibrosis. General edema. Mild congestion. Exudate in some alveolar sacs. Dilated blood vessels.

759-Numerous foci of fibrosis some lymphocytic accumulations around bronchi extending into bronchioles.

Spleen

548-Mostly white pulp not organized in discrete masses. Mild congestion.

688-Senile.

745-Senile, congested.

746-Mostly white pulp not organized in discrete masses. Mild congestion.

746-Senile, markedly congested.

759-Senile.

759-Senile, congested. (2 rats)

Intestine	Testis	Adrenal
746-Lymphocytic nodular masses in propria which extend into lumen in foci. Generally eroded epithelial lining.	759-Sparse germ cells. Senile gland	759-Markedly congested medullary area; larger than normal cortex of organ.
746-Generally eroded epithelium.		
746-Markedly eroded epithelium.		
746-Colon-eroded epithelium with abscess.		
759-Lymphocytic nodular masses in propria which extend into lumen in foci. Generally eroded epithelial lining.		
759-Surface epithelium mostly necrotic. Massive collections of lymphocytes.		
759-Intestinal abscess.		
759-Excessive growth of villi, obstructing lumen.		

0.4 PER CENT L-GLUTAMIC ACID GROUP

Liver

752-One focus showing several necrotized tubules.
752-1
746-Interlobular hepatic necrosis. General degeneration of parenchyma.

Skin

746-Keratin cyst, non-malignant.

Kidney

752-Nephritis, slight, chronic.
548-1
746-3
746-3
746-3
746-4
750-3
750-3
752-1

Lungs

63-No fibrosis. No congestion or edema. No evidence of inflammatory areas. Normal.
696-Foci of fibrosis. Terminal bronchiole walls thickened. Normal, senile type lung.
696-Extensive foci of hemorrhage. Dilated cystic areas. Lymph nodule in area surrounding bronchioles. Thickened bronchiolar walls. Focal, abscess.
548-1 (2 rats)
548-1
746-1 (2 rats)
746-2 (2 rats)
750-1
750-2
750-3
752-1
752-1

Spleen

63-White and red pulp discrete. No congestion. Connective tissue normal. No obvious pathology.
63-Mild congestion. Slight disorganization of white pulp.
548-Senile, congested. (2 rats)
696-Senile. (2 rats)
746-Senile and congested. (2 rats)
746-Senile, congested (2 rats).
750-Senile, congested.
752-Senile.
752-Senile, congested.

Intestine

746-General eroded epithelium-colitis.

Colon

746-Marked eroded epithelium with abscess.
746-Marked erosion of mucous epithelium. Fibrosis of villi forming polyposis appears to be partially obstructing lumen. Another area shows actual obstruction.
746-Pinpoint sterile abscess.
750-Colon. Reduced glands indicating chronic inflammatory polyposis regressing in some glands with accompanying fibrosis.
752-Chronic colitis with polyposis.

Genital Gland

632-Testis senile.

Trachea	Spleen	Intestine
778-Foci of erosion of epithelium.	548-Mild congestion. (2 rats) 745-Senile, congested. 759-Senile, mild congestion. 778-Mild congestion.	745-Corroded epithelium with residual substance in lumen. 745-Colon abscess. 745-Eroded epithelium. 752-Intestinal sarcoma, benign. Colon abscess.

CONTROL GROUP

Liver	Kidney	Lungs
752-One focus of hepatitis -- mixed.	63-Foci of congestion in blood vessels in cortex. Occasional atrophied glomerulus. Some tubules contain concretions. Medullary section normal.	63-Foci of alveolar fibrosis. Pinpoint accumulation of lymphocytes around bronchioles. No obvious edema or congestion in lung parenchyma.
	63-Foci where concretions appear in tubules in cortex. Some congestion in blood vessels. Glomeruli not affected.	63-Extensive areas of fibrosis.
	548-2	63-Pinpoint accumulation of lymphocytes around bronchioles.
	548-3	63-Focal fibrosis. Pinpoint areas of inflammation around bronchioles and bronchi penetrating wall bronchus in one area. (2 rats)
	548-2	548-1 (2 rats)
	745-Large area of degeneration.	745-1
	745-1	745-2
	745-2	745-2
	759-2	752-1
	779-2	752-2
		759-1
		778-1

Section 3.—Description of Tumors

DESCRIPTION OF TUMORS IN RATS FED ON DIET SUPPLEMENTED WITH 0.1 PERCENT L-MSG

Sex	Tumor location	Description	Attachment and vascular supply	Consistency	Appearance on section
M	Right gluteal region, ventral surface	External to body wall, encapsulated	No attachment	Firm	Vascular, fibrous.
F	Posterior to left forelimb, ventral surface	External, encapsulated. Tumor surface ulcerated.	do	do	Fibrous.
F	Ventral surface, involving right pectoral mammary region and right forelimb.	External, encapsulated. Measures 2¾ by 3 in.	On ventral aspect of body wall apparently by a strip of muscle. Blood vessel from pectoral mammary region terminates in tumor.	do	Fibrous and white. Free blood escaped from supplying blood vessel.
F	Ventral surface involving left forelimb and mammary region.	External to body wall, encapsulated, small in size.	None apparent	do	Fibrous and white.
F	Abdominal area much enlarged	Internal tumor mass. Abdominal cavity filled with gelatinous fluid within which was a large round mass, probably the uterus. Attached to the tumor mass was a structure resembling Fallopian tube.	do	do	Gelatinous material covered tumor mass. Tumor tissue was firm but not fibrous.
M	Large tumor mass abdominal region	Internal, not encapsulated, tumor mass in abdominal cavity.	Mesentery attached to tumor. 1 lobe of intestine attached to mesentery.	Soft	Internal part of tumor tissue was light brown, outer part white.
F	Very large tumor on ventral surface near right inguinal mammary region.	External to body wall and encapsulated. Right leg and genito-urinary organs surrounded by tumor.	Appeared to be attached to muscle sheath near leg.	Firm	Hard and fibrous; many lobes.
F	2 tumors; 1 on left ventral surface which included area of 1st pectoral mammary gland to chin. 2d tumor between hind legs involving genitals.	External to body wall, encapsulated	No attachment	1 tumor firm, 1 soft	Tumor in anterior position was hard, lobed and white. Tumor between legs in genital region was soft, lobed, and grayish in color.
F	Ventral surface median to right leg	do	None apparent	Firm	Hard with light and dark areas.
F	2 tumors on ventral surface extending to dorsal surface; 1 over forelimb and 1 over hind leg.	do	do	do	
M	Dorsal surface at base of spine	do	do	do	Very hard to cut; tissue had yellow and white areas.
F	Ventral surface from chin and pectoral mammary region to abdominal region.	External to body wall, encapsulated. Trilobed.	Supplied by a vessel leading from the axillary region.	do	Tissue was convoluted and composed of white and yellow areas.
F	3 small tumors on ventral surface. 1 was beginning under the right leg. 1 on right side of chest region. 1 forming under left forelimb.	External to body wall, encapsuated	Tumor on chest supplied by a large blood vessel.	do	2 young tumors were homogeneous. Larger tumor located on chest was tough, convoluted, and composed of yellowish, whitened tissue.
F	2 tumors on left ventral surface; 1 under forelimb and 1 beside it. Third tumor under right forelimb.	do	None apparent		
F	Left ventral surface, inguinal region	do	do	Firm and soft areas	

WITH 0.4 PERCENT L-MSG

Sex	Tumor location	Description	Attachment and vascular supply	Consistency	Appearance on section
F	Right ventral surface from submaxillary region to midportion of body.	External, encapsulated, bilobed		Firm	Lobulated, vascular.
F	Right ventral surface, mammary region from chest to midsection of body.	External, encapsulated, measured 2 by 3 ins.	2 large blood vessels from chest to tumor	do	Tough and fibrous.
F	Ventral surface from arm to abdominal region.	External to body wall encapsulated. Scabbed on external surface from pressure.	Tumor supplied by large vessel	do	Thin, watery, blood-tinged liquid escaped from tumor. Gristly, tough and fibrous
F	Two tumors, larger on upper left mammary region, ventral surface. Small tumor on ventral surface, right abdominal mammary region	External to body wall, encapsulated	Attached to underlying tissue near mammae. Large tumor supplied by subclavian artery, small tumor by femoral artery.	do	Tough and fibrous.
F	Large tumor on left ventral surface in pectoral mammary region. Smaller tumor on left inguinal mammary region.	do	Large tumor supplied by bloodel vessel from axillary region.	do	Do.
M	Involved neck and submaxillary region on either side of head and extended to forelimbs on ventral surface.	External to body wall, did not appear to be encapsulated.	None apparent	Soft	Jelly like consistency; a large amount of amber fluid escaped deflating tumor mass.
F	Right ventral surface between axillary and inguinal region.	External to body wall, encapsulated	Easily separated from surrounding tissue	Firm	Areas of whitened tissue and areas containing free blood.
F	Right ventral surface in pectoral mammary region near axilla.	do	do	do	Areas of tan and red color.
M	Dorsal surface in mid-line	External to body wall, small in size	No apparent attachment or supplying blood vessel.	do	Tumor mass appeared to be cavities with in the skin, filled with granular material and containing material resembling pus.
F	3 tumors on ventral surface. 2 in inguinal mammary region, 1 on each side. Third tumor in right pectoral mammary region.	External to body wall, encapsulated. Inguinal tumors show ulceration from pressure sores.	Tumors separated easily from surrounding tissue.	do	1 tumor contained a small amount of material resembling pus. Tissue of tumors varied from whitened to dark areas.
FF	Midline of right ventral surface from inguinal region to costal margin.	External to body wall, encapsulated	Large vessel from groin supplying tumor	Firm	1 part of tumor was filled with a white, milky material. Other areas were fibrous.
F	Ventral surface between hind legs extending toward left side and involving anus and genital region.	do	Attached to intestine in region of rectum	Soft	1 lob was yellow and filled with a viscous material. 2d lobe was fibrous but not hollow.
M	Ventral surface, left lateral aspect	External to body wall, not encapsulated	None apparent	do	Filled with gellow, granular material which was pasty in consistency.
F	Left ventral surface, inguinal mammary region.	External to body wall	Tumor easily separated from surrounding tissue.	do	Soft.
F	Internal mass palpable from ventral surface anterior to and including genital region.	Internal tumor mass, elongated in shape. 1 horn of uterus involved.	Small lumps of tissue attached to elongated mass.	do	Center of tumor mass filled with a thick, yellow-gray material. Outer portion of tissue was gray and soft like cotton.

WITH 0.1 PERCENT DL-MSG

M	Right side ½ inch below axillary region on ventral surface.	Small hardened mass in skin	None apparent		
M	Ventral surface from right forelimb to lower abdominal region.	Tumor mass was very large, external to body wall and encapsulated.	Attached to forelimb at muscular sheath. Blood vessels running through this sheath into tumor mass.	Soft	Appearance of connective tissue; soft in texture.
F	Over entire ventral surface from neck to abdominal region involving mammary glands.	Very large, external to body wall; encapsulated. 1 mammal very prominent.	Attached to the skin of the forelimb by tissue strands. Tumor supplied by blood vessels from axillary region of both limbs.	Firm	Tough, fibrous, whitened tissue composed of many large lobes in which the tissue was convoluted.
F	From neck to below midbody covering the entire ventral surface.	Very large. External to body wall, encapsulated. Pressure sore on tumor.	Attached by tissue strands to both forelimbs.	do	Lobed, hard to cut; areas of light and dark color.
F	3 tumors on right ventral surface each involving a nipple.	External to body wall, encapsulated	None apparent		
M	Right side extending over ventral and dorsal surface in inguinal region.	do	No attachements apparent. Supplied by a large blood vessel leading from peritoneal cavity.	do	Hard and whitened.
F	Large tumor on ventral surface from abdominal region down to the left leg and extending to midline. Small tumor under left forelimb.	do	Large tumor was supplied by a blood vessel leading from the groin.	Firm	Large tumor was lobed with some darkened areas. Small tumor was hard and composed of knotty, white tissue.
F	2 developing tumors on ventral surface; 1 in genital region, 1 in region of groin on right.	do	No attachment apparent	1 firm and 1 soft tumor.	Tumor of hard consistency was white and fibrous. Tumor of soft consistency, yellow in color.
M	Lump below chin on ventral surface of neck.	External to body wall	Mass appears to be attached to the thyroid.	Soft	Blood-tinged fluid escaped. Tissue was soft and gelatinous; some areas contained clotted blood.
F	Ventral surface from neck to abdominal region.	External to body wall, encapsulated	Attached in thoracic region	Firm	Tough and fibrous; tissue convoluted.
F	Left ventral surface in inguinal mammary region.	do	Easily separated from surrounding tissue	do	Tough and fibrous.

WITH 0.4 PERCENT DL-MSG

M	Left side of face above the eye. Eye was distorted and enlarged.	Mass was large, about the size of a walnut, scabbed surface.	None apparent	Soft	Yellow pasty material, resembling pus filled tumor.
M	Abdominal cavity	Internal mass composed of many small lobes.	Attached to intestine	do	Soft.
F	2 tumors on right ventral surface in pectoral and inguinal mammary regions.	External to body wall, encapsulated	Larger tumor in pectoral mammary region supplied by a blood vessel from axillary region. Smaller tumor supplied from vessel coming from groin, possibly the femoral artery.	Firm	Large tumor, tough, white, and fibrous. Smaller tumor was convoluted, varying in color. Areas of white, orange, and red-brown tissue.

Sex	Tumor location	Description	Attachment and vascular supply	Consistency	Appearance on section
F	Large tumor on ventral surface in midline (posterior).	External to body wall, encapsulated	Separated easily from surrounding tissue		Tough and fibrous, 1 portion very dark in color.
F	3 separate locations. 1 tumor on right side extending from axillary to abdominal region. 2d tumor similar in position on left side. 3d tumor anterior to 2d.	External to body wall, encapsulated. 2d tumor ulcerated from pressure sores.	Tumor on right side attached in axillary region. Supplied by large blood vessel from axilla; other 2 tumors with no apparent attachment.	2 large tumors, firm; small tumor soft.	Larger tumors were lobed, hard, and white. Small tumor was soft and yellow-orange.
F	Right ventral surface from pectoral to abdominal mammary region.	External to body wall, encapsulated and lobed.	None apparent	Firm	Anterior tumor was hard and white; posterior tumor purple in color.
F	Left ventral surface between neck and midthorax.	Small in size, encapsulated. External to body wall.	No attachment apparent	do	
F	Left ventral surface from neck to middle of body.	Tumor ulcerated with external opening. Filled with material resembling pus. External to body wall and encapsulated.	Base of skull at level of ear	Spongy on section. Outer portions tough and fibrous.	Milky-gray fluid escaped.
F	Swelling on left ventral surface from abdominal region to hind limb.	Internal tumor mass encased in a thin membrane and occupying most of the lower abdominal area. Left leg limp and useless.	Large branched vessel from liver into a lobed part of the tumor. Attached to dorsal body wall; 1 kidney and 1 ovary attached to tumor.	Soft	Both free and clotted blood escaped. Tumor was composed of tissue white strings.
M	Dorsal surface in caudal portion of body involving hind limbs.	Tumor was bilobed, external to body wall and encapsulated.	Attachment at base of spine; vascular supply not apparent.	Firm	Tissue was white and fibrous.
M	Left dorsal surface near hind leg	External to body wall, encapsulated	Attachment at base of spine	do	Fibrous.
F	Right ventral surface in pectoral mammary region.	do	Supplied by blood vessel in groin	do	Fibrous and tough.
M	Left dorsal surface in region of ribs	A large cavity, 3¾ by ⅓ in. deep in which there was a wart-like growth.	None apparent	Rough, horny	
F	Tumor on dorsal surface in gluteal region	External to body wall, encapsulated. Darkly colored surface.	Lying freely within skin	Firm	Tissue was red-brown in color. Inside of tumor was filled with yellow, thick material resembling pus.
M	Large tumor on left dorsal area involving scapula.	External to body wall, encapsulated	Lying freely within surrounding tissue	do	Very hard and white.
F	Left ventral surface involving pectoral mammary region.	External to body wall, encapsulated, small in size.	Easily separated from surrounding tissue	do	
F	Right ventral surface, involving inguinal mammary region.	External to body wall, encapsulated	do	do	Tissue composed of many convolutions darker in some areas, fibrous.
F	Right ventral surface, involving inguinal mammary region.	do	do	do	Brownish, white tissue; interior was quite spongy.
F	Right ventral surface from axillary to abdominal region involving nipples.	External to body wall, encapsulated, small in size.	Tumor easily separated from surrounding tissue.	do	Tissue convoluted; very hard to cut.
F	Right ventral surface involved inguinal mammary region.	do	Easily separated from surrounding tissue	Soft	Tumor was small, homogeneous in appearance.

F	Series of lumps on left dorsolateral surface.	External to body wall, 1 lump with a warty surface.	None apparent	Most lumps soft in texture. Lump under forelimb firm.	Lumps were filled with a granular material and thick paste resembling pus. Lump under forelimb was very hard and white.
F	Left ventral surface in inguinal mammary region involving mammae.	External to body wall, encapsulated. Small in size.	do	Soft	Homogeneous.

WITH 0.4 PERCENT L-GA

F	Left ventral surface in pectoral mammary region.	External, encapsulated, 2 x 2 ins	1 large and 1 small vessel from axillary region.	Firm	Tough and fibrous; white in color.
F	Left ventral surface in inguinal mammary region.	External to body wall, encapsulated		do	Gristly and fibrous; 1 portion deep brown in color.
F	Right ventral surface in inguinal mammary region.	do	Appeared to be attached to tissue around mammae.	do	Tough and fibrous.
F	Left ventral surface in pectoral mammary region.	do	Blood vessel from axillary region	do	Do.
F	2 large tumors on ventral surface. 1 involved right pectoral mammary region, second involved left pectoral mammary region near axilla.	do	Easily separated from surrounding tissue	do	Fibrous.
F	Right ventral surface, covering entire side.	External to body wall encapsulated, large in size. Pressure sore on tumor surface.	do	do	Hard to cut; fibrous.
F	Left ventral surface covering region of the 3 pectoral mammae.	External to body wall, encapsulated. Medium size, multiple lobes.	do	do	Free blood escaped from supplying vessels. White fibrous areas and yellow areas seen.
M	Right lateral surface extending from axillary region to costal margin.	External to body wall, encapsulated	do	Firm	Very hard.
F	2 tumors on right ventral surface in pectoral mammary region.	do	do	Soft	Both tumors soft; dark and light areas throughout the tumor tissue.
F	Left ventral surface in pectoral mammary region.	do	do	Firm	Fibrous.
F	Left ventral surface in lower inguinal region.	do	do	do	Do.
F	Left lateral aspect from axillary to abdominal region.	do	do	Soft	Hard and coarse on section.
F	Encircling neck on ventral surface	External to body wall and involving submaxillary.	No attachment apparent	do	Spongy (measured 2 ins. by 2 ins. by 2½ ins.).

DESCRIPTION OF TUMORS IN RATS FED ON CONTROL OR UNSUPPLEMENTED DIET

Sex	Tumor location	Description	Attachment and vascular supply	Consistency	Appearance on section
F	Large round mass in center of peritoneal cavity.	Tumor was internal. A round mass in the peritoneal cavity. Attached to the firm ball of tissue was a soft red mass like clotted blood.	Fallopian tubes were attached to tumor mass. Abnormal tissue growth around tumor in which spleen and kidneys were enmeshed.	Firm	Spongy, darkly colored tissue on inside. Outer edges of tissue gray and tough.
F	Left ventral surface from axilla to middle of body.	External to body cavity, encapsulated. Measured 2 by 6 ins.	None apparent	do	2 kinds of tissue; a soft-gray-white and a tough fibrous white tissue. Orange fluid esacped from openings in center of mass.
F	Involved neck and axillary region	External to body wall	Adherent to skin	do	Fibrous, vascular, convoluted.
F	Left ventral surface in mammary region	External to body wall, encapsulated	Subclavian artery attached to body wall on left side.	do	Fibrous, white.
F	2 tumors on left ventral surface. Larger tumor in inguinal, mammary region. Smaller tumor in abdominal mammary region.	External to body wall, encapsulated. Larger tumor had an area of hemorrhage about 2 cm. in diameter.	Larger tumor supplied by a blood vessel in groin.	do	Very hard and fibrous. Tissue convoluted and colored white or yellowish, brown.
F	2 tumors, 1 on each side of inguinal mammary region. Tumor on left side involves vagina.	External to body wall, encapsulated, bilobed.	Each tumor supplied by a blood vessel coming from region of groin of its respective side.	do	Tissue was very hard and convoluted.
F	Left ventral surface involving inguinal mammary region.	External to body wall, encapsulated	Stripped easily from underlying tissues	do	Hard and fibrous.
F	Right ventral surface involving mammary region.	External to body wall, encapsulated. Composed of many lobes.	Easily stripped from surrounding tissue	do	1 lobe was composed of many channels containing a yellow, pasty material.
F	Right ventral surface in pectoral mammary region near axilla.	do	Freely separated from surrounding tissue.	Soft	Soft in texture and white in color.
F	Right ventral surface involving inguinal mammary region.	Large in size, bilobed, external to body wall, encapsulated.	do	Firm	1 lobe was dark red, the other white. Consistency hard.
F	Right ventral surface in axillary region	Small in size, external to body wall, encapsulated.	do	Soft	On section texture was cheese-like.

F	3 tumors on ventral surface. 2 on right side on lower inguinal mammary glands, 1 in left inguinal mammary region.	----do----	Tumors easily separated from surrounding tissue.	----do----	Yellow in color.
M	Small mass on neck. Small lump on dorsal surface near midline.	External to body wall. Mass on back in spinal region warty in appearance. Mass at neck not encapsulated.	No attachment apparent----	----do----	Warty tumor was filled with a granular material. Mass at neck contained a fatty, gelatinous collection of tissue.
F	Left ventral surface in inguinal region----	External to body wall, encapsulated. Large in size.	Easily separated from surrounding tissue-	Firm----	White secretion resembling milk in tumor. Center of tumor very dark purple color.
M	Tumor on right ventral surface, from pectoral to midsection of body.	External to body wall, encapsulated, bilobed----	----do----	Soft----	
F	Left ventrolateral part of body from axilla to abdominal area.	External to body wall, encapsulated----	Supplied by vessel from axillary region----	----do----	Tumor tissue orange in color with scattered blue-white areas and a small hard lump in center.
F	Small tumor on left lateral aspect anterior to hind leg. Large tumor on ventral surface which covered gentital region and extended over right hind leg from patella to urinary meatus.	External to body wall, encapsulated. Large tumor was trilobed.	Large tumor supplied by vessel from groin.	Firm----	Large tumor was white in color, tough and fibrous. Small tumor was hard and white.
F	3 small tumors; one on right side of head from ear to axillary region; second, right ventral surface involving pectoral mammary glands; third, posterior to second.	External to body wall, encapsulated. Largest tumor, most anterior in position, was trilobed.	Tumor easily separated from surrounding tissue.	Large tumor firm. Smaller tumors soft.	Largest tumor was hard. Smaller tumors were soft, and had areas of orange and white tissue.
F	Left ventral surface including gential region.	External to body wall, encapsulated----	----do----	Firm----	
M	Small mass on neck under chin----	External to body wall.	None apparent----	Soft----	Filled with a blood-tinged fluid and gelatinous substance.
M	Small mass on face below left eye----	External to body wall, surface of tumor mass was eroded.	----do----		
M	Left side of neck----	External to body wall, dry scabbed surface--	Attached to submaxillary gland----	Soft----	

SECTION 4.—CLASSIFICATION OF TUMORS BY MICROSCOPIC EXAMINATION

NOTE.—Number preceding description represents number of test day on which autopsy was performed.

TUMORS

0.1 PER CENT L–MONOSODIUM GLUTAMATE GROUP

1) 176 Fibrosarcoma, benign, origin unknown
2) 270 Adenoma, benign mammary origin
3) 347 Mixed tumor, penetrating fibrosarcoma, with areas of adenoma, benign
4) 666 Mixed sarcoma and adenoma, benign. Adenoma of mammary origin
5) 650 Fibrosarcoma, benign, some areas of necrosis, origin unknown
6) 772 Adenoma, benign, probably mammary origin
7) 772 Mixed sarcoma and adenoma, benign, origin not apparent
8) 773 Adenoma, benign, unknown origin
9) 773 Adenoma, benign, unknown origin
10) 773 Fibrosarcoma in connective tissue mass, benign
11) 641 Adenoma, benign, mammary origin

0.4 PER CENT L–MONOSODIUM GLUTAMATE GROUP

1) 63 Fibrosarcoma, adenomatous type, benign
2) 347 Mixed, fibrosarcoma with areas of adenoma, benign
3) 176 Adenoma, benign, mammary origin
4) 374 Fibroma, benign, mammary origin
5) 641 Adenoma, benign, mammary origin
6) 750 Adenoma, surrounded by fibrous mass, benign. Perforated with gland-like-structures
7) 667 Adenoma, benign, mammary origin
8) 773 Uterine fibroadenoma, benign. Blood vessels contained excess number of white blood cells, suggestive of chronic irritation with hyperplosia, now regressive
9) 750 Adenoma, benign, unknown origin
10) 635 Fibrosarcoma, benign, regressive, epithelial origin

0.1 PER CENT DL–MONOSODIUM GLUTAMATE GROUP

1) 777 Adenocarcinoma, benign, origin unknown
2) 777 Adenoma and fibroma, benign, mammary origin
3) 548 Adenoma, mammary origin, benign
4) 772 Mostly fibroma, some adenoma, benign, mammary origin
5) 772 Mostly fibroma, some adenoma, benign, mammary origin
6) 777 Fibrosarcoma and adenoma, mixed, benign. Origin unknown
7) 777 Adenoma, benign, origin unknown
8) 773 Adenoma, regressing, benign, origin unknown
9) 779 Sarcoma, benign, origin unknown
10) 779 Adenocarcinoma, benign. Accumulations of fat in some living cells suggest regression. Origin unknown

0.4 PER CENT DL–MONOSODIUM GLUTAMATE GROUP

1) 779 Mixed tumor, mostly fibrosarcoma with some adenomatous components. Benign, possibly mammary origin
2) 779 Adenoma with cellular regression, benign. Origin unknown
3) 688 Fibroma, benign, origin unknown
4) 772 Adenoma, surrounded by fibrous mass. Benign. Origin unknown
5) 772 Adenoma, surrounded by fibrous mass. Benign. Origin unknown
6) 773 Adenoma in a fibrous stroma, benign, probably mammary origin
7) 675 Probably carcinoma, masses of fibrotic tissue indicating regression, benign, origin unknown
8) 772 One section of tumor adenomatous surrounded by fibrous mass, benign, mammary origin

0.1 PER CENT L–GLUTAMIC ACID GROUP

1) 281 Adenoma, benign, evidence of regression (loss of glandular configuration, increase in connective tissue). Origin unknown
2) 406 Adenoma, benign, evidence of regression (loss of glandular configuration, increase in connective tissue). Origin unknown
3) 406 Mostly fibroma with trace of adenoma, benign, probably mammary origin
4) 688 Mixed fibroadenoma, benign, origin unknown
5) 645 Mixed fibroadenoma, benign, origin unknown
6) 703 Remains of fibroadenoma (regression). Mammary origin
7) 745 Remains of fibroadenoma (regression). Mammary origin
8) 759 Fibrous mass, benign, origin unknown

0.4 PER CENT L–GLUTAMIC ACID GROUP

1) 696 Mixed—mostly a fibrous mass with some adenomatous tissue, benign, probably mammary origin
2) 746 Mixed fibroadenoma, benign, mammary origin
3) 750 Adenoma, benign, mammary origin

CONTROL GROUP

1) 274 Carcinoma, benign, primary focus unknown, possibly epidermoid origin
2) 274 Mixed, fibrosarcoma and epidermoid carcinoma, benign
3) 274 Epidermoid, carcinoma, benign, origin unknown
4) 548 Adenoma, benign, origin unknown
5) 688 Adenoma in fibrous mass, mammary origin, benign
6) 752 Intestinal sarcoma, benign, origin unknown

ADDITIONAL TUMORS [1]

(*From rats sacrificed to obtain blood for glutamic acid analysis, 745 to 759 test days*)

0.4 PER CENT L–MONOSODIUM GLUTAMATE GROUP

1) Adenoma, benign, sweat-gland origin. Well encapsulated with no evidence of active proliferation, but cells suggest fatty secretory activity
2) Adenoma, old, fibrous type. Less secretory activity than (1) above, origin unknown
3) Fibroadenoma, sweat-gland origin, benign
4) Cystic adenoma, mammary origin, benign
5) Adenoma, mammary origin, benign. Now relatively inactive with some evidence of regression
6) Adenoma, mammary origin, benign. Now inactive with some evidence of regression
7) Fibrotic, wart-like mass, not identifiable but definitely not malignant. Origin unknown
8) Fibrous metaplosia, epithelial origin, benign

0.1 PER CENT L–GLUTAMIC ACID GROUP

1) Adenoma, benign, epithelial origin
2) Adenoma, benign, glandular origin, non-secretory
3) Adenoma, benign, glandular origin, non-secretory
4) Adenoma, benign, glandular origin, non-secretory
5) Adenoma, mammary or sweat-gland origin, benign
6) Adenoma, mammary or sweat-gland origin, benign

0.4 PER CENT L–GLUTAMIC ACID GROUP

1) Adeoma, mammary origin, benign
2) Adenoma, old, benign, now all fibrotic, mammary origin
3) Adenoma, sweat gland or mammary origin, benign

[1] Tumors not included in preceding pages.

4) Adenoma, mammary, benign. Fibrous tissue associated with tumor had a scattering of macrophages with melanotic granules suggesting low degree of chronic irritation
5) Adenoma, sweat-gland origin, benign
6) Fibroadenoma, benign, origin unknown
7) Adenoma, mammary, benign
8) Fibroma, benign, near glandular growth, probably site of origin

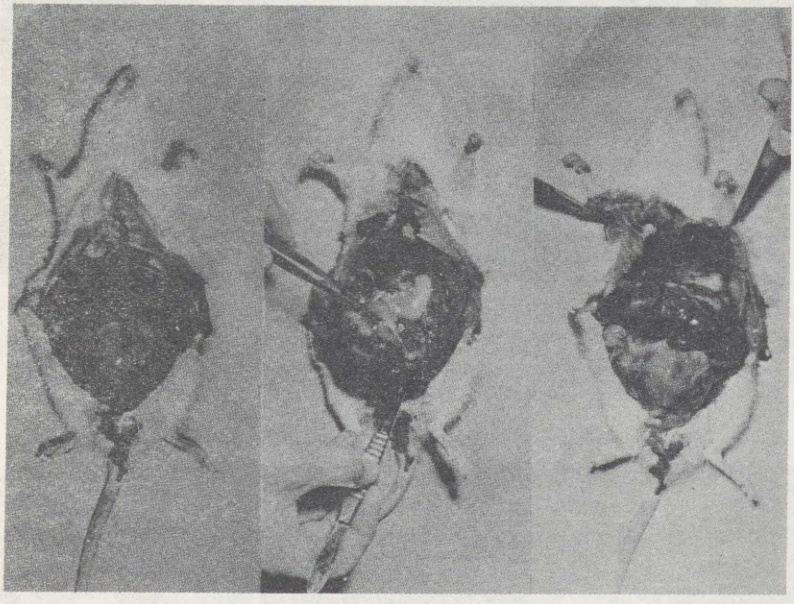
CONTROL GROUP

1) Non-secretory adenoma, benign. origin unknown
2) Non-secretory adenoma, benign, origin unknown
3) Adenoma, mammary origin, benign
4) Adenoma, mammary, benign, actively secretory, origin unknown
5) Adenoma, mammary, benign, actively secretory, origin unknown
6) Adenoma, mammary origin, benign
7) Adenoma, mammary origin, benign
8) Adenoma, mammary origin, benign
9) Cystic fibroadenoma, mammary origin, benign
10) Cystic fibroadenoma, mammary origin, benign

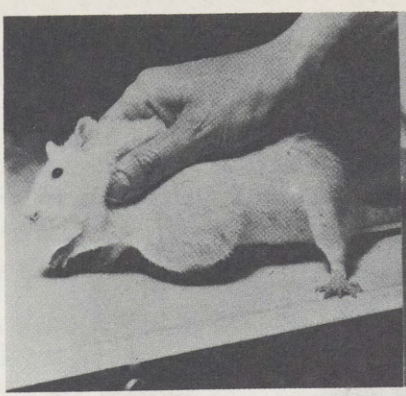
Male rat (F_1) fed on 0.4 percent DL-monosodium glutamate supplemented diet in whom tumor transplant was made. Donor was female rat (F_o) generation on 0.1 percent DL-monosodium glutamate supplemented diet with tumor in inguinal mammary region. No growth in recipient in 174 days.

Female rat (F_1) fed on control diet approximately 180 days after caesarian section performed without complications.

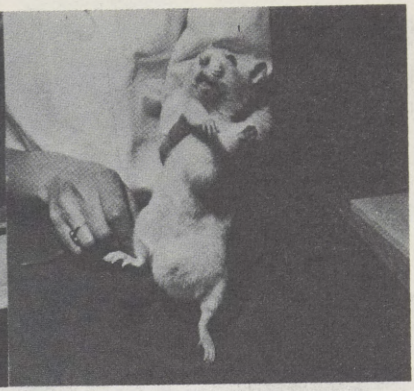
24-235 O—69—pt. 13E——8



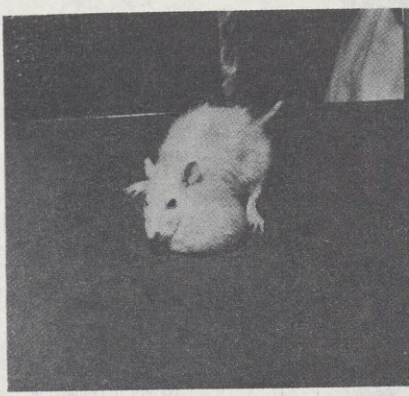
Control rat (F_1) sacrificed after 274 days because of enlarged abdominal swelling. At autopsy, abdominal cavity contained a uterine tumor.



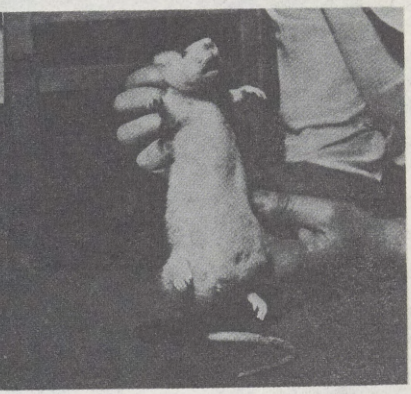
Female rat (F_1) fed on control diet for approximately 570 days. Well-developed left mammary tumor present.



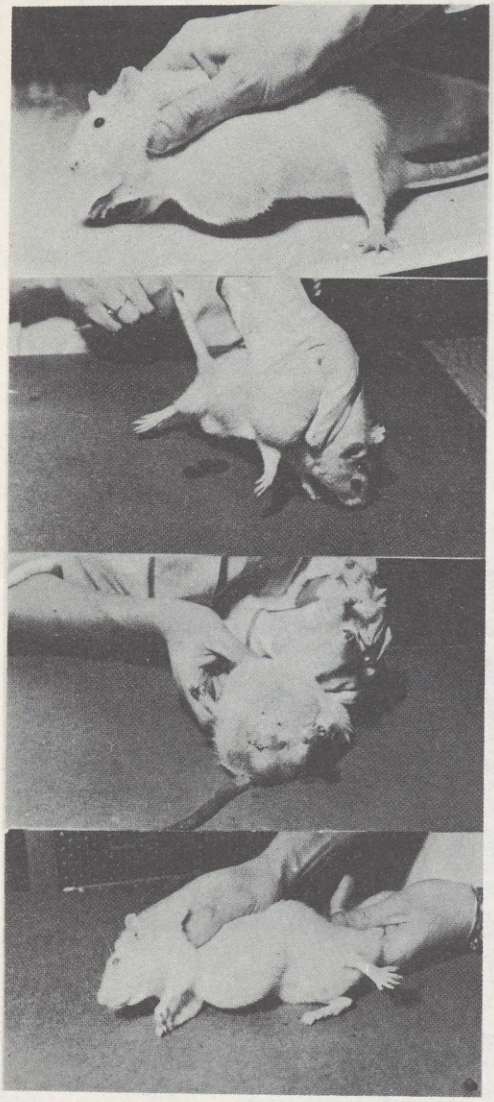
Female rat fed on control diet for 826 test days. Two ventral tumors, one in left inguinal mammary region, one in left pectoral mammary region.



Female rat fed on 0.1 percent DL-monosodium glutamate supplemented diet. Large tumor on ventral surface extending from submaxillary to thoracic region. 826 test days.



Female rat fed on 0.4 percent DL-monosodium glutamate supplemented diet with tumor in left inguinal mammary region and on lower right ventral surface involving genitals. 826 test days.

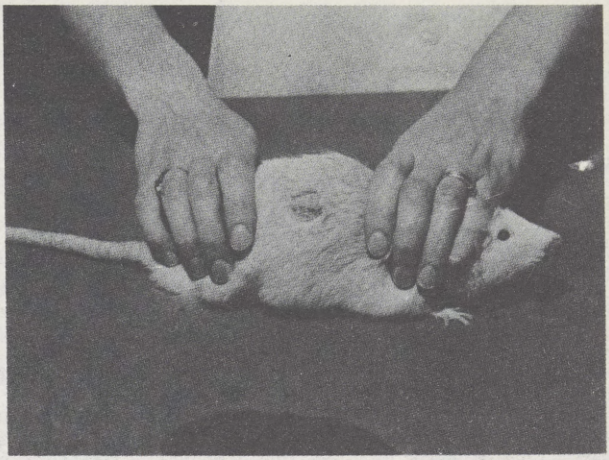


Female rat on control diet for 570 days. Well developed tumor present in left mammary region.

Female rat fed on control diet for 826 test days. Large right ventral tumor.

Female rat fed on control diet for 826 test days. Large bilobate tumor involving anal region and inguinal mammary region.

Female rat fed on 0.4 percent L-glutamic acid supplemented diet with left ventral tumor and smaller tumor involving inguinal mammae. 826 test days.



Male rat fed on 0.1 percent L-monosodium glutamate supplemented diet with horny growth on back. 826 test days.

Female rat fed on 0.1 percent L-monosodium glutamate supplemented diet approximately 570 days. Small tumor present in left pectoral mammary region.

ARTHUR D. LITTLE, INC.,
Cambridge, Mass., July 21, 1952.

Dr. PAUL D. V. MANNING,
Vice President, Research Division,
International Minerals & Chemical Corp.,
Chicago, Ill.

DEAR DR. MANNING: We are sending you herewith our report on a study of the potential carcinogenicity of L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid. This work has been carried out by the use of C–57 black mice who were maintained under controlled experimental conditions for two years during which time they were fed standard laboratory diets supplemented by the materials under test. At the end of the two-year period, the surviving mice, including a control group, were sacrificed and a careful post-mortem examination of their tissues made.

The tissue changes were those consistent with advanced age and were chiefly senile alterations of the kidney, liver and lungs. A few mice showed areas of lymphocytic infiltration in these tissues, but all were of low-grade, subacute type. There were no appreciable differences between the control animals and those fed on diets supplemented as indicated above. At autopsy, a single tumor was found. It was an adenoma of the lung (benign) and its type was established by microscopic examination. The survival rate was approximately the same for control and test animals at the end of the experiment. The C–57 mouse is notoriously combative; many deaths resulted from fighting and the bodies of survivors were much scarred from this cause.

It is our conclusion based on the detailed observations reported herein that L-monosodium glutamate, DL-monosodium glutamate and L-glutamic acid do not possess carcinogenic properties.

Respectfully submitted.

ARTHUR D. LITTLE, INC.

REPORT ON A STUDY OF L-MONOSODIUM GLUTAMATE, DL-MONOSODIUM GLUTAMATE, AND L-GLUTAMIC ACID WITH RESPECT TO POTENTIAL CARCINOGENICITY TO INTERNATIONAL MINERALS & CHEMICAL CORP.

INTRODUCTION

From time to time, the attention of persons engaged in cancer research has been attracted to the role of the amino acids in the etiology and metabolism of neoplastic tissues. Kogl and Erxleben [1] announced in 1939 that the protein of cancerous tissue is distinguished from normal proteins by the occurrence of amino acids of unnatural stereochemical configuration, in particular *D*-glutamic acid. (the natural form, now referred to as *L*-glutamic acid). Five years later, after more experimental work, the existence of stereochemical abnormality as a characteristic of tumor protein remained unsettled.

Kogl and Erxleben did not indicate the function of *D*-glutamic acid, nor did they suggest whether its presence is due to altered metabolic processes in neoplastic cells, or to its elaboration as an organic defense against carcinogenic factors. The synthesis and testing of glutamic acid conjugates in the treatment of cancer (Diopterin and Triopterin), which in man has caused regression of tumors and analgesia, has not elucidated the observation of Kogl and Erxleben to any extent. Pfeiffer commented upon Kogl's work at a symposium on monosodium glutamate sponsored by the Quartermaster Food and Container Institute for the Armed Forces at Chicago in 1948, and questioned whether cancerous growths on embryonic cell rests may not be matured by glutamic acid. In 1951, a paper was published by Beaton, McGanity and McHenry [2] of Toronto in which they claimed that the concentration of blood glutamic acid was greatly increased in animals and human subjects suffering from malignant tumors. Such increase was said to be peculiar to malignant tumors and could be utilized for diagnostic purposes; the order of elevated concentration was several times that encountered in the blood of animals and human subjects who were hosts for benign growths. Whether the glutamic acid reportedly involved in tumor metabolism is of etiological significance, or whether it is a metabolite of tumor tissue has never been clearly established so far as we can learn.

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[1] Kogl, F. and Erxleben, H.; *Zur Ätiologie der malignen Tumoren I. Mitteilung über die Chemie der Tumoren.* Z. physiol. Chem. 258, 57, 1939.

[2] Beaton, J. R., McGanity, W. J. and McHenry, E. W.; *Plasma Glutamic Acid Levels in Malignancy.* Canad. M. Ass. J. 65, 219, 1951.

The uncertain significance of glutamic acid in tumor tissue, its increasing therapeutic use, and the lack of information on its side actions have made it appropriate for study. The manufacturers of glutamic acid and its salts were properly interested in learning whether the compounds possessed any carcinogenic action, and to that end authorized a study of this phenomenon; it is the results of that investigation which are reported herewith. The closely related monosodium glutamate was included because it is the principal derivative of glutamic acid used in food.

In planning a study of this general type, in which the route of administration was to be gastro-intestinal, several factors warranted reflective consideration. The choice of species and variety of experimental animal was probably of greatest importance. The duration of the experimental work had to be sufficient to insure that the carcinogenic action, if any, would be allowed to operate throughout the entire life span of the selected species. An animal of uniform genetic constitution was required, and one for which an impressive body of data was available with respect to its response to carcinogenic agents. The incidence of spontaneous tumors in the selected species should be low, but it should have been established that the selected species would be able to support tumor growth without succumbing immediately to the effect of a neoplasm. Should death occur early, it is possible that many tumors might have failed of observation before the size of the tumor mass became appreciable.

Our objective was not comparable to that of the investigator who transplants known tumor tissue to a susceptible host, nor could it be compared with the problem confronting an investigator who wishes to observe spontaneously-occurring tumors. Essentially, we wished to expose the subject animals to factors of unknown weight with respect to their tumor-producing properties. Our objective differed, too, from that in which the significance of a suspected carcinogen with respect to its industrial hazard is of interest. In that latter situation, the exposure is most commonly of the epithelial tissues and their appendages. Throughout our investigation, it has been important to remember that the projected use of the test materials might be repeated (in human subjects) through a large part of the life span whether used therapeutically (*L*-glutamic acid) or as an ingredient of food (*L*-monosodium glutamate). The racemic isomer (DL-monosodium glutamate) although not commonly ingested by humans, warranted study in view of its possible future use.

GENERAL DISCUSSION OF CARCINOGENESIS

The awareness of tumors in plants and animals is almost as ancient as man. The knowledge of tumor behavior has advanced materially in the twentieth century, but the basic facts regarding causation are almost as obscure as they were several centuries ago. Carcinogenic potency, i.e. the ability of a chemical substance to cause tumors, is a property widely distributed among chemical compounds, and there is little or no correlation between carcinogenicity and chemical structure.[1] The difference in tissue response to a suspected carcinogen is a matter of general concern, but it is of lesser importance when the carcinogen is administered by mouth than when applied to the body surface, since it will be more uniformly distributed by the blood stream. The establishment of the appropriate dosage is important, and if variation from the optimum is necessary, it had better be on the side of more than less. The latent period of carcinogens is frequently given too little consideration in studies of this type, but if the material is administered throughout the life span of the animal, it will be of minimal significance.

All neoplastic growths may be referred to as "tumors"; further classification may depend on such characteristics as site, invasiveness, cell type, embryonic origin of host tissue, or rapidity of growth. Tumors, by very derivation of the name, are swellings, yet they do not cause an increase in the size of normal cellular elements. Their intrinsic danger lies in their tendency to encroach on normal vital tissues. *Malignant* tumors are invasive, and have no capsules, but the *benign* type push normal structures out of the way or press upon them. The benign type do not metastasize and are usually enclosed in a fibrous capsule or sac. Their growth is confined to localized areas and the growth rate is moderate. Malignant tissues, on the contrary, encroach on and encompass any tissues in

[1] Hartwell, J. L.: *Survey of Compounds . . . Tested for Carcinogenic Activity*, Second edition, 1951. United States Public Health Service, Publication No. 149.

their way. They penetrate the lymphatic and blood vessels and tend to metastasize or spread to distant areas. Malignant tumors originate from primitive or embryonic types of cells which never reach mature function. They reproduce by cell division; they are never encapsulated but infiltrate rapidly into surrounding tissues. Metastases occur when a few malignant cells are carried by the lymph and blood vessels to new sites. The rapid growth, the tendency to recur after surgical removal, and the dissemination of toxic products of tumor metabolism quickly endanger the life of the host.

A tumor, whether benign or malignant, is essentially an autonomous new growth of tissue, whose cells possess atypical structure and manifest atypical behavior. Tumor tissue possesses no useful function, and there is no limit to its possible extent of growth. If growth is uninterrupted, it can destroy the host by utilizing nutritive material, thus depriving normal tissue of sustenance, giving rise to a "wasting" in all tumor-ridden tissues. Tumors may arise from embryonic cell rests[1] so called, or from normal body cells. Growth is by cell division or mitosis, and may take place by *expansion* in which case there occurs the formation of a connective tissue capsule due to the pressure of the growth on the surrounding, supporting cells. Growth may also take place by *infiltration* in which case the spread of the tumor occurs along tissue spaces and via the lymphatic vessels. A secondary growth of the same type may occur at some distance from the primary site. This latter type of growth is more characteristic of malignant growths than of the benign type. Incomplete removal of tumor tissue may result in recurrence with an increase in the growth rate.

The connective tissue type forms its own stroma or supporting structure and vascular supply. Epithelial tumors, on the other hand, are formed around stroma from the surrounding tissue, and their blood vessels arise from the same source. No new lymphatic vessel or nerve elements are formed in tumors. As the tumor increases in size, greater nutritional demands are made upon the host, and metabolic changes result from pressure upon or infiltration of vital organs. Degenerative changes in tumors may result from deficient blood supply; the tumor may become necrotic in whole or in part, pouring waste products into the blood stream. Sometimes only a cyst is found to indicate the earlier presence of a fully developed tumor which has been resorbed except for the cystic relic.

Benign tumors are usually slow-growing. They increase in size by expansion and are usually encapsulated, but do not infiltrate the surrounding tissues, nor do they metastasize. They are non-recurrent if removed surgically. Some benign tumors are believed capable of metamorphosis to a malignant form such as that which occurs in mammary tumors in mice.

Tumors are commonly classified on the basis of type and origin involved, but in either case, the histological characteristics are important in diagnosis. The tumor is named according to the tissue it resembles and in which it occurs. However, certain malignant tumors do not resemble any normal tissue, and their most characteristic appearance when examined microscopically, is the total lack of cellular organization. Tumors which develop in tissues having their origin in the ectodermal layers of the embryo become carcinomas, while those coming from connective tissue of mesodermal origin (cartilage, bone, muscle) become sarcomas. The latter are usually far more malignant than carcinomas, and develop in individuals of younger age than do the former type, whose onset occurs in middle or late life. The typical sarcoma cell is spindle-shaped, but may be round or giant in type. The most malignant forms have a great number of round cells. Ulceration is a common event in the life of a tumor. In this condition, a cavity develops and fills with tissue fluid. The walls of the tumor may regress and leave only scar tissue behind.

CRITERIA

In a study of carcinogenesis, the animals represent biological tools. Their nutritional and general physical status must be followed, and the criteria for verifying the existence of a tumor must be established in general terms before the experimental work begins. They may be altered in some details as the work proceeds, but the general criteria will remain unchanged. Sufficient time must elapse for the latent period of a carcinogen to be completed.

Obviously, the principal criterion will be formation of a lump, either exterior to the body wall or palpable in deep tissues and organs. When a tumor develops

[1] Embryonic cell rests represent a persistence of immature cells, ordinarily found only in fetal life.

in a laboratory animal, its clinical condition eventually degenerates and is marked by loss of weight, malnutrition, ruffling of the hair, generalized weakness, and possibly lowered body temperature. The animal may appear shrunken in size or it may show respiratory distress and generalized accumulation of fluid in the tissues (edema). In a sick animal, any local hardness or undue firmness of the tissues, any asymmetry of the abdomen, failure to eat, appearance of emaciation or disturbance of respiration warrants close daily observation until the cause becomes apparent. If comparative survival rates are to be determined, the animals cannot be sacrificed indiscriminately, but if they appear to be moribund, sacrifice and immediate post-mortem examination is indicated. In the C–57 black strain of mice, overnight delay may mean that should an animal die, its cage mates will have cannibalized the entire body by morning.

Once tumor formation is suspected, the body must be searched for possible metastases to new sites, and any tendency toward regression in size must be individually evaluated. The ultimate and conclusive proof of the existence of a tumor will depend upon post-mortem examination of the tumor-bearing host and histological examination of the suspect tissues.

EXPERIMENTAL ANIMALS—DESCRIPTION—BASES FOR SELECTION

The selection of suitable experimental animals received careful consideration. The advice of a number of persons familiar with tumor growth was sought; without exception, they recommended mice, and in particular, one of the strains bred so effectively at the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. At this institution, established in 1929 "for the study of cancer, genetics and behavior", over a million mice a year are bred and the permanent mouse colony numbers 150,000. Although many strains were destroyed at the time of a disastrous forest fire in 1947, all had been reconstituted by gifts from institutions to whom the Jackson Laboratory had previously supplied mouse stock. Great emphasis is placed there on the maintenance of inbred stocks of mice and systematic breeding has produced mice strains which are 98 percent (or more) homozygous so that when raised under uniform experimental conditions, these animals are for practical purposes, a single mouse, "blessed for the experimenter's purpose with many times nine lives".[1] The greater uniformity of inbred[2] stock permits detection of quantitative differences in the reaction of animals than would be possible with hybrid stock.

When the general nature of our problem was explained to one of the resident investigators at the Jackson Laboratory, Dr. George Snell, he recommended without hesitation that we use the Jackson strain denoted "C–57 black". These result from brother-sister matings. Occasionally, an internal sarcoma has been seen in this species, but for the most part they are free of spontaneous tumors. Dr. Snell suggested that we use only male[3] mice of the C–57 black strain since they are notoriously pugnacious and cannibalistic when caged near females of the same variety, unless caged individually. Later experience proved that other factors than the presence of females stimulated pugnacious behavior! We wished to use 800 individuals so that an individual caging scheme would have been formidable.

Another investigator who had used the C–57 black mouse advised us that we would not see a spontaneous tumor in fewer than 10,000 individuals. In previous reports, we have referred to this type mouse as "highly susceptible" to tumors. In light of increased information from various sources and our own observations, we would wish to modify this to state that the strain is not highly susceptible to spontaneous tumors. It is susceptible to carcinogenic chemicals and the tissues of this strain are well able to support tumor growth of this origin.

In November, 1949, we obtained 800 male mice of the C–57 black strain, approximately 28 days of age.

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[1] Lancet. Editorial. 262, 6701, 1952.

[2] By inbreeding, (brother x sister) or by linebreeding (mother x son or daughter x father) it is possible to bring about an increase in the proportion of homozygous gene pairs. A given line will become as pure as it can be in 30–40 generations. Further matings after that time will result in spontaneous mutations sufficient in number to outweigh the value of continued inbreeding. Thus, inbreeding results in reduction of the number of variations for a given characteristic and produces a greater uniformity of response to drugs and carcinogens. Inbred stocks may show some reduction in so-called "hybrid vigor" but this can be minimized by decreasing the size of the newly born litter by culling the runts.

[3] Little and his associates had established in 1939 that when spontaneous tumors occur in the C–57 black strain, the incidence is the same in both sexes (Little, C. C., Murray, W. F., and Cloudman, A. M., *Genetics of Non-Epithelial Tumor Formation in Mice.* Am. J. Cancer. 36, 431, 1939).

In the C–57 black mouse, no mammary tumors are expected to occur, except in breeding females (one percent) and lung tumors are almost non-existent. Approximately 90 percent or more C–57 black mice can be expected to die free from spontaneously developing tumors.

The description furnished with the mice by the Jackson Laboratory indicated that they were recorded as "C–57 black, subline 6, inbred 27 generations with considerable inbreeding previous to that. The origin of this stock was by mutation from the C–57 brown strain. They show high fertility and have a genetic constitution described as aa".

EXPERIMENTAL CONDITIONS

The C–57 black mice were approximately four weeks old when received from the Jackson Laboratory; the ages within the total group did not vary more than two weeks. For a two week period, the mice were quarantined to eliminate sick or sub-standard individuals. Ultimately, they were divided into six test groups of 100 mice each. Two hundred mice were reserved for a control group.

The basic ration was Purina Lab Chow and the test compounds were incorporated in it in pellet form. This ration has been found to be appropriate to the nutritional requirements of the mouse and has been used successfully in our laboratory for ten years. The individual ration fed to the test groups contained one of the supplements at 1.0 percent or 4.0 percent concentration. Thus, the seven groups were fed throughout the experiment as follows:

Group 1 200 mice basic ration control
Group 2 100 mice basic ration plus 1% *L*-Glutamic Acid
Group 3 100 mice basic ration plus 4% *L*-Glutamic Acid
Group 4 100 mice basic ration plus 1% *L*-Monosodium Glutamate
Group 5 100 mice basic ration plus 4% *L*-Monosodium Glutamate
Group 6 100 mice basic ration plus 1% *DL*-Monosodium Glutamate
Group 7 100 mice basic ration plus 4% *DL*-Monosodium Glutamate

The selection of levels of 1.0 and 4.0 percent was to bring the supplement to concentrations ten times those of supplements fed in a parallel study of the chronic toxicity of the same compounds in rats. The higher concentrations fed to the mice bears some approximate relation (with respect to glutamic acid) to the therapeutic dosage level in human subjects.

The mice were housed in wire mesh cages of adequate size in groups of 20. Five cages were required for each test group, and ten for the control group. The floors of the cages were of wire mesh with draw pans beneath containing sawdust, which was replaced each day to insure a clean floor at all times. The food was supplied in pellet form and a constant supply provided by placing the pellets in a wire mesh feeder. Water was supplied from glass bottles which were wired to the outside of the cage and closed with a rubber stopper through which a glass tube led into the cage, providing a "demand" source of water. Cages and water bottles were washed frequently. The temperature of the cage room was maintained automatically at 75° F. and the relative humidity at 45–50 percent.

The supplemented ration was prepared at the Experimental Food Division of the Ralston Purina Company, Checkerboard Square, St. Louis. The standard ration,[1] Ralston Purina Laboratory Chow, ordinarily in pellet form, was reground and mixed with the proper concentration of the supplement and repelleted before shipment directly to us. The food for the control animals was purchased from a local supplier with assurance from Mr. Emmett Johnson of the Ralston Purina Company of the uniformity of the basic ration from either source.

[1] Copy of analysis attached to each bag:

GUARANTEED ANALYSIS

	Percent
Crude Protein (minimum)	23.0
Crude fat (minimum)	5.0
Crude Fibre (maximum)	6.0
N.F.E. (minimum)	44.0

INGREDIENTS

Meat meal, dried skimmed milk, wheat germ, fish meal, liver meal, dried beet pulp, corn grits, oat middlings, soybean oil meal, dehydrated alfalfa meal, molasses, vitamin B_{12} feed supplement, riboflavin supplement, brewers' dried yeast, thiamin, niacin, vitamin A and D feeding oils, D activated plant sterol, 1% steamed bone meal, .5% iodized salt, .02% manganese sulphate.

Whenever a new shipment of the supplemented food was received by us, representative samples were taken and sent to Dr. M. J. Blish, Supervisor of Organic Chemical Research of the Amino Acid Division of International Minerals and Chemical Corporation, Rossford, Ohio, for analysis of the amount of supplement actually contained. To avoid vitamin loss, large supplies were not stored, and each lot was completely used before starting another.

The results of the assays made at Rossford are summarized in the table which follows:

ASSAYS OF MOUSE RATION WITH SUPPLEMENTS—DATE OF REPORT AND AMOUNT OF SUPPLEMENT FOUND (IN PERCENT)

Presumptive supplement	Jan. 30, 1950	Feb. 21, 1950	Oct. 16, 1950	Feb. 28, 1951	Sept. 26, 1951	Average
1 percent L–MSG.H20	1.37	1.01	1.70	0.86	0.82	1.15
4 percent L–MSG.H20	3.38	3.68	3.30	3.10	3.50	3.37
1 percent DL–MSG.2H20	1.17	1.06	1.10	8.9	1.10	1.06
4 percent DL–MSG.2H20	3.64	3.61	3.80	3.40	3.90	3.67
1 percent L–GA	1.56	.95	1.00	1.10	1.00	1.12
4 percent L–GA	3.74	3.59	3.10	3.60	3.70	3.55
Control (L–GA)	.05					

The reported values show some discrepancy from the intended amount of supplement incorporated into pellets. The Ralston Purina Company reported some difficulty in obtaining a uniform dispersion of supplement in lots less than one half ton. The probability of major vitamin loss during storage before use made it inadvisable to have half-ton lots prepared at one time.

The average discrepancy of actual supplement content from intended content was ±13 percent, tending to be higher than intended for the 1.0 percent supplement and lower for the 4.0 percent supplement. However, the average discrepancy for the food intended for mice was not greater than limit of error inherent in work of this type.

Previously reported figures (Report of March 22, 1950) of actual food consumption for a group of mice selected at random indicated an average daily food intake of 6.8–7.5 grams per day per mouse. From observations throughout the feeding program the food consumption did not vary significantly. As the mortality rate increased, the feeders did not require refilling as often, but the food consumption remained relatively constant per animal. On the basis of the probable food consumption per individual mouse, and the average concentration of supplement, by assay, the actual intake was probably that shown in the following table:

THEORETICAL AND PROBABLE INTAKE OF SUPPLEMENTS

[In grams]

Supplement	Theoretical intake per mouse-day	Probable intake	Theoretical intake, 2 mouse-years	Probable intake 2 mouse-years
1 Percent L–MSG	0.068 –0.075	0.0781–0.0863	49.64– 54.75	57.013– 62.999
4 Percent L–MSG	.272 – .300	.230 – .253	198.56–219.0	167.900–184.690
1 Percent DL–MSG	.068 – .075	.072 – .0795	49.64– 54.75	52.560– 58.035
4 Percent DL–MSG	.272 – .300	.250 – .275	198.56–219.0	182.500–200.750
1 Percent L–GA	.068 – .075	.076 – .084	49.64– 54.75	55.480– 61.320
4 Percent L–GA	.272 – .300	.241 – .266	198.56–219.0	175.930–194.180
Control	.0034– .0037			

There was no conclusive evidence that one supplement caused a greater total food intake than any other. In these mice, the nutritional status was good and did not contribute significantly to the mortality rate throughout the experiment.

The mice fed 4.0 percent DL-MSG received careful attention in view of the slightly higher toxicity of the racemic form demonstrated when determination of the acute toxicity (LD_{50}) of these compounds was made in rats. It was found to possess no greater toxic effects than either of the other supplements.

BLOOD EXAMINATIONS

The blood of representative mice was examined at intervals for correlation with their general condition. Blood was obtained by incising the tail vein. The total erythrocyte and leukocyte count, a differential count, and a hemoglobin determination, whenever possible, were made. The Thoma standard type blood pipettes were used. Hayem's diluting fluid was used in making the erythrocyte count and 3 percent acetic acid was used as a diluent for the leukocyte count. The differential count was made by staining the blood smear with Wright's stain. One hundred leukocytes were counted and their distribution among the five main classifications of neutrophils, eosinophils, basophils, lymphocytes, and monocytes was expressed as percentages of total leukocytes. Hemoglobin determination by the Sahli method was not entirely successful since the total blood volume in the mouse is very small.

The following tables present the blood values of mice at 241–251 test days and 275–280 test days which are representative of all determinations made. A table of normal blood values is given.

In a later series of blood counts (275–280 Test Days) hemoglobin determinations were made by matching the tail blood of the mouse with the Tallquist Hemoglobin scale. The determinations are expressed in such terms that 15.0 grams of hemoglobin (average value for mouse) per 100 ml. of blood is equivalent to 100 percent. The range for the normal mouse is 12.0–17.1 grams hemoglobin per 100 ml. blood.

The average blood values found are within the established normal range for the laboratory mouse. The relatively high white counts for the groups fed 1.0 percent *L*-MSG and 1.0 percent *L*-GA are noteworthy. In view of other normal blood values, especially the differential count in both groups, no significance is attached to the elevated white count in these animals.

The tumor-bearing host, both human and animal, is often found to suffer from blood dyscrasias. From the representative data presented and other blood examinations made at random intervals, no evidence of significant abnormalities in the blood cytology was seen at any time.

AVERAGE BLOOD VALUES IN C–57 MICE AFTER 241–251 TEST DAYS

Supplement	Erythrocytes millions/mm³ blood	Hemoglobin (grams/100 ml. blood)	Leukocytes count/mm³	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
1 percent L–MSG	9,410,000	13.5	16,900	17	1.0	0	74	9.0
4 percent L–MSG	10,005,000	13.5	10,925	25	1.0	0	63	11.0
1 percent DL–MSG	7,750,000	11.0	13,150	16	3.0	0	74	6.5
4 percent DL–MSG	9,780,000	----------	8,650	23	0.0	0	66	11.0
1 percent L–GA	10,942,000	12.5	16,100	20	1.0	0	70	10.5
4 percent L–GA	10,765,000	----------	13,200	31	1.0	0	53	15.0
Control	9,000,000	6.5	10,100	28	0.5	0	65	7.5

AVERAGE BLOOD VALUES IN C–57 MICE AFTER 275–280 TEST DAYS

Supplement	Erythrocytes millions/mm.³ blood	Hemoglobin (grams/100 ml. blood)	Leukocytes count/mm.³	Differential count				
				Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
1 percent L–MSG	8,765,000	11.7	16,700	22	0	0	68	10
4 percent L–MSG	9,675,000	11.7	12,700	28	0	0	60	12
1 percent DL–MSG	9,905,000	11.7	16,200	12	1	0	83	5
4 percent DL–MSG	10,145,000	10.9	18,500	17	0	0	73	10
1 percent L–GA	9,580,000	11.8	21,600	27	1	0	62	10
4 percent L–GA	12,975,000	10.5	16,770	21	0	0	69	10
Control	9,510,000	12.5	11,180	15	0	0	77	8

NORMAL RANGE OF BLOOD VALUES IN THE LABORATORY MOUSE[1]

	Average	Range
Erythrocytes (millions/mm.^{3} blood)	9,229,000	5,500,000–13,900,000
Blood hemoglobin concentration (grams per 100 ml.)	15.05	12.0–17.1
Leukocytes (count/mm.^{3})	14,080	7,800–22,500
Differential count (distribution per 100 cells):		
Neutrophils	20.62	8.0–57.9
Eosinophils	2.58	0.0–15.1
Basophils	Rare	
Lymphocytes	66.58	36.2–89.8
Monocytes	5.73	0.7–14.0

[1] Standard Values in Blood. Air Force Technical Report No. 6039, July 1951. Gardner, M. V.; The Blood Picture of Norma Laboratory Animals. A Review of the Literature 1936–46. J. of Franklin Institute, 243, 172, 1947.

GENERAL PHYSICAL CONDITION AND EXAMINATION FOR TUMORS

At intervals, each mouse was examined for swellings, asymmetry of body, lesions of skin and appendages, bleeding from body orifices and other findings indicative of poor clinical condition or suggestive of tumor formation (see section above on Criteria). A series of eight complete physical examinations, plus a final examination at autopsy of each individual C–57 mouse was made during two years' time. The data below shows the interval and age of mice at the time of examination.

EXAMINATION FOR TUMORS

Examination	Date	Number of test days	Approximate days of age
1	Jan. 5, 1950	30	58
2	May 1–16, 1950	146–152	174–180
3	July 11–14, 1950	215–220	243–240
4	Sept. 18 to Nov. 13, 1950	286–342	314–378
5	Dec. 12, 1950 to Jan. 14, 1951	370–403	398–431
6	May 18–23, 1951	529–534	557–562
7	Oct. 2–3, 1951	664	692
8	Nov. 21, 1951	715	743

In addition, random examinations were made at more frequent intervals. Complete notes on the condition of animals at each complete physical examination are given in the appendix.

There was no evidence of any tumor formation or other neoplastic activity at the time of the first complete physical examination. The only lesions seen were injuries which were obviously sustained in fighting. There appeared to be a definite pattern of attack on the part of a single aggressor in a cage for the mice which had been attacked showed similar anatomical distribution of injuries. Usually, one mouse showed no injuries at all!

The condition of the mice at the second physical examination followed the same general pattern as described for the first. Although injuries from fighting were still present, they were not increased in number or severity. In some groups the previous injury had healed entirely, especially in the group fed a supplement of *L*-monosodium glutamate. Those being fed *DL*-monosodium glutamate were at this time suffering more numerous injuries from fighting.

In one mouse in the group fed 4.0 percent *L*-glumatic acid a small, internal mass was palpated in the genital region. The mouse was isolated for observation. Forty-four days later, the mass was no longer palpable and the mouse was returned to the original group. It is believed that the mass in question may have been an unretracted testis.

The third physical examination was made July 11–14, 1950, after 215–220 test days, when the age of mice was 243–248 days. Each individual mouse was handled, the body carefully palpated and examined for lumps, ulcerations, loss of hair or other grossly perceptible changes.

The injuries from fighting were greatly reduced in number from the two previous examinations. One animal in the 1.0 percent *L*-monosodium glutamate group had lost a leg but moved about as agilely as the others. The mice who

showed signs of possible neoplastic growth were identified for continued observation.

One month later, or at 245 test days, they were re-examined.

The observations are presented below:

Cage 1---- The lump was still present, not enlarged, freely movable.
Cage 10---- No evidence of lump.
Cage 24---- Do.
Cage 27---- A very small lump on dorsal surface was still present under skin, not enlarged.
Cage 30---- No change from previous examination. The lump appeared to be just under the skin, possibly an area of infection from fighting injuries.
Cage 37---- Lump in genital region under skin was very prominent, similar in appearance to that seen in cages 27 and 30.

The palpable lumps described in mice from Cage 1 and Cage 10 (of which there was no evidence in the latter one month later) may well have been the unretracted testes. This was suggested as the probable explanation in the one case described in a previous examination. The disappearance of the small lumps on the dorsal surface of two mice can not be explained unless the mass was an area of ulceration which was absorbed on healing. The lumps which were still present were external to the body wall in the region of the genitals. The incidence of suspicious swelling at time of this examination was confined to one mouse on the 4.0 percent *L*-glutamic acid supplemented diet and two on the control diet.

On September 18, 1950 (286 test days) and on several days up to November 13, 1950 (342 test days) the fourth physical examination was made for presence of tumors or other suspicious lesions.

The mice which showed suspicious swellings and other surface changes were identified for continued observation. One mouse on the 4.0 percent *DL*-monosodium glutamate supplemented diet had a wart on his chin. One mouse at the 1.0 percent *DL*-monosodium glutamate level and two on the 4.0 percent *L*-glutamic acid supplemented diet each had a small lump (approximately $\frac{1}{16}$'' in diameter) on the ventral surface above the genital region but it was difficult to determine whether it was the beginning of a tumor or a point of healing of a previously injured area. Two mice fed on the control diet showed a similar lump visible to the eye in the same region which was palpable. When re-examined later at different times, there was no change in appearance or size.

The incidence of lesions suspected of being tumors at the fourth examination is presented below in tabular form:

INCIDENCE OF LESIONS SUSPECTED OF BEING TUMORS

Supplement	Number of mice with suspect lesions	Description
1 percent L-MSG	0	None.
4 percent L-MSG	0	Do.
1 percent DL-MSG	1	1 mouse with a hard lump under skin near penis (possibly an area of infection).
4 percent DL-MSG	1	1 mouse with a wart on chin.
1 percent L-GA	0	None.
4 percent L-GA	2	2 mice with a lump under the skin on ventral surface near genitals (possible areas of infection).
Control	2	2 mice with a lump on ventral surface above genitals.

The descriptions of suspected neoplasms present the same pattern previously discussed and are not verified tumors. From their location involving the endocrine system and reproductive organs, it is believed that they may be the result of the aging process.

At the time of the fifth examination the study had been in progress approximately one year. An interesting observation at this time was the noticeable graying of the fur of some animals. A colony count was made as well as a description of the physical condition of each animal. A great many injuries resulted from fighting. Several had badly bitten faces, some had swollen, infected legs, others had crookedly healed broken legs or had completely lost one limb; some

shortened tails or not any tail at all. The genital and anal region of many was bitten and infected. Many had scabs over the back and the ears had been chewed.

At one year, the persisting suspect lesions were equally distributed between control and test groups of mice.

SUSPICION OF DEVELOPING TUMORS

Supplement	Mice with suspicion of developing tumors	Description of suspected tumor
1 percent L-MSG	0	None.
4 percent L-MSG	1	Small wart on chin.
1 percent DL-MSG	0	None.
4 percent DL-MSG	1	Projecting wart on chin.
1 percent L-GA	0	None.
4 percent L-GA	1	Questionable lump above genitals (condition from previous report unchanged).
Control	3	Scabbed areas (like lumps) external to body wall above the genitals.

It was concluded at the end of one year that no bona fide tumors had been observed in any living mouse. Such suggestive lesions as were seen failed to increase in size; many had disappeared on subsequent examination.

The sixth physical examination was made May 18–23, 1951 and a detailed description is recorded in the appendix of the condition and appearance at this time. The pugnacious habits persisted with the same general results described previously. In addition, some mice showed corneal opacities with scabbed and crusted lids from injuries sustained in fighting; some had an eye exudate of questionable origin. These conditions occurred in all groups including the control animals. There were numerous chewed ears, scabbed backs and faces, swollen legs, infected anal and genital areas, and amputations. Some were denuded of fur in large areas over the back or genitals. The possibility of tumor formation having its origin in traumatic irritation was not ignored.

Observations of lesions believed to be incipient tumors are tabulated from the data recorded at the sixth complete physical examination.

NUMBER OF MICE SHOWING SUSPECT LESIONS

Supplement	Original number in group	Number of mice showing suspect lesions	Description
1 percent L-MSG	100	2	Small lumps above genitals.
4 percent L-MSG	100	0	None.
1 percent DL-MSG	100	1	Small lump on ventral surface above genitals.
4 percent DL-MSG	100	2	Do.
1 percent L-GA	100	4	Each mouse had evidence of a small lump above genitals.
4 percent L-GA	100	2	Do.
Control	222	5	Each mouse had a small lump above the genitals.

One month later when these animals with suspect swellings were re-examined there was no indication in any one of the previously described hard lumps above the genitals. The lumps may have been liquefied and resorbed or they may have been due to injuries which were healing. Certainly none had increased in size nor were other lesions present in these mice. It was concluded that the swellings were not related to neoplastic activity and were not due to carcinogenic activity of the food supplements.

The seventh general physical examination was made October 2–3, 1951 after 664 test days at an average age of 692 days. At this time the mice were at the age when spontaneous tumors might have been expected, if any were to occur.

The incidence of swellings suggestive of incipient neoplasms are summarized below: (Does not include one animal on 4.0 percent *L*-glutamic acid supplemented diet with a small blood blister under right hind leg.)

INCIDENCE OF SWELLINGS SUGGESTIVE OF INCIPIENT NEOPLASMS

Supplement	Number of mice involved	Description of suspected incipient neoplasms
1 percent L–MSG	1	Small lump on lower genital region.
4 percent L–MSG	0	None.
1 percent DL–MSG	0	Do.
4 percent DL–MSG	2	1 mouse with lump near left testis. 1 mouse with lump on chest near right side.
1 percent L–GA	0	None.
4 percent L–GA	4	1 mouse with lump on upper part of chest. 1 mouse with lump near region of genitals. 1 mouse with lump near testis. 1 mouse with small lump on back (may be injury from fighting).
Control	10	8 with lumps in genital region (possibly the prostate gland). 1 mouse with lump on right side of genitals. 1 with possible internal tumor.

The suspected incipient neoplasms were of two general types. One type observed is described as a lump under the skin but external to the body wall in the region of the genitals, which had usually disappeared at subsequent examination, and if still present was not enlarged. The lump in some cases suggested trauma. Another possibility considered was that it may have been an involvement of the prostate gland, but when these animals came to autopsy, no abnormality was seen. The second type observed was described as a lump on the chest.

In order to explore the exact nature of these findings, four mice were autopsied, two from the 4.0 percent *L*–glutamic acid supplemented diet and two from the control group. Post-mortem examination showed no gross indication of tumor formation. The lump near the genitals on the mouse on the 4.0 percent *L*–glutamic acid supplemented diet was seen to be a small cyst containing a thick, yellow material. The lump was under the skin but external to the abdominal cavity.

The swelling on the mouse with an enlargement in the chest area on the 4.0 percent *L*–glutamic acid supplemented diet was an enlarged thyroid gland but was non-tumorous. The mouse on the control diet with a questionable visceral tumor presented no gross evidence of neoplasm at autopsy. The second mouse on the control diet sacrified for exploration of the small lump under the skin near the genitals presented a similar picture to the one described on the 4.0 percent *L*–glutamic acid supplemented diet. The lump under the skin near the genitals was yellow and hard. Adjacent to it was a yellow leaf-like structure later identified as the bulbo-urethral gland. A more detailed account of autopsy findings is presented in the section on pathological findings.

On November 21, 1951, the eighth complete physical examination was made. This represented observations after 715 test days and an average age of 743 days. They were extremely senile mice and the survivors had outlived the average life span by approximately 25 percent. In the detailed description (see appendix) the occupants of several cages had been combined into a single cage because of their decreased numbers.

The incidence of lesions suspected of being tumors at the eighth examination is presented below in tabular form:

LESIONS SUSPECTED OF BEING TUMORS

Supplement	Number of mice with suspect lesions	Description
1 percent L–MSG	0	None.
4 percent L–MSG	3	2 had lumps near genitals; 1 had internal lump (palpable in region of liver).
1 percent DL–MSG	0	None.
4 percent DL–MSG	2	1 mouse had lump on chest near throat; 1 had lump near genitals.
1 percent L–GA	0	None.
4 percent L–GA	0	Do.
Control	3	3 instances of lumps near the genital region.

Summarizing, then, the mice showed the results of injuries sustained in fighting, many of which resulted in death. There were, in some mice, swellings which invariably subsided and did not continue to increase in size. No *authenticated* tumors were seen during life in any animal.

The general physical condition of the mice at the pre-sacrifice inspection followed the same pattern as at previous examinations. Fighting had persisted and many had bald patches or scabbed areas over the body surface. A favorite site for attack had been the eyes. On some mice both eyes were completely closed because of scabbed or crusted lids; others had opacities of either or both eyes. The usual cases of chewed ears, broken but crookedly healed legs, and graying of fur were present but to the same extent in both test and control groups.

Parasites in the laboratory mouse are not uncommon and if the infestation in a colony is unchecked may result in many deaths. The most common parasites in the C–57 mouse are *Endamoeba muris*, *Giardia muris* and *Coccidia muris*. In our colony, no evidence of infestation by the former two were seen but a few animals showed signs of old coccidiosis when they came to autopsy. Because of our caging scheme, cross infestation was probably held to a minimum.

Hemorrhagic septicemia is sometimes seen in laboratory mice and is caused by an organism named *Erysipelothrix*. Two other common infectious diseases are pseudotuberculosis of rodents (*Corynebacterium pseudotuberculosus*) and arthritis of the mouse (*Streptobacillus moniliformis*) in which there is marked edema of the legs and tails. A few animals in our group showed the latter condition but in all but two cases it cleared spontaneously without specific treatment.

We must consider the possibility that the low-grade infectious process found at autopsy may have been mouse typhoid caused by Salmonella organisms (*Salmonella typhimurium* and *Salmonella enteriditis*). This disease is characterized by loss of normal activity. The affected mouse sits with its head hunched on its shoulders; its hair is ruffled and the coat gloss disappears. There is loss of appetite, conjunctivitis and increased respiration. Death usually occurs within one week. The post-mortem appearance shows enlargement of the liver and spleen with serosanguineous fluid in the peritoneal cavity. The lungs may be free from involvement or they may show pin-point hemorrhages with congestion and hyperemia. In our mice, the diagnosis of mouse typhoid is questionable in view of the long survival.

The low incidence of disease and of parasitic infestation is believed due to the quarantine period at the beginning of the study during which any animal found to be in less than perfect condition was eliminated and a substitution made in the actual test group.

MORTALITY DATA

From the numerical counts of each group which were made at the time of complete physical examinations, tables showing the population at approximately three months intervals were made to show survival ratios.

Because of heavy losses in the control group early in the experiment, replacements were added. However, due allowance for these was made in computing losses and in evaluating other data depending on the total number of animals represented.

Deaths were due to three main causes, namely: a) sacrifice, b) known trauma from fighting or accidental causes and c) unexplained causes.

Many unexplained deaths occurred as a result of injuries received from combat. Whenever possible, the aggressive mouse in a cage was isolated, but this was not usually possible until identification had been made by the loss of several cage mates. Another difficulty in determining accurate mortality rates was the trait of cannibalism among C-57 black mice. Frequently, the only evidence remaining of a deceased mouse was a small amount of skin and fur in the bottom tray or a few bone fragments. Occasionally, a mouse would disappear without trace. Deaths from fighting or of unexplained cause were recorded daily but the body, if found, was often so much eaten that a post-mortem examination was futile. A daily record was maintained of known casualties and injuries and their effect on the population record. (A few mice died of known accidental causes such as being crushed in feeder or cage door.)

Most varieties of laboratory mouse can be expected to live to the age of eighteen months; they have been known to live until three years of age but this is exceptional. After they reach the age of average life expectancy, they are physiologically senile and the clinical appearance and post-mortem condition of organs and

tissues will be consistent with their age. This was found to be true in our colony in all animals surviving more than fifteen months. No increase in alertness or better physical condition was seen in mice whose diets were supplemented with *L*-glutamic acid over the condition of other test mice or controls.

The survival rate during the first year of observation was approximately the same for all test groups, and for the control group. The maximum loss during this period occurred in the 1.0 percent *L*-glutamic acid group (24 percent). The smallest loss during this period was seen in the group receiving 1.0 percent DL-monosodium glutamate (8 percent). From that point to the end of the test period, the cumulative losses varied so that at one point, the greatest may have been in the control group and at another in any one of the test groups. The cumulative survival rates are shown in an accompanying table, and in complete tables entitled "Cumulative Population Record" in the Appendix. The final survival rates show variations between test groups and controls (from 13 percent in the 1.0 percent *L*-glutamic acid groups to 24 percent in the 4.0 percent *L*-glutamic acid groups and 24 percent in the control group). The average final survival figure for all test mice was 19 percent which should be compared with 24 percent for the control group. The total number of survivors (both test and control) after 733 days for all mice was 19.8 percent. In view of the large number of deaths from trauma, the difference between the survival rate for test mice and controls is apparently of minimal significance.

After one year, the number of deaths in all groups increased very rapidly (see Figure 1). At 664 test days, approximately one third of the original mice were living; 51 days later (715 test days) the number of survivors was reduced to less than one quarter of the original number. At no time did a large number of mice in a single group die within a short period either in test or control groups, which corroborates the findings in the collateral study of chronic toxicity in rats. In the latter six months of the test period many more deaths were due to natural causes than in the first eighteen months. The correlation between physical appearance, senile deaths and autopsy findings in the mice surviving to 733 test days[1] is very close. Certainly no deaths characterized by cachexia and emaciation, fever and any other signs associated with neoplastic growth were seen at any time. We feel confident that carcinogenicity of any of the supplements was not the major lethal factor.

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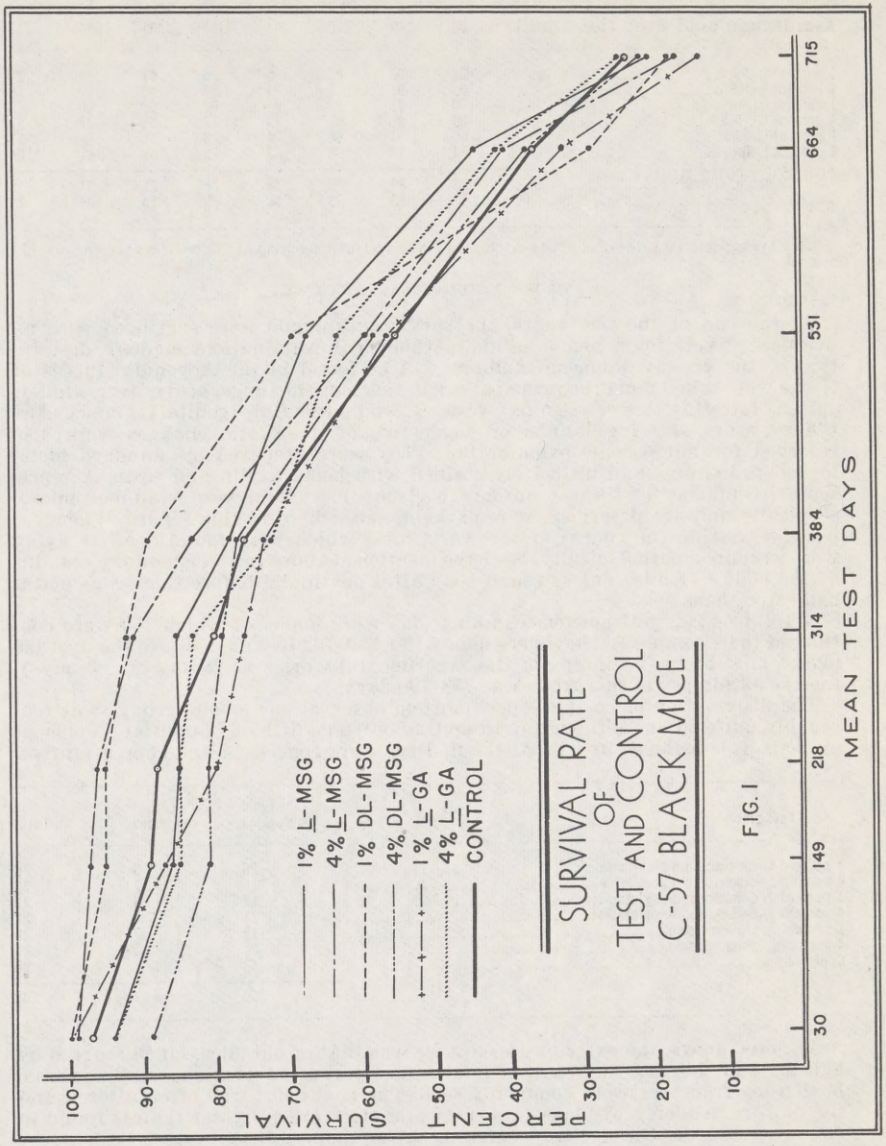
[1] To obtain age at death, 28 days should be added. This was the age at the beginning of the experiment.


SURVIVAL RATE
OF
TEST AND CONTROL
C-57 BLACK MICE
FIG. 1
PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
30
149
218
314
384
531
664
715
MEAN TEST DAYS
1% L-MSG
4% L-MSG
1% DL-MSG
4% DL-MSG
1% L-GA
4% L-GA
CONTROL

SURVIVAL RATES

[In percent]

Mean Test days	30	149	218	314	384	531	664	715
1 percent L-MSG	94	86	85	85	78	67	44	20
4 percent L-MSG	99	97	6	91	83	59	40	16
1 percent DL-MSG	100	95	95	92	89	69	28	17
4 percent DL-MSG	89	81	81	79	77	58	37	21
1 percent L-GA	100	87	80	76	73	56	32	13
4 percent L-GA	94	85	85	83	72	63	41	24
Average, all test mice	96	89	87	84	78	62	37	19
Control	97	89	88	80	76	55	36	24

Note: Average interval between complete examinations, 90 days; total survivors at 733 test days (all groups), 19.8 percent.

GROSS FINDINGS AT AUTOPSY

At the end of the two years, the surviving animals were sacrificed with an overdose of veterinary nembutal and pathological examinations made. A description of the grossly abnormal findings will be found in the Appendix. Pieces of tissue were taken from the principal organs such as the lungs, heart, liver, kidney, spleen, intestine, testes, seminal vesicles, and preputial (genital) glands. Any other tissues showing lesions or suggestive of neoplastic changes were also reserved for microscopic examination. They were prepared by standard histological procedures and ultimately stained with hematoxylin and eosin. A representative number of tissues, normal to visual inspection, were examined microscopically and are described, if remarkable, elsewhere in this report. Whenever possible, during the course of the work, mice which were found dead or dying were examined pathologically. We have mentioned above the fragmentary remains of the bodies of mice unless found soon after death and before their cage mates had eaten them.

A total of 202 post-mortem examinations were made, of which 159 were considered to be complete. They were done after 730–762 test days. Since the average age of mice at the beginning of the experimental work was 28 days (± 3 days), the age at autopsy of this group was 758–790 days.

The distribution of complete post-mortem observations among groups was reasonably uniform and although representing only one fifth of the initial number of animals, it is believed by us that the findings were consistent and representative.

Test group	Final autopsies	Earlier autopsies	Total
1 percent L-monosodium glutamate	20	5	25
4 percent L-monosodium glutamate	16	7	23
1 percent DL-monosodium glutamate	17	6	23
4 percent DL-monosodium glutamate	21	6	27
1 percent L-glutamic acid	13	7	20
4 percent L-glutamic acid	24	5	29
Control group	48	7	55
Total	159	43	202

As noted above, the exterior appearance was that of old mice, much scarred by fighting and showing the result of numerous injuries. Lacerations, abrasions and healed leg fractures were commonly seen. The coat color was often altered and the uniform leaden grey-black was rusty and often much lighter than is found in young specimens. On section, numerous gross abnormalities were seen, varying in severity from simple changes in the color of viscera to pneumonic consolidation in two control animals. Only a single verified tumor was seen, a lung adenoma occurring in an animal who had been fed on a diet supplemented with 1.0 percent DL-monosodium glutamate. The actual diagnosis was made by microscopic examination but an alteration in the consistency of the lung was apparent by visual inspection. The detailed observations are presented in the Appendix but a summary of the incidence of abnormalities other than minor changes in color is presented here to show the location with respect to organs involved and the number observed in each group of mice.

LOCATION OF GROSS POST MORTEM ABNORMALITIES

Supplement	Tissue involved	Total	External appearance	Total	Lesions suggestive of abnormal growth	Total
1 percent L-MSG	Liver 4, kidney 3, lung 1, testes 1.	9	Corneal opacity 3	3	None	0
4 percent L-MSG	Liver 1 (abscess), testes 2.	3	Corneal opacity 2	2	Liver abscess 1, genital swelling 2.	3
1 percent DL-MSG	Lung 1, spleen 1, seminal vesicles 2, preputial gland 1.	5		0	Genital swelling 1, growth on seminal vesicles 1.	2
4 percent DL-MSG	Lung 3, liver 1 (abscess), seminal vesicles 3, kidney 3, spleen 2, testes 3.	15		0	None	0
1 percent L-GA	Thyroid 2, lung 1, spleen 2, seminal vesicles 2, testes 1.	8		0	Enlarged thyroid 2, genital swelling 1.	3
4 percent L-GA	Kidney 1, spleen 2, seminal vesicles 2 (hypertrophy), testes 1, thyroid 1, preputial gland 1 (atrophy).	8	Corneal opacity 1	1	Thyroid cyst 1, peritoneal cyst 1, genital swelling 2.	4
Control	Thryoid 4, preputial gland 7, seminal vesicles 6, heart 1, lung 5 (consolidation in 2), kidney 1, liver 3, spleen 7.	34	Corneal opacity 4	4	Thyroid cyst 1, genital swelling 3, subcutaneous lump 1.	5

STATISTICAL DISTRIBUTION OF GROSS ABNORMALITIES

Incidence of gross abnormalities

(Average number lesions per animal × 100)

Controls	70.8
All animals	51.5
All test animals	43.4
Mean incidence	57.1
Deviation from mean incidence:	
All animals	−5.6
All test animals	−13.7
Controls	+13.7

In the following summaries, tissues and organs not specifically described were considered entirely normal and not remarkable.

COMMENT ON FINDINGS BY TEST GROUPS

1.0 percent L-monosodium glutamate group

The changes in the livers in this group worthy of note were chiefly paleness. The livers of two mice showed tiny yellow spots on the surface. The kidneys of two animals were small and shrunken. One spleen had a small, circumscribed, whitened area near the edge. One testis showed gross atrophy, apparently associated with senile changes and loss of function. Three animals showed corneal opacity, obviously traumatic in origin.

4.0 percent L-monosodium glutamate group

A liver abscess, partially healed and having much fibrous tissue at its margin was the chief gross abnormality seen in this group. One testis was herniated into the peritoneal cavity but did not appear otherwise damaged. The left testis in another animal was hemorrhagic but the right testis was unchanged. Corneal opacity was seen in two animals, but only one eye was involved.

1.0 percent DL-monosodium glutamate group

The general condition of this group was good. There were no corneal opacities. The lung of one animal showed calcification of one lobe; apparently the process followed an old pulmonary infection. The spleen in one individual was shrunken and appeared atrophic. Both seminal vesicles in one animal were definitely hy-

pertrophic and markedly enlarged. A palpable abdominal swelling (before the body cavity was opened) was seen to be a swelling of the preputial gland. Comment on this finding is made elsewhere in the report; this may have been the remains of an old abscess. Microscopic examination proved that it was not carcinogenic in nature but resembled an acute process which had subsided rapidly.

4.0 percent DL-monosodium glutamate

The animals in this group showed more gross pathological changes than did those in any other test group. Although the external appearance was good, on section it was found that the viscera of nine animals showed pathological lesions. Especially notable were the kidneys of three animals; one showed evidence of an old and widespread hemorrhage. Another showed gross enlargement and hypertrophy, being almost twice the normal size but also showing microscopic evidence of cystic changes and loss of function. A third kidney was hydronephrotic and showed cystic changes in the pelvis. The kidneys of several other animals were altered to a minor degree, chiefly in color, tending to be pale. These were not considered to be more than suggestive of a renal toxic effect manifested by the supplement at the 4.0 percent level. In three animals, the lungs were dark red, possibly hemorrhagic. One mouse showed the results of coccidial infection in the form of a liver abscess. The spleen of a single animal was hemorrhagic and in another animal, the spleen was enlarged. The seminal vesicles of two animals were enlarged and had been palpable during life as nodules. One seminal vesicle had herniated and another showed considerable atrophy. The testes of one mouse were enlarged and cystic; of another, definitely enlarged while a third mouse showed a scrotal hernia. The incidence of gross abnormalities in this group was greater than for any other test group (71.4 percent) and was slightly greater than that for the control group (70.8 percent).

1.0 percent L-glutamic acid group

The thyroid gland in two animals showed enlargement. One mouse showed a curious mottling of the lungs. Two animals showed abnormal spleens, one being enlarged and the other showing a mottled surface. In two animals, the seminal vesicles were altered in size, one being enlarged and the other reduced in size. The testes in one mouse were so shrunken as to be almost invisible. This was also true of the preputial gland in another mouse.

4.0 percent L-glutamic acid group

In one animal, both kidneys were pale and enlarged; two spleens showed the same type of mottling remarked upon in the 1.0 percent *L*-glutamic acid group. Two animals had enlargement of the seminal vesicles and one animal had an atrophic, shrunken testis. The preputial gland in another mouse in this group was atrophic but otherwise normal in appearance.

Control group

In the large group of grossly atypical organs seen in the control group, no changes were seen that had not been observed in other groups with the exception of a calcified mass lying freely in the abdominal cavity. In one animal, the thyroid was shrunken in size but in five others, it was enlarged to a noteworthy degree. In five animals, the preputial gland was enlarged and in two others it was shrunken. The subcutaneous lump noted in the summary table was found to be an apparently normal preputial gland which was surrounded by fibrous tissue and loosely attached to the skin of the lower abdomen. In five animals, the seminal vesicles were enlarged and in one they were small in size, presumably atrophic. A thyroid cyst was found in the neck of a single animal and in the same animal the myocardium appeared dark red in color but was otherwise normal. The lungs of five animals showed a generalized mottling. Two other animals showed moderately advanced consolidation of the lungs; pulmonary complications had not been evidenced by their clinical condition before death. Three livers were unusual in appearance, one being cystic to visual inspection, one granular in texture and one enlarged to a moderate degree. The kidneys of the group were essentially normal although in one animal, they appeared small in size. In seven animals, the spleen appeared changed in appearance. In three animals, the spleen was mottled; in three other animals, it was enlarged and in one animal, it was decreased in size. Corneal opacity was present in four animals in this group.

The chief and most significant observations were that the genital swellings noted in the living mice appeared in all cases noted to be enlargement of one of the genital glands or organs. None were found on microscopic examination

to show neoplastic changes. Throughout the course of the project, these swellings had been carefully observed and considered suggestive of abnormal growth. However, both gross and microscopic criteria proved that such was not true. A second observation which appears significant was the kidney pathology in animals fed on 4.0 percent DL-monosodium glutamate. It has been suggested that this isomer is toxic[1] to the kidney. In the light of these findings, it may warrant independent investigation. The high incidence of pathological changes in this group (71.4 percent) must be compared with an incidence of 51.5 percent in all animals, both test and control and again with an incidence of 43.2 percent in animals on supplemented diets. The incidence of lesions in 71.4 percent of the animals maintained on standard ration plus 4.0 percent DL-monosodium glutamate is very slightly higher than seen in the control group (70.8 percent). No other test group approached this level except that fed on 1.0 percent *L*-glutamic acid (61.5 percent). However, in view of the few animals in this latter group coming to complete autopsy (13) the number of gross abnormalities may weight the incidence unduly, particularly in light of the lower incidence of gross abnormalities in the 4.0 percent *L*-glutamic acid group which showed an incidence of gross abnormalities of only 33.3 percent.

Perhaps the most significant comparison is between all test animals and all control animals. Here, the incidence of abnormalities for control animals is 27.6 percent higher than for test animals. For all animals, the incidence of abnormalities is 8.3 percent higher than for the test animals but this may be a strongly weighted figure.

It would be possible to argue that maintaining mice (and presumably other animals) on diets supplemented by *L*-glutamic acid or its derivatives had a favorable effect in reducing pathological lesions. We are satisfied to conclude that no marked pathological changes are produced by feeding these diets over the life span of the animal.

The incidence of suggestive abnormal growths have little meaning since the suspect lesions were found to be non-carcinogenic, usually non-tumorous and probably non-neoplastic. It is of passing interest to note that the variation from the mean incidence of suspect lesions of three summary groups (i.e. all animals, all test animals, control animals) is ± 0.65 percent.

MICROSCOPIC EXAMINATIONS

The tissue specimens reserved at autopsy for microscopic examination were prepared by standard techniques and stained with hematoxylin and eosin. They were examined and screened by Dr. M. G. Gray of our staff and reviewed by Dr. Lloyd Fogg, our consultant in pathology. Approximately 800 sections were prepared from tissue material resulting from 159 + post-mortem examinations. Of these, 340 were included in the review by Dr. Fogg. A comment on atypical sections will be found in the Appendix. The appearance of all other sections was either not remarkable or consistent with the age of the animal.

The total number of sections examined was 798 of which 141 showed abnormalities chiefly associated with age. One section permitted the diagnosis of "benign adenoma of the lung" in an animal fed on 1.0 percent DL-monosodium glutamate. Several showed abscess formation but were free from neoplastic changes.

In selecting tissues for microscopic examination a representative number were taken from each group. In addition, all tissues which appeared grossly abnormal were prepared for microscopic examination. The organs represented were: trachea, bronchi, lungs, heart, kidneys, spleen, pancreas, submaxillary gland, thyroid, stomach, liver, intestine, skin.

1.0 percent L-Monosodium Glutamate Group

Number sections examined	76
Number showing abnormalities	30
Liver	4
Kidney	5
Lungs	9
Intestine	2
Stomach	1
Spleen	8
Testes	1

[1] A higher LD_{50} in rats was found for DL-monosodium glutamate than for *L*-monosodium glutamate or *L*-glutamic acid.

Liver: Foci of inflamation around central veins; foci of necrotizing parenchyma cells. Inflammation varies in degree from mild cellular infiltration to necrosis.

Kidney: Interstitial inflammation; fibrosis of glomeruli and tubular atrophy. Focal necrosis in renal pelvis. Cortical tubules involved in one section. In another section, chronic interstitial nephritis involving glomeruli and tubules.

Lung: Inflammatory foci around bronchioles; lymphocytic infiltration. Focal fibrosis of parenchyme. Occasional mild congestion. Massive abscess in one section.

Intestine: Polyp formation in colon, focal corrosion of epithelium.

Stomach: Hyperkeratosis with hyperplasia of underlying stratum germinativum.

Spleen: Congestion, with disorganization of red and white pulp. Senile appearance.

Testes: Reduced germinal population; consistent with non-functional, senile organ.

4.0 percent L-Monosodium Glutamate Group

Number sections examined	84
Number showing abnormalities	22
Liver	3
Kidney	5
Spleen	5
Lungs	4
Testes	4
Genital gland	1

Liver: Accumulation of blood cells around central vein with foci of cellular necrosis. General distribution of hyperchromatic cells with trace of hepatitis (3 sections).

Kidney: Some interstitial inflammation with focal glomerular fibrosis. Trace of focal glomerulo-nephritis (4 sections). Exudative infiltration of intertubular connective tissue with focal atrophy of tubular cells. Inflammatory infiltration by lymphocytes.

Spleen: Mild congestion; disorganized pulp; typical of senile spleen. Thickened trabeculae (5 sections).

Lung: Focal fibrosis with reduction in number of expanded alveoli. Occasional focal edema. Collection of lymphocytes around bronchioles.

Testes: Germinal cells reduced in number (4 sections).

GENERAL COMPARISON OF MICROSCOPIC FINDINGS L-MONOSODIUM GLUTAMATE GROUP (751 TEST-DAYS)

	1 percent	4 percent
Liver	Sections about equally divided between those showing no pathology and those showing traces of hepatitis as evidenced by foci of inflammatory cells around veins which also affect neighboring parenchymal cells.	Same as 1 percent group.
Kidney	Sections vary from those showing no pathology to extensive focal areas indicating interstitial inflammation, the effect extending to glomerular fibrosis and atrophy of tubules. Some focal necrosis in renal pelvis.	All sections show some focal interstitial inflammatory indications involving nuclear toxicity in glomeruli, or fibrosis. In 1 case, there were foci of atrophied tubular cells, some dilated tubular areas which in a few foci showed casts. General mild chronic nephritis.
Lung	Most sections showed pinpoint areas of inflammation around bronchi and bronchioles as evidenced by infiltration of lymphocytes. Focal fibrosis of parenchyma. One lung has an abscess.	Only 1 animal showed pinpoint areas of inflammation. Others showed focal fibrosis, traces of edema or reduction in number of expanded alveoli as might be expected in lungs of aged animals.
Spleen	All spleens show a mild congestion with a general lack of organization of red and white pulp. No actual pathology.	2 normal animals. Remainder as in 1 percent group.
Heart	Normal	Normal.
Genital glands	No pathology	1 showed focal abscess.
Testes	Reduced population of germinal cells as might be expected in senile organ. No pathology.	Same as in 1 percent.
Intestinal tract	1 case of focal corrosion of epithelium, otherwise no pathology. 1 case of polyp formation in colon. 1 case of hyperkeratosis with concomitant hyperplasia of underlying stratum germinativum.	No pathology.

1.0 percent DL-Monosodium Glutamate Group

Number sections examined	105
Number showing abnormalities	22
Liver	4
Kidney	6
Lungs	5
Spleen	4
Testes	3

Liver: Pinpoint foci of inflammation around some central veins, involving necrosis of parenchyma.

Kidney: Pinpoint areas of interstitial inflammation in cortex evidenced by accumulations of lymphocytes and degenerating tubule cells. Many fibrotic glomeruli.

Lung: Reduction in number of alveoli with slight focal fibrosis. Peribronchiolar inflammation.

Spleen: Mild congestion. Red and white pulp not clearly demarcated. Trabeculae enlarged.

Testes: Reduction in number of germinal cells in tubules.

4.0 percent DL-Monosodium Glutamate Group

Number sections examined	103
Number showing abnormalities	25
Liver	4
Kidney	7
Lung	5
Spleen	5
Testes	4

Liver: Pinpoint areas of inflammation around central vein, hepatic vein and arteries.

Kidney: Foci of interstitial inflammatory reactions, mostly collections of lymphocytes. Some necrosis in renal pelvis.

Lung: Focal fibrosis; reduced number of alveolar sacs. Peribronchiolar inflammation. Some fibrosis.

Spleen: Mild congestion with disorganization of red and white pulp.

Testes: Reduced population of germinal cells and tubules.

GENERAL COMPARISON OF MICROSCOPIC FINDINGS DL-MONOSODIUM GLUTAMATE GROUP (720–751 TEST-DAYS

	1.0 percent	4.0 percent
Liver	Pinpoint foci of inflammation around central veins; in these areas there is a trace of necrosis of parenchyma. Nuclei stain intensely.	Same as in 1.0 percent.
Lung	Some focal fibrosis with reduced number of alveoli, present in all animals. In 1 section there are areas of inflammation around bronchioles as evidenced by accumulation of lymphocytes. In another case, a lung tumor, benign.	All slides show inflammatory changes around bronchiloes, in some cases, extensive. Focal fibrosis, reduced number of alveolar sacs. This is suggestive of aged lung.
Kidney	In all sections there are pinpoint areas of interstitial inflammation in cortex, involving glomeruli and tubules. Also present in renal pelvis in some sections.	Pinpoint foci of interstitial inflammatory reactions, mostly collection of lymphocytes. Cases vary from above to involvement of extensive areas in cortex involving tubules and connective tissue but not glomeruli. 1 case of a concretion in pelvis.
Spleen	Mild congestion. Red and white pulp not clearly demarcated. Trabeculae thickened. Suggests aged spleen in every case.	Same as 1 percent.
Skin	Normal	Normal.
Submaxillary gland	do	Do.
Genital glands	do	Do.
Testes	Reduction in number of germinal cells in tubules, as in aged or senile testis; no pathology.	Same as in 1 percent.
Heart	Normal	Normal.
Pancreas	do	Do.
Digestive tract	do	Do.
Thyroid	do	Do
Trachea	do	Do.

1.0 percent L-Glutamic Acid Group

Number sections examined	105
Number showing abnormalities	32
Lung	6
Spleen	9
Liver	5
Kidney	4
Seminal vesicles	3
Intestine	2
Testes	3

Lung: Inflammation of bronchi; thickening of alveolar sacs. Fibrosis.
Spleen: Mild congestion.
Liver: Perivascular inflammation; hyperchromatism and binucleated cells.
Kidney: Mild pelvic inflammation. Fibrosis of glomeruli.
Seminal Vesicles: Epithelial disorganization.
Intestines: Focal destruction of epithelium.
Testes: Senile.

4.0 percent L-Glutamic Acid Group

Number sections examined	118
Number showing abnormalities	16
Lung	7
Spleen	4
Liver	2
Kidney	1
Testes	1
Seminal vesicles	1

Lung: Bronchiolar inflammation; fibrosis, focal edema.
Spleen: Focal abscess.
Liver: Hyperchromatic nuclei.
Kidney: Necrosis in pelvic tubule cells.
Testes: Sparse germinal cells.
Seminal vesicles: Areas of corroded epithelium.

GENERAL COMPARISON OF MICROSCOPIC FINDINGS L-GLUTAMIC ACID GROUP (752 TEST DAYS)

	1.0 percent	4.0 percent
Lung	Nearly every slide showed traces of inflammation around bronchi or bronchioles. Some fibrosis of walls of parenchyma.	Every section showed some indication of inflammation around bronchi or bronchioles varying from slight to extensive.
Submaxillary gland	Normal	Normal.
Spleen	All sections show a mild congestion. General disorganization of red and white pulp. No obvious pathology. Interpreted as indication of senility.	Varied from normal, through mild congestion to 1 case with an abscess.
Liver	Frequent binucleate cells. General slight hyperchromatism of nuclei. No obvious pathology.	Slight hyperchromatism to normal.
Kidney	Only traces of inflammation such as collection of lymphocytes around connective tissue in pelvis.	Normal. 1 slide showed slight necrosis in tubule of pelvis.
Seminal vesicles	Foci of corroded epithelium	Normal to 1 case of corroded epithelium.
Intestines	do	Normal.
Testes	Germinal tubules only sparsely populated indicating senility.	Terminal tubules sparsely populated; senile.
Heart	Normal	Normal.

Control Group

Number sections examined	207
Number showing abnormalities	45
Liver	9
Lung	11
Kidney	7
Skin	1
Bladder	1
Testes	6
Spleen	8
Seminal vesicle	2

Liver: Perivascular lymphocytic infiltration; some hyperchromatism. One section shows general necrosis.

Lung: Peribronchiolar lymphocytic infiltration. Reduced number of alveoli. Inflammation of lymph nodes around bronchus.

Kidney: Interstitial inflammation; scattered glomerular fibrosis.

Skin: Cyst in sub-cutis.

Bladder: Lymphocytic infiltration in epithelium.

Seminal Vesicles: Some semi-solid particles in lumen. Foci of corrosion in epithelium.

Spleen: Mild congestion. Red and white pulp not clear demarcated. Some thickening of trabeculae.

SUMMARY OF MICROSCOPIC FINDINGS—CONTROL GROUP

Liver: In general, sections show pinpoints of accumulation of lymphocytes around veins. One section shows necrosis of one lobe.

Lung: Generally mild inflammation as indicated by lymphocyte collections around bronchioles. Focal fibrosis and reduced number of alveolar sacs, typical of aged lung.

Kidney: Some interstitial areas of inflammation as indicated by presence of lymphocytes. Extent of effect varies from:

(a) Rarely affecting glomeruli.
(b) Rare fibrotic glomeruli.
(c) Some necrosis in distal medullary tubules, otherwise negative.
(d) Rare dilated tubules.

Suggests a trace of chronic nephritis.

Spleen: Mild congestion. Red and white pulp not clearly demarcated. Some thickening of trabeculae. Generally suggests aged spleens.

Seminal Vesicles: Essentially normal. One case of casts and another of a focus of corroded epithelium.

Submaxillary Gland: Normal.

Heart: Normal.

Testes: Germinal cells reduced in number. Otherwise no pathology. Typical of senile testes.

Skin: Normal.

Bladder: Normal. Focus of infection in epithelial lining in one section.

Thyroid: Normal.

DISTRIBUTION OF ABNORMALITIES

Supplement	Number of sections examined	Number showing abnormalities	Liver	Kidney	Lungs	Spleen	Testes	Intestine	Stomach	Genital gland	Seminal vesicles	Skin	Bladder
1 percent L–MSG	76	30	4.0	5.0	9	8	1.0	2	1		1	1	1
4 percent L–MSG	84	22	3.0	5.0	4	5	4.0			1			
1 percent DL–MSG	105	22	4.0	6.0	5	4	3.0						
4 percent DL–MSG	103	25	4.0	7.0	5	5	4.0						
1 percent L–GA	105	32	5.0	4.0	6	9	3.0	2			3		
4 percent L–GA	118	16	2.0	1.0	7	4	1.0				1		
Average for test animals		25	3.7	4.7	6	6	2.6	(1)	(1)	(1)	(1)	(1)	(1)
Control	207	45	9.0	7.0	11	8	6.0				2	1	1
Total	798												

[1] Less than 1.0.

The absence of microscopic evidence of tumor formation is obviously the most significant observation which can be made. With absence of gross evidence of tumor growth, we can safely conclude that under the conditions of this experimental study that the carcinogenicity of any one of the supplements is zero.

In the control animals there was microscopic evidence of lowgrade infection in the liver, lungs and kidney which is not unusual in aged animals. In isolated cases, corroded epithelium of genital glands or a focus of infection in the bladder was noted. As isolated cases, it can be concluded that they represent nonspecific etiology, having minimal significance.

In general, no marked pathology was found in any group of mice. The animals fed with DL-monosodium glutamate showed no clear-cut differences from the controls. There was a suggestion that the low-grade infection noted in the controls showed a marginal intensification in these animals which can not be ascribed even indirectly to specific supplements. There is no evidence that potential carcinogenesis can be related to it.

The mice fed with *L*-monosodium glutamate, likewise, did not slow clear-cut differences from the controls. The kidneys reveal more extensive, mild chronic nephritis than did those of the control group with no distinction between the 1.0 percent or 4.0 percent concentrations fed. No evidence was found suggesting carcinogenesis related to this supplement.

The livers and kidneys of mice fed on a supplement of *L*-glutamic acid showed slighly less evidence of inflammation. Foci of corroded epithelium were noted in the seminal vesicles and intestines, but it is not clear that this could be traced to the specific diet. In general, there existed no significant microscopic difference between this group and any other.

On the basis of the microscopic data, we conclude:

1) There is no evidence of carcinogenicity possessed by the supplements tested.

2) There is evidence of a low-grade inflammatory process in all animals, probably related to their age.

3) The supplements did not produce any characteristic pathology. Such microscopic alterations as were found are consistent with the age of the animals.

DISCUSSION

With one exception, a benign lung adenoma in a mouse fed on DL–monosodium glutamate, no tumors were observed in any mouse included in the colony, either test or control. To have concluded that *L*-monosodium glutamate, DL-monosodium glutamate or *L*-glutamic acid possessed carcinogenic properties, it would have been necessary to have observed abnormal neoplastic tissue activity in a significant percentage of the total group.

The absence of specific pathological lesions other than those consistent with the advanced age of the subject mice, (which at the termination of the experimental work represented from 90–120 percent of the average life expectancy for the C–57 black mouse) makes it possible to conclude that under the conditions of this investigation the supplements fed do not possess toxic properties, and that they do not cause cumulative effects resulting in organic tissue damage when fed for almost the entire life span. The failure to find tumors, with the single exception noted, leads to a conclusion that the supplements are not carcinogenic when fed as a part of the normal dietary intake throughout life.

The majority of pathological examinations were made on a definitely aged group of animals. Because the major objective was the identification of abnormal growths of carcinogenic origin, the changes which occurred as a part of the aging process did not confuse the total picture. A secondary and somewhat adventitious objective was to observe general toxicological phenomena which might have been related to the supplements fed during the two-year period.

In an investigation of this type, certain limitations are inherent. Of these we are aware, and have given due consideration to them in evaluating our findings. The outstanding limitation is the high mortality rate, resulting chiefly from the combative behavior of the strain of mice used. The reasonably uniform distribution of deaths at various intervals among the test groups would seem to demonstrate that deaths are less particularly related to the supplements fed than to the behavior of the C–57 black mouse. Fortunately, the number of animals used was sufficiently large so that a representative number survived to the end of the experimental work.

SUMMARY

An investigation of the potential carcinogenicity of *L*-monosodium glutamate, DL-monosodium glutamate and *L*-glutamic acid has been carried out for a two-year period using the C–57 black mouse. No tumors were authenticated with the exception of a single benign adenoma of the lung occurring in a mouse fed DL-monosodium glutamate. This diagnosis was not made during life, but was based solely on the microscopic appearance of the lung tissue. Such organic tissue changes as were observed were consistent with the advanced age of the subject mice at the termination of the experimental work. There were no significant differences between the appearance and behavior during life of test and control groups, and the appearance of the tissues after sacrifice was essentially the same for both test and control animals. It is our opinion that no evidence has been derived in the investigation reported above that any of the test materials fed for a period representing approximately 90–120 percent of the average life span of the mouse strain used, possess carcinogenic properties.

APPENDIX

Tables Covering Detailed Physical Examinations

TABLE I.—1ST COMPLETE PHYSICAL EXAMINATION OF C–57 MICE: 30 TEST-DAYS, 58 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L-MSG	19	Most of the animals had tails which were bitten; some had scabs on their backs from injuries sutained from fighting.	No evidence.
2	do	20	Condition very good	Do.
3	do	20	do	Do.
4	do	19	Some lost tails bitten off in fighting	Do.
5	do	16	Only 1 mouse in cage whose tail or back was not bitten.	Do.
6	4 L-MSG	20	Condition very good	Do.
7	do	20	do	Do.
8	do	20	do	Do.
9	do	20	do	Do.
10	do	19	do	Do.
11	1 DL-MSG	20	do	Do.
12	do	20	do	Do.
13	do	20	do	Do.
14	do	20	do	Do.
15	do	20	do	Do.
16	DL-MSG	20	do	Do.
17	do	18	A number of mice had swollen feet and legs from injuries sustained in fighting.	Do.
18	do	13	Same as cage 17	Do.
19	do	18	Condition very good	Do.
20	do	20	do	Do.
21	1 L-GA	20	do	Do.
22	do	20	do	Do.
23	do	20	do	Do.
24	do	20	do	Do.
25	do	20	do	Do.
26	4 L-GA	20	do	Do.
27	do	19	do	Do.
28	do	19	do	Do.
29	do	19	do	Do.
30	do	17	do	Do.
31	Control	20	do	Do.
32	do	20	do	Do.
33	do	20	do	Do.
34	do	20	do	Do.
35	do	20	do	Do.
36	do	20	do	Do.
37	do	20	do	Do.
38	do	20	do	Do.
39	do	20	do	Do.
40	do	20	do	Do.

TABLE II.—2D COMPLETE PHYSICAL EXAMINATION OF C–57 MICE: 146–152 TEST-DAYS, 174–180 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L–MSG	17	Very good	No evidence.
2	do	17	do	Do.
3	do	19	do	Do.
4	do	18	do	Do.
5	do	14	do	Do.
6	4 L–MSG	20	do	Do.
7	do	19	do	Do.
8	do	20	do	Do.
9	do	19	do	Do.
10	do	19	do	Do.
11	1 DL–MSG	19	do	Do.
12	do	19	1 mouse with a sore on foot; one mouse with a sore on back.	Do.
13	do	19	Very good	Do.
14	do	19	1 mouse with faulty dentition; teeth were clipped.	Do.
15	do	19	Very good	Do.
16	4 DL–MSG	19	do	Do.
[1] 17	do	11	do	Do.
18	do	6	do	Do.
19	do	16	do	Do.
20	do	20	do	Do.
21	1 L–GA	9	do	Do.
22	do	20	do	Do.
23	do	19	do	Do.
24	do	19	do	Do.
25	do	19	do	Do.
26	4 LGA	18	Some with badly bitten tails, one with scarred genital area.	Do.
27	do	18	Very good	Do.
28	do	17	do	1 mouse with questionable lump in genital region. Isolated for further examination.
29	do	19	do	No evidence.
30	do	13	Some mice with sores on back which were healing.	Do.
31	Control	20	Very good	Do.
32	do	20	do	Do.
33	do	20	do	Do.
34	do	20	do	Do.
35	do	20	do	Do.
36	do	20	do	Do.
37	do	20	do	Do.
38	do	20	do	Do.
39	do	20	do	Do.
40	do	20	do	Do.

[1] A total of 9 animals from cages 17 and 18 were placed in a separate cage because of badly swollen feet sustained in fighting.

TABLE III.—3D COMPLETE PHYSICAL EXAMINATION OF C-57 MICE: 215-220 TEST-DAYS, 243-248 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L-MSG	17	Normal	1 animal had a small lump on ventral surface near left hind quarter.
2	do	16	Normal in appearance	No evidence.
3	do	19	do	Do.
4	do	19	1 animal with no leg	Do.
5	do	13	Normal in appearance	Do.
6	4 L-MSG	20	do	Do.
7	do	18	do	Do.
8	do	20	do	Do.
9	do	19	do	Do.
10	do	19	do	1 animal had a small lump on ventral surface, near right hind quarter.
11	1 DL-MSG	19	do	No evidence.
12	do	19	1 animal had swollen legs from fighting; one animal with injured, scabbed back.	Do.
13	do	19	Normal in appearance	Do.
14	do	19	do	Do.
15	do	19	do	Do.
16	4 DL-MSG	19	do	Do.
17	do	14	do	Do.
18	do	12	do	Do.
19	do	16	do	Do.
20	do	20	do	Do.
21	1 L-GA	7	do	Do.
22	do	20	do	Do.
23	do	18	do	Do.
24	do	15	do	1 animal had a small lump on dorsal surface near shoulder.
25	do	19	do	No evidence.
26	4 L-GA	18	do	Do.
27	do	18	do	1 animal had a small lump on dorsal surface.
28	do	17	do	No evidence.
29	do	19	do	Do.
30	do	13	do	1 animal had a small lump on ventral surface in lower abdominal region, area denuded.
31	Control	20	do	No evidence.
32	do	20	do	Do.
33	do	20	do	Do.
34	do	20	do	Do.
35	do	19	do	Do.
36	do	19	do	Do.
37	do	19	1 animal accidentally killed by being crushed in feeder.	1 animal had a small lump in the left genital region under skin.
38	do	20	Normal in appearance	No evidence.
39	do	20	do	Do.
40	do	20	do	Do.

TABLE IV.—4TH COMPLETE PHYSICAL EXAMINATION OF C-57 MICE: 286-342 TEST-DAYS, 314-370 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L-MSG	17	Normal in appearance	No evidence.
2	do	15	do	Do.
3	do	20	do	Do.
4	do	18	do	Do.
5	do	14	do	Do.
6	4 L-MSG	18	do	Do.
7	do	17	do	Do.
8	do	20	do	Do.
9	do	17	do	Do.
10	do	18	do	Do.
11	1 DL-MSG	18	do	Do.
12	do	19	1 animal had a swollen, infected leg; 1 animal had a denuded back and infected tail.	
13	do	18	Normal in appearance	1 mouse had a small hard lump under skin near penis; appeared to be area of infection.
14	do	18	do	No evidence.
15	4 DL-MSG	19	do	Do.
16	do	19	do	Do.
17	do	12	do	Do.
18	do	12	do	Do.
19	do	16	do	Do.
20	do	20	do	1 animal had a wart on chin.
21	1 L-GA	6	do	No evidence.
22	do	19	do	Do.
23	do	17	do	Do.
24	do	14	do	Do.
25	do	19	do	Do.
26	4 L-GA	17	do	Do.
27	do	18	do	Do.
28	do	17	do	Do
29	do	18	do	Do.
30	do	13	1 animal was without a tail; others were normal in appearance.	2 animals have a lump under the skin on ventral surface near genitals, may be injury or infection from fighting.
31	Control	20	Normal in appearance	No evidence.
32	do	16	do	Do.
33	do	19	do	1 animal with lump on ventral surface above penis, appeared to be a scab.
34	do	17	do	Similar to above.
35	do	17	do	No evidence.
36	do	18	do	Do.
37	do	18	Mouse previously with lump near genitals showed no evidence of any mass; surface scab with no palpable lump.	Do.
38	do	19	Normal in appearance	Do.
39	do	19	do	Do.
40	do	16	do	Do.

TABLE V.—5TH COMPLETE PHYSICAL EXAMINATIONS OF C–57 MICE: 370–403 TEST-DAYS, 398–431 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L–MSG	16	2 mice showed graying of fur	No evidence.
2	do	11	2 with swollen hind legs, 1 with face badly bitten.	Do.
3	do	19	1 with crookedly healed broken leg; 2 or 3 with noticeable graying of fur.	Do.
4	do	17	1 with healed stump (no leg); 3 or 4 with noticeable graying of fur.	Do.
5	do	14	Many badly scarred on back and face from fighting; 2 showed some graying of fur.	Do.
6	4 L–MSG	18	1 with noticeable graying of fur	Do.
7	do	14	Normal in appearance	Do.
8	do	18	1 mouse very thin	1 mouse had small wart on chin.
9	do	15	Normal in appearance	No evidence.
10	do	17	1 mouse badly scarred on face; 1 mouse with noticeable graying of fur.	Do.
11	1 DL MSG	18	1 mouse with broken leg which mended crookedly.	Do.
12	do	16	2 mice with swollen hind legs	1 mouse with small wart on chin.
13	do	18	1 animal very noticeably gray of fur	No evidence.
14	do	18	2 mice with infected areas near genitals.	Do.
15	do	19	1 badly bitten about face and body, and with swollen, infected anus.	Do.
16	4 DL–MSG	18	Normal in appearance	Do.
17	do	12	2 mice with swo len, infected areas around anus; 2 mice with scarred backs	Do.
18	do	12	1 with swollen feet; 1 with swollen feet which were constricted and appear gangrenous; 1 with only a stump for the hind leg; 4 scarred on dorsal region.	Do.
19	do	16	1 mouse noticeably gray and many had 1 or both ears bitten.	Do.
20	do	19	1 mouse noticeably gray on the ventral surface; 1 mouse was very fat, stomach appeared to protrude.	1 mouse, as previously reported, had a projecting wart on chin.
21	1 L–GA	6	1 mouse with bitten anus; 1 with scabbed back, regrowth of hair was white; 1 graying on ventral surface.	No evidence.
22	do	16	1 with bitten arm, 1 graying slightly; 1 graying over ventral surface and head; 2 with scabbed backs.	Do.
23	do	17	Normal in appearance	Do.
24	do	14	do	Do
25	do	19	3 or 4 mice with chewed ears	Do.
26	4 L–GA	13	1 mouse very gray; 2 mice with base of tail bitten from which there was frank bleeding.	Do.
27	do	18	Normal in appearance	No evidence of lump on dorsal surface under skin on mouse previously reported to have swelling.
28	do	13	do	No evidence.
29	do	17	2 mice with swollen feet; 2 with badly bitten faces; 1 with a short tail which had been amputated in fighting.	Do.
30	do	11	1 mouse noticeably gray; hind legs badly bitten; 1 mouse with legs and back badly bitten. 3 others with scarred backs (1 of these had a short tail and swollen feet).	Mouse which on previous examination had a lump above the penis was unchanged.
31	Control	17	Normal in appearance	No evidence.
32	do	14	3 with bitten faces; 1 was noticeably gray.	Do.
33	do	19	1 mouse very thin, appeared moribund; 1 mouse with injured genitals.	1 mouse had a lump on ventral surface above genitals.
34	do	17	Normal in appearance	Condition of mouse with lump on right ventral surface near genitals which appeared to be a scab at previous examination, unchanged.

TABLE V.—5TH COMPLETE PHYSICAL EXAMINATIONS OF C–57 MICE: 370–403 TEST-DAYS 398–431 DAYS OF AGE—Continued

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
35	Control	17	Normal in appearance	No evidence.
36	do	18	1 mouse graying; 1 mouse with bitten tail.	Do.
37	do	18	Normal in appearance	No evidence of previously reported lump in 1 mouse.
38	do	18	do	No evidence.
39	do	17	do	Do.
40	do	15	1 mouse noticeably gray and very thin; 1 very emaciated; several showed moderate graying; 1 with bitten anus; 1 with bitten face; 1 with bitten swollen leg.	1 mouse with 2 scabbed lumps above the genitals; appear more like injuries than tumor.

TABLE VI.—6TH COMPLETE PHYSICAL EXAMINATION OF C–57 MICE: 529–534 TEST DAYS, 557–562 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L–msg	13	Mice healthy in appearance; 1 was noticeably gray; 2 others graying.	No evidence.
2	do	12	1 with scabbed back and face; 1 with bitten feet; 1 with tail falling off, very thin; 1 with scabbed back; 1 with discharge from eye.	2 mice with small lumps above penis.
3	do	14	1 with inflamed area around anus; 1 with healed leg stump; 1 with opaque eye and scabbed face; 1 very gray; several others show graying of fur.	No evidence.
4	do	16	Almost every mouse had a chewed ear, scabbed back and face; 1 had an open wound on neck and cheeks were swollen; 1 with a leg stump; 1 with no hind feet; 1 with both eyes scabbed.	1 mouse was bloated in appearance on lower half of body; at autopsy the peritoneal cavity was filled with a watery fluid. When drained off, ascites reduced; no evidence of abnormal growth internally.
5	do	11	1 with opaque eye; 3 mice had both eyes closed from scabs on lids; several lost hair in areas on the back and had scabbed backs and faces; 2 with swollen anal regions.	No evidence.
6	4 H–MSG	13	1 very gray; 1 very thin; 2 with scabbed faces and infected eyes; 2 with denuded backs.	Do.
7	do	9	General condition is good; 1 mouse has amputated tail; 2 have scabbed faces.	Do.
8	do	11	5 mice had chewed ears; 1 mouse with scabbed closed eyelids.	Do.
9	do	12	General condition was good; 2 mice with scabbed eyelids.	Do.
10	do	13	General condition was good; one mouse graying on upper half of body.	Do.
11	1 DL–MSG	12	General condition was good; 1 mouse with broken but crookedly healed leg; 1 mouse with infected leg.	Do.
12	do	14	1 with swollen hind legs; 1 with legs and anal region denuded and infected.	1 with small wart on face.
13	do	16	General overall condition was good	1 mouse with small lump visible and palpable on the ventral surface.
14	do	13	General condition was good; several mice were large and fat.	No evidence.
15	do	13	Several with chewed ears and scabbed faces; 1 graying, with scabbed eyelids. 1 mouse bleeding around eyelids and face.	Do.
16	4 percent DL–MSG.	13	Scabbed faces and eyelids; 1 mouse with corneal opacity in both eyes.	Do.
17	do	8	1 with swollen legs and loss of hair on dorsal surface and anal region.	1 mouse with small palpable lump above the genitals.
18	do	9	Several mice with scabbed, denuded backs and chewed ears; 2 with swollen feet; 1 with missing hind limb.	Do.
19	do	15	1 with denuded, infected face; 5 with 1 ear completely chewed off: 1 very gray of fur.	No evidence.
20	do	13	3 with scabbed faces and infected eyes.	1 mouse with small wart on chin.
21	1 percent L–GA	5	1 mouse with prolapsed rectum and extended penis; 1 had a corneal opacity of the left eye; 1 with slightly chewed ear.	No evidence.

TABLE VI.—5TH COMPLETE PHYSICAL EXAMINATIONS OF C-57 MICE: 523–534 TEST-DAYS 557–562 DAYS OF AGE—Continued

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
22	1 percent L-GA	8	General condition was good; 1 mouse with short tail.	1 mouse with a small lump near genitals.
23	do	12	3 animals had scabs over the right eye; 1 mouse with a short tail; general condition of others was good.	1 mouse with a small lump above genitals; 1 very thin mouse with large lump on right side of genitals.
24	do	9	1 mouse had an open wound on back; 1 mouse with chewed ears; 1 very thin. General condition of others was good.	No evidence.
25	do	15	6 mice with either 1 or both ears completely chewed off; 1 with broken leg which healed crookedly.	1 mouse with a small lump on the left genitals.
26	4 L-GA	13	Several had scarred backs; 1 with crookedly healed, broken leg; 1 very gray; 1 with reddened area near genitals (blood blister).	No evidence.
27	do	14	1 mouse with scarred back; general condition of others was good.	1 mouse with small lump near genitals.
28	do	12	3 mice with swollen genital and anal regions; 1 turning gray of fur.	No evidence.
29	do	15	3 mice with infected, discharging eyes; 2 with chewed ears; 1 with crusted eyes and swollen leg.	Do.
30	do	9	6 mice with scarred backs; 1 with closed eye; 1 with swelling around anus and genitals.	1 mouse graying with lump above genitals.
31	Control	14	2 mice with scarred backs; 1 with swollen front leg; 1 with crookedly healed broken leg.	No evidence.
32	do	11	2 mice with scarred faces and infected eyes which were discharging pus; 1 mouse very thin and gray of fur.	1 mouse with large lump near genitals.
33	do	11	2 mice with scarred faces and infected eyes.	No evidence.
34	do	9	1 with broken leg which healed crookedly.	1 mouse with small lump on ventral surface near genitals.
35	do	12	1 mouse with scarred denuded area around genitals; 3 with scabbed faces.	No evidence.
36	do	9	1 mouse graying: 4 were denuded in face and with infected eyes; 1 had opacities of both eyes; 1 with broken leg.	Do.
37	do	15	1 very thin and graying; 1 very thin but in good condition; 1 with scabbed face and distended genitals.	Do.
38	do	14	5 mice with scabbed faces; 5 with no right ear; 2 mice were graying; 1 with broken leg; 1 with amputated tail.	Do.
39	do	15	3 mice showed graying; 1 very thin but sleek; general condition of others was good.	Do.
40	do	13	1 mouse with opacity over left eye; 1 with prolapsed anal region; 1 graying; 1 with scabbed eyelids; 1 with injured right foot; 1 with no leg.	3 mice each had a small lump over the genitals.

TABLE VII.—7TH COMPLETE PHYSCAL EXAMIINATION OF C-57 MICE: 664 TEST-DAYS, 692 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L-MSG	11	1 mouse with open sore at base of tail; 1 mouse with opacity of both eyes; all others in good condition.	No evidence.
2, 3	do	10	1 with scabbed back; 1 with swollen hind legs.	1 with lump on posterior ventral region.
4	do	13	1 with scabbed back; 1 with opaque eye; 2 with scabbed eyes; 2 with shortened tails; 1 with right ear missing; 2 mice graying.	No evidence.
5	do	9	2 mice all gray; 1 with eyes scabbed; 1 with broken but healed tail.	Do.
6	4 L-MSG	9	1 partially gray; 1 with scabbed eyelids; 1 with scabbed face; 1 with amputated tail.	Do.
7	do	9	1 mouse graying; 2 with scabbed faces; 1 with shortened tail.	Do.
8	do	8	1 mouse graying; 1 mouse with chewed ears; 1 mouse with short tail; 1 mouse with scabbed eyelids.	Do.

TABLE VII.—7TH COMPLETE PHYSICAL EXAMINATION OF C–57 MICE: 664 TEST-DAYS, 692 DAYS OF AGE—Cont.

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
9	4 L–MSG	4	2 mice were very thin and had scabbed, crusted eyelids.	No evidence
10	do	10	3 mice had scabbed lids; 2 had swollen hind legs; 1 mouse was graying; 1 with healed injury of tail.	Do.
11	1 DL–MSG	3	1 mouse with scarred face	Do.
12	do	8	1 mouse graying; 1 mouse very thin, with scabbed eyelids; 1 with bare area on back.	Do.
13	do	9	4 mice graying; 1 mouse with scabbed lids.	Do.
14	do	6	5 with very sleek fur; 1 mouse with opacity of right eye.	Do.
15	do	1	The 1 mouse left in cage had a mangy face and crusted eyelids.	Do.
16	4 DL–MSG	8	4 mice with scabbed eyelids; 2 with mangy faces; 1 with no left eye and opaque right eye.	Do.
17	do	6	1 mouse with scarred face and no right eye; 1 mouse with crusted lids.	1 mouse had a lump near left testis.
18	do	2	Both mice in cage had scars from fighting and appeared mangy.	No evidence.
19	do	9	3 with right ear chewed off	1 mouse with lump on chest near right side.
20	do	10	1 mouse very small and thin; 1 with half of body gray and opaque left eye; 1 with bald area around eyes; 1 with crusted eyelids.	No evidence.
21	1 L–GA	2	1 gray mouse with left ear chewed off and right ear partially off.	Do.
22	do	5	1 mouse with open wound on back. 1 mouse with broken but crookedly healed right leg; 1 mouse with short tail.	Do.
23	do	8	1 mouse graying; 1 mouse with broken but crookedly healed left hind leg.	Do.
24	do	5	1 mouse gray; others appeared very sleek.	Do.
25	do	8	All mice had both ears chewed off; 1 of these with scabbed face and 1 with crookedly healed broken leg.	Do.
26	4 L–GA	11	2 animals very thin; 1 graying; 1 mouse with scarred back; 1 mouse brown with broken but crookedly healed left leg.	1 mouse with lump on upper part of chest; 1 mouse with small blood blister under right hind leg.
27	do	7	1 mouse very thin; 1 with no left eye; 1 with crookedly healed broken leg.	1 very large large mouse with lump nea testes.
28	do	8	1 mouse with opaque left eye; 1 mouse with no left eye; 1 with prolapsed rectum; 1 mouse very thin.	No evidence.
29	do	10	1 mouse had turned brown and had scarred face; 1 mouse had crookedly healed left hind leg; 2 mice very thin.	Do.
30	do	5	2 mice completely gray	1 mouse with lump near region of genitals; 1 mouse with small lump on back.
31	Control	10	1 mouse with crookedly healed left hind leg.	2 with enlargements near region of genitals (possible preputial); 1 with possible internal tumor.
32	do	6	1 mouse had turned gray on half of body; 1 with opaque eye.	No evidence.
33	do	9	1 animal had turned gray and 1 had turned brown.	2 mice with lumps near genitals (possibly the preputial).
34	do	3	1 mouse very thin and bony	1 mouse with lump near genitals (possibly preputial); animal died on day of examination.
35	do	8	2 mice very thin	1 mouse with lump on right side of genitals.
36	do	6	1 mouse with opaque left eye; 1 mouse with right hind leg broken, healed crookedly.	No evidence.
37	do	13	1 mouse gray, 1 with opaque right eye; 1 with prolapsed rectum.	Do.
38	do	4	2 with broken but healed right legs; general condition good.	Do.
39	do	6	1 mouse graying; 1 mouse with no right eye; 1 mouse with short tail.	Do.
40	do	13	2 mice graying: 1 with opaque eye; 2 with injured, swollen feet; 1 with no left leg; several were mangy in appearance.	2 mice with small lumps near genital

TABLE VIII.—8TH COMPLETE PHYSICAL EXAMINATION OF C–57 MICE: 715 TEST-DAYS, 743 DAYS OF AGE

Cage No.	Supplement (percent)	Count	Physical condition	Possible tumors
1	1 L–MSG	6	3 mice had crusted lids and one had crusted skin.	No evidence.
2 and 3	do	5	3 mice with mangy fur; 1 very thin with swollen deformed feet; 1 with scabbed, closed eye.	Do.
4 and 5	do	9	3 mice had an opacity of 1 eye. The others showed some degree of manginess with scabbed areas on body or face.	Do.
6 and 7	4 L–MSG	8	General appearance was very good; sleek coats; 1 with scabbed eyes; 1 with bald spot on back; 1 thin and graying; 1 completely gray.	2 mice with a lump on 1 side of the genitals, possibly an enlarged genital gland.
8, 9, and 10	do	8	Half the body of 1 mouse was gray, other half brown (discharge from right eye), 1 with short tail; several with scarred bodies or faces.	1 mouse with an internal lump which was palpable in the vicinity of the liver.
11 and 12	1 DL–MSG	6	1 with large bare spot on back; 2 with scabbed faces, body turning brown on 1; 1 graying with bald face.	No evidence.
13	do	6	Several mice were thin with scarred areas on body and head; 1 with prolapsed anus.	Do.
14 and 15	do	5	General condition was good	Do.
16	4 DL–MSG	3	1 mouse very thin; body was scarred. General condition of remaining 2 was good.	Do.
17	do	5	1 mouse with scabbed and swollen eyes; 1 mouse with scarred head.	1 mouse with large lump on 1 side of genitals and under leg.
18 and 19	do	9	4 mice with scarred heads	1 mouse with large lump on chest near throat.
20	do	3	General condition was good	No evidence.
21 and 22	1 L–GA	2	do	Do.
23 and 24	1 percent L–GA	2	General condition is good	No evidence.
25	do	7	4 mice had either 1 or both ears completely chewed off.	Do.
26	4 percent L–GA	6	2 mice were thin and with scabbed areas over body; 1 mouse graying. 2 mice with badly damaged eyes from fighting (1 had discharge from left eye).	1 mouse with blood blister under right hind leg.
27	do	5	1 mouse with broken right hind leg which healed crookedly; 1 mouse had scabbed areas over body	No evidence.
28 and 29	do	9	1 mouse with broken right hind leg which healed crookedly; 3 others had scabbed injuries from fighting (1 of these was very thin).	Do.
30	do	3	All 3 mice showed scabbed areas over body from fighting. 1 mouse had turned completely gray.	Do.
31	Control	10	1 mouse with hind right leg broken, crookedly healed; 1 mouse with prolapsed rectum; 1 thin; 2 mice with scabbed areas. General condition of others was good.	Do.
32	do	5	2 mice had opacities of 1 eye; 1 mouse turned completely gray.	Do.
33	do	7	1 mouse with opacity of left eye, scabbed face and head. General condition of other mice was good.	Do.
34	do	2	1 mouse scabbed from fighting injuries.	1 mouse with a small lump near genitals.
35	do	4	1 mouse with scabbed area near genitals; 1 thin; 1 mouse with opacity of right eye.	No evidence.
36	do	5	1 mouse had bald areas over body surface and had opacity of right eye. 1 mouse with healed broken legs and opacity of right eye.	Do.
37	Control	13	2 mice with scabbed eyes; 2 mice with prolapsed rectum; 2 mice graying; 2 mice with bald areas on back.	1 mouse had a lump near genitals.
38	do	3	1 mouse with crookedly healed right leg.	No evidence.
39 and 40	do	4	1 mouse with infected right eye; remaining animals in good condition.	1 mouse with lump near genitals.

Cumulative Population Records

TABLE IX.—1 PHYSICAL EXAMINATION, CUMULATIVE POPULATION RECORD C-57 MICE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L-MSG	100	6	0	94	94.0
4 percent L-MSG	100	1	0	99	99.0
1 percent DL-MSG	100	0	0	100	100.0
4 percent DL-MSG	100	11	0	89	89.8
1 percent L-GA	100	0	0	100	100.0
4 percent L-GA	100	6	0	94	94.0
Control	200	6	6	200	97.1

The population record indicates a slightly higher survival in the 1% supplemented diets except for the *L*-MSG supplement where the situation is reversed. The group fed a diet supplemented with 4% DL-MSG showed the greatest loss and were closely observed. The survival of the control group compared favorably with the supplemented groups. At this point, it was too early in the experiment to make valid conclusions or to predict survival rates.

TABLE X.—CUMULATIVE POPULATION RECORD, C-57 MICE, 146 TO 152 TEST-DAYS, 174 TO 180 DAYS OF AGE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L-MSG	100	15	0	85	85.9
4 percent L-MSG	100	3	0	97	97.0
1 percent DL-MSG	100	5	0	95	95.0
4 percent DL-MSG	100	19	0	81	81.0
1 percent L-GA	100	14	0	86	86.8
4 percent L-GA	100	15	0	85	85.0
Control	200	25	25	200	89.4

The greatest losses occurred in the 1% *L*-GA supplemented group and the 4% *L*-GA group. The loss had increased by 13.2 and 9.0 percent respectively over the loss at the first examination. There was no indication in the physical description of these groups which would explain the decrease in survival rate. The lowest increase in deaths, 2.0 and 5.0 percent respectively, occurred in the 4% *L*-MSG and 1% DL-MSG supplemented groups respectively.

TABLE XI.—CUMULATIVE POPULATION RECORD, -57 MICE, 215-220 TEST-DAYS, 243-248 DAYS OF AGE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L-MSG	100	16	0	84	84.8
4 percent L-MSG	100	4	0	96	96.0
1 percent DL-MSG	100	5	0	95	95.0
4 percent DL-MSG	100	19	0	81	81.0
1 percent L-GA	100	21	0	79	79.7
4 percent L-GA	100	15	0	85	85.0
Control	200	31	28	197	87.7

The survival rate at the time of the third physical examination was again highest for the animals on the 4% *L*-MSG and 1% DL-MSG supplemented diets.

TABLE XII.—CUMULATIVE POPULATION RECORD C-57 MICE, 286-342 TEST-DAYS, 314-370 DAYS OF AGE

Supplement	Orignial number	Deaths	Replacements	Survivors	Percent
1 percent L-MSG	100	16	0	84	84.8
4 percent L-MSG	100	10	0	90	90.9
1 percent DL-MSG	100	8	0	92	92.0
4 percent DL-MSG	100	21	0	79	79.0
1 percent L-GA	100	25	0	75	75.7
4 percent L-GA	100	17	0	83	83.0
Control	200	49	28	179	79.8

The largest loss of animals up to this time was in the 1% *L*–GA supplemented group. The largest increase in casualties since the previous examination occurred in the control group. The survival rate varied from 75.7 percent to 92 percent which is high in consideration of the life span of the mouse and the test period which was then almost one year.

TABLE XIII.—CUMULATIVE POPULATION RECORD, C–57 MICE, 370–403 TEST-DAYS, 398–431 DAYS OF AGE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L–MSG	100	23	0	77	77.7
4 percent L–MSG	100	18	0	82	82.8
1 percent DL–MSG	100	11	0	89	89.0
4 percent DL–MSG	100	23	0	77	77.0
1 percent L–GA	100	28	0	72	72.7
4 percent L–GA	100	28	0	72	72.0
Control	200	58	28	170	75.9

At a little over one year of age and after one year on test food, the percentage survival ranges from 72 to 89 percent. The 1.0% and 4.0% *L*–GA supplemented diets are the lowest in survival rate with the control group slightly higher, but there is no significant difference. The 1% DL–MSG and 4.0% *L*–MSG supplemented diets had the highest survival rate at this time.

The greatest percentage loss since the fourth complete examination occurred in the 4% *L*–MSG supplemented group.

If the average life span of a man in relation to mice is in the ratio of 30:1, the survival rate at this time represents approximately one half of the life expectancy of the colony.

The population record up to May 23, 1951 (533 test days, or 17 months and 17 days) is presented below. The death rate from supposedly natural causes seemed to have increased more in the period between the fifth and sixth physical examinations. This might be explained by the fact that approximately three-fourths of their life span had passed, and a longer time interval had elapsed between the fifth and sixth examination.

The lowest survival rate of 55.4% was in the control group; the highest, 69.4% was in the group being fed the 1% DL–MSG supplemented diet. The greatest loss since the previous examination was observed in the 4% *L*–MSG group.

TABLE XIV.—CUMULATIVE POPULATION RECORD, C–57 MICE, 528–533 TEST-DAYS, 556–561 DAYS OF AGE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L–MSG	100	34	0	66	67.4
4 percent L–MSG	100	42	0	58	58.7
1 percent DL–MSG	100	32	0	68	69.4
4 percent DL–MSG	100	42	0	58	58.0
1 percent L–GA	100	51	0	49	56.3
4 percent L–GA	100	37	0	63	63.0
Control	200	105	28	123	55.4

TABLE XV.—CUMULATIVE POPULATION RECORD C–57 MICE, 664 TEST-DAYS, 692 DAYS OF AGE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L–MSG	100	57	0	43	43.9
4 percent L–MSG	100	60	0	40	40.4
1 percent DL–MSG	100	73	0	27	27.6
4 percent DL–MSG	100	65	0	35	36.9
1 percent L–GA	100	72	0	28	32.2
4 percent L–GA	100	59	0	41	41.0
Control	200	150	28	78	35.5

The highest survival rate was in the 1% L–MSG and 4% L–MSG and 4% L–GA supplemented diets. The lowest survival rate was in the 1% DL–MSG, 1% L–GA and control groups. The greatest loss since the previous examination was in the 1% DL–MSG supplemented diet and the lowest in the 4% L–MSG supplemented diet.

TABLE XVI.—CUMULATIVE POPULATION RECORD C–57 MICE, 715 TEST-DAYS, 743 DAYS OF AGE

Supplement	Original number	Deaths	Replacements	Survivors	Percent
1 percent L–MSG	100	80	0	20	20.2
4 percent L–MSG	100	84	0	16	16.2
1 percent DL–MSG	100	83	0	17	17.3
4 percent DL–MSG	100	80	0	20	21.0
1 percent L–GA	100	89	0	11	12.6
4 percent L–GA	100	77	0	23	23.8
Control	200	175	28	53	24.3

The percent survival at almost two years shows no correlation to the supplement or concentration in the diet. The control and the 4% *L*–GA supplemented diet groups had the highest percent survival, and the lowest is seen in the 1% *L*–GA and 4% *L*–MSG supplemented diet.

Notes on Gross Pathological Examinations

Gross findings at autopsy

With 1 percent L-MSG

Cage No.	Nature of death	Number, test-days	General description	Description of suspected neoplasms	Organs showing gross pa thology
2	Spontaneous	45	Found about 2 hours post mortem, external appearance good.	None	Lungs: Very dark, possibly post mortem changes. Liver: Discolored at periphery; an occasional whitened area through liver tissue. Kidneys: White areas over surface. Spleen: 1 margin deeply discolored from post morten changes. Digestive system: Whitened areas along intestinal mesentery.
4	Sacrificed by decapitation	532	General ascites; thin watery fluid in abdomen	do	Lungs: Mottled. Liver: Pale, small yellow spots on dorsal aspect of lobes, 1 lobe attached to stomach Kidneys: Pale. Spleen: White areas over surface Digestive system: Stomach appeared shrunken but contained food.
1	Sacrificed veterinary nembutal.	720	Right eye closed from fighting injuries; left eye suggestive of developing cataracts. Abrasion on right upper lip. Abdomen appeared distended.	do	Liver: Slightly enlarged.
1	do	720	Mouse had turned very gray. Fur was sparse about the face and especially over the sternal region. Abrasion on left eye. Injury on back of left ear.	do	Liver: Slightly enlarged. Kidneys: Appearance of hyalini zation. Testes: Some evidence of gross atrophy.
2	do	720	Hair over body was thinning; otherwise mouse was in good condition.	do	Liver: Small white spots on dorsal aspect.
4	do	720	Coat had turned brown. No loss of hair. Injury above left eye. Right eye opaque. Right jaw lacerated.		None.
4	do	730	Left hind leg had been broken and healed crookedly.	do	Do.
4	do	730	External appearance was good, slight watery discharge from left eye.	do	Kidneys: Small, discolored area on anterior tip of kidney.
4	do	730	External appearance was good	do	Liver: Yellow material present in 1 lobe of the liver possibly a liver abscess. Kidneys: Left kidney was yellow-white and almost completely devoid of color, shrunken and granular. Other kidney not remarkable.

10	Sacrificed veterinary nembutal.		720	Abdomen appeared enlarged and distended. Right and left eyes were opaque.	Generalized peritoneal abscess; left side of abdomen filled with greenish creamy exudate. Inflammation involves the mesentery, liver, and bladder.	Liver: Left side of organ has areas exuding pus.
6	do		720	Changing in color beginning with left shoulder, fore part brown, back part black. Left eye opaque.	Swelling involving genitals on the left side, possibly a testicular tumor.	Testes: White mass lying loosely within abdomen, believed to be contents of testes.
6	do		720	Very good condition	None	None.
8	do		720	Many scarred areas over body from fighting	do	Do.
8	do		720	External condition good	do	Do.
6–7	do		730	External appearance was exceptionally good	do	Testes: Hemorrhagic area on right testis.
6–7	do		730	Animal was very thin, ⅔ of fur was gray. Left ankle had been broken but healed well.	do	None.
6–7	do		730	External condition was good	do	Do.
13	Spontaneous. Examined 4 to 5 ins. postmortem.		115	Animal was very bony, no external injuries	None	Spleen: Extremely small (0.2 cm. width, 0.75 in length).
12	Sacrificed veterinary nembutal.		720	External condition was good	do	Digestive system: Gelatinous mass between skin and abdominal wall.
13	do		720	External condition was good; loss of hair above face.	do	None.
14	do		720	External appearance was good	do	Do.
14	do		270	do	do	Do.
12	do		759	Animal was large, very healthy	Area around penis enlarged; there was a lump above the penis.	Kidneys: 1 kidney pale. Spleen: Mottled. Seminal vesicles: Enlarged. Preputial glands: Slightly enlarged; a hard whitish material pressed out of lump adjacent to preputial glands.
12	do	759		External appearance was good except for bald spot on dorsal surface.	Fleshy growth attached to seminal vesicles	Lungs: Calcified area involving 1 lobe of lung; seminal fleshy growth attached. Vesicles: 1 seminal vesicle small.

Cage No.	Nature of death	Number, test-days	General description	Description of suspected neoplasms	Organs showing gross pathology
19	Animal rolling over cage floor, expired while being observed.	69	External appearance normal	None	Lungs: Dark red patches. Spleen: Darkened area in center.
19	Sacrificed veterinary nembutal.	728	External appearance good, except for loss of right ear.	do	
20	do	728	External appearance good	do	Testes: Enlarged and yellow in color, when sectioned contained a thick, yellow material.
20	do	728	External appearance good; 2 calloused areas on lower jaw.	do	None.
19	do	728	Almost all of the dorsal surface was denuded of fur. A scab on right lumbar area was probably from a bite. Tail was covered with scabs, wounds on feet. Mouse was very small in size.	do	Spleen: Appeared to be large.
16	do	759	General appearance good	do	None.
16	do	759	Animal very thin, lower teeth very long, uppers missing, which was probable reason for emaciated appearance.	do	Kidneys: Small yellow area on the surface of kidney on section seen to be a dark hemorrhagic area Seminal vesicles: Enlarged.
16	do	759	External appearance good	do	Lungs: Scattered pinpoint areas over lungs which are dark red in color. Seminal vesicles: Very large.
17	do	759	do	do	None.
17	do	759	do	Lump above genitals which was external to to body. When dissected contained purulent material.	Seminal vesicles: Very small.
17	do	759	do	Large lump in left groin. On dissection was comprised of large amount of fat encasing 1 testicle and seminal vesicle, part of the intestine was enclosed; appeared to be a scrotal hernia.	Liver: Small protuberance. Kidneys: 1 kidney greatly enlarged with vessels on surface filled with watery fluid; other kidney slightly enlarged. Seminal vesicles: Vesicle encased in hernia was very small. Testes: Testicle involved in hernia encased in fat and very small. Preputial glands: Only part of preputial gland visible.
17	do	759	do	None	Seminal vesicles: Small in size. Testes: Greatly enlarged.
17	do	759	do	do	Lungs: Dark pinpoint areas. Preputial glands: Contained yellow fluid.
19	do	762	External appearance good. Mouse turning gray; 1 ear had a deep cut.	do	Spleen: Mottled.
19	do	762	External appearance good	do	None.
19	do	762	do	do	Lungs: Fresh hemorrhage.
19	do	762	do	do	Kidneys: Kidneys had white spots on exterior surface. Preputial glands: Normal in size but pale in color; not like usual yellow leafy structure.
14	do	759	General appearance was excellent	do	Seminal vesicles: Greatly enlarged.

WITH 1 PERCENT L-GA

24	Sacrificed veterinary nembutal.	728	External appearance good except for chewed ears.	None	None.
24	do	728	External appearance good	Thyroid gland was unusually large	Do.
24	do	728	External appearance good, except that tail was chewed. Herniated xyphoid cartilage.	None	Thyroid: Very markedly enlarged.
25	do	728	Enlarged, fleshy area under chin	Thyroid gland was unusually large	Testes: Small in size.
25	do	760	External appearance was good except for ears which were chewed.	None	Spleen: Enlarged. Seminal vesicles: Slightly enlarged.
25	do	760	Eyelids were scabbed and ears chewed	do	None.
25	do	760	External appearance good	do	Lungs: Mottled, few areas contained fluid.
25	do	760	External appearance good but ears had been chewed off.	do	Seminal Vesicles: Very small.
25	do	760	External appearance good but ears had been chewed off.	Small yellow lump above genitals under the skin.	Spleen: Mottled. Preputial gland: Very small in size.

WITH F PERCENT L-GA

27	Convulsive death, animal on side, shaking expired while observed.	115	Animal was thin and bony but with no external injuries.	None	Kidneys: Both enlarged, left being larger, mottled very pale, very little color.
26	Sacrificed veterinary nembutal.	680	External appearance good; fat, fleshy area under chin.	Fleshy tissue under chin was bilobed	Lungs: Gray-white spots. Seminal vesicles: One side enlarged and very white in color. Other side shrunken.
27	do	680	Very healthy animal Lump near genitals	When skin and muscle were cut away external to periitoneal wall, the lump was seen to be a small ball filled with a thick, yellow fluid.	Thyroid: Circular ball of tissue on neck near thyroid, when punctured, clear fluid was discharged.
30	do	728	Good condition	None	None.
30	do	729	Good condition, bald spot over buttock	do	Do.
26	do	728	Good condition	do	Thyroid: Appeared enlarged.
26	do	728	do	do	None.
26	do	728	Few scabbed areas over body, loss of hair	do	Do.
27	do	760	Opacity of the right eye. Genitals injured, probably from fighting.	do	Seminal vesicles: Enlarged.
27	do	760	Very mangy in appearance, scabbed face and bruises. Eyes closed from scabs. Both eyes showed a whitish opacity and appeared small and shrunken.	do	None.
27	do	760	Small lump (like wart) on nose. Skin scaly and flaky.	do	Liver: Areas on lobes of the liver which contained clear fluid. Testes: Appeared shrunken.
29	do	760	Skin was scaly	do	Spleen: Mottled.
29	do	760	Many scabs over the body surface	do	Spleen: Slightly mottled.
29	do	760	Scabbed over body surface, bald in places, skin flaky.	do	Preputial glands: 1 lobe was shrunken and white in appearance.

GROSS FINDINGS AT AUTOPSY—Continued

CONTROL

Cage No.	Nature of death	Number, test-days	General description	Description of suspected neoplasms	Organs showing gross pathology
33	Sacrificed veterinary nembutal	680	External appearance good	A small lump was present between skin and abdominal wall near genitals. On dissecting, was yeallow and hard.	Spleen: Mottled.
33	do	680	do	Question of internal tumor	Seminal vesicles: 1 side enlarged and white. Other side normal.
36	do	729	do	None	None.
36	do	729	Good condition, except that hair was sparse	Lump above genitals	Do.
36	do	729	Good condition	None	Do.
38	do	729	Good condition but with broken leg which healed crookedly.	do	Thyroid: Thyroid gland was extremely small.
38	do	729	Good condition	do	Liver: Enlarged. Adbominal Cavity: Calcified mass lying freely in lower abdominal cavity.
39	do	729	Good	do	None.
39	do	729	do	do	Do.
39	do	729	Good, mouse had wart on nose	do	Do.
32	do	729	Good, except for opacity of right eye	do	Preputial glands; Sacculated, increased in size on left and shrunken on right. Thyroid: Questionable enlargement of thyroid.
39	do	729	Hair was very thin. Wound in right axillary region. Cyst in neck.	do	Neck tissues: Translucent-like cyst in deeper tissues of neck.
34	do	728	Good condition	Small amount of tissue under chin which turned out to be enlarged thyroid.	None.
34	do	728	do	None	Do.
31	do	728	do	do	Preputial glands: Shrunken.
31	do	728	do	Thyroid appeared to be very much enlarged	None.
39	do	729	do	None	Do.
39	do	729	do	do	Do.
39	do	729	do	do	Do.
33	do	729	do	do	Liver: Slightly pale. Seminal vesicle: Greatly enlarged.
37	do	733	In good condition, losing hair around the head and neck.	do	None.
37	do	733	Scarred areas around the neck. Opacities of both eyes.	do	Do.
37	do	733	Good condition	do	Do.
37	do	733	Graying of hair over neck and head	do	Kidneys: Appeared small in size.
37	do	733	Good condition	do	None.
37	do	733	Loss of hair over rump and between ears. Overgrowth of tissue on chin.	do	Seminal vesicle: 1 side enlarged.
37	do	730	Good	do	Preputial glands: 1 part was enlarged.

37	do	730	Good; ⅔ of the animal had turned gray	do	Thyroid: Appeared enlarged. Spleen: Enlarged. Preputial glands: Part of preputial gland was white and part yellow; 1 lobe enlarged. Thyroid: Appeared enlarged.
37	do	730	Good	do	Lungs: Dark, mottled area on one lobe.
37	do	730	do	do	Liver: 1 lobe of liver had a lumplike large blood blister. Spleen: Mottled, long and thin in shape.
31	do	730	do	A lump about the size of a pea was palpable above the left side of the genitals. When dissected, blood vessels from skin of outer part of body wall were supplying the lump. The lump was attached to the skin of the body wall in the position of the preputial gland. Opposite half of gland was enlarged and yellow in color.	Spleen: Very small in size. Preputial gland: See description under suspected neoplasms.
31	do	730	do	None	None.
31	do	730	Good, except for crookedly healed left leg	do	Spleen: Mottled. Seminal vesicle: Very small in size. Preputial gland: Half of preputial gland was shrunken.
31	do	730	Large animal, external appearance was good	do	Liver: Granular. Seminal vesicle: On 1 side it was enlarged, creamy in color and very hard. Opposite side was white in color and soft. Appeared to be enlarged.
31	do	730	Good	do	Lungs: Dark tan in color. Appearance of small watery blebs throughout lung tissue. Sank in water. Preputial gland: Normal in size but opaque and filled with a yellow purulent material.
33	do	730	Normal in size, both eyes had discharge of yellow purulent material, scabbed lids.	do	Lungs: Spotted with white mottled areas. Spleen: Very enlarged. Thyroid: Thyroid gland had 6 large, dark red blebs.
33	do	730	1 eye appeared puffy and had a yellow discharge.	do	Heart: Very dark in color, over one-half. Lungs: Pale and mottled, 1 lobe was tan in color, sank in water.
33	do	730	Animal graying, scabbed areas over the ventral surface.	do	Lungs: Few pinpoint dark areas over lobes. Spleen: Appeared to be slightly enlarged. White bleb the size of a pearl in center of spleen.
33	do	730	Good in appearance, except for one opaque eye.	do	Thyroid: Appeared slightly enlarged. Lungs: Mottled areas. Thyroid: Appeared enlarged.

Notes on Atypical Microscopic Findings

ATYPICAL MICROSCOPIC FINDINGS—1 PERCENT L-MONOSODIUM GLUTAMATE GROUP (751 TEST-DAYS)

Liver: Foci of inflammatory cells around veins. Foci of necrotizing parenchyma cells. Some giant or binucleate cells. Foci of inflammation extending from cell infiltration to necrosis (3 secs.).

Kidney: Extensive focal areas showing interstitial inflammation, the effect extending to glomerular fibrosis and atrophy of tubules. Focal necrosis in renal pelvis (3 secs.). Pinpoint areas of inflammatory areas extending to cortical tubules. Extensive foci showing chronic interstitial nephritis involving both glomeruli and tubules.

Lungs: Inflammatory foci around bronchioles, as evidenced by infiltration of lymphocytes. Focal fibrosis of parenchyma. Massive abscess. Inflammatory foci around bronchioles as evidenced by infiltration of lymphocytes. Focal fibrosis of parenchyma (4 secs.). Inflammatory foci around bronchioles. Mild congestion (2 secs.).

Intestines: Focal corrosion of epithelium.

Colon: Polyp formation.

Stomach: Hyperkeratosis with concomitant hyperplasia of underlying germinativum.

Spleen: Congested. Red and white pulp disorganized. No actual pathology. Senile type.

Testes: Reduced population of germ cells.

ATYPICAL MICROSCOPIC FINDINGS—4 PERCENT L-MONOSODIUM GLUTAMATE (751 TEST-DAYS)

Liver: Foci of blood cells around central vein. Foci of cell necrosis. General distribution of hyperchromatic cells. Trace of hepatitis (3 secs.).
Kidney: Some interstitial inflammation. Focal nuclear toxicity in glomeruli. Focal glomerular fibrosis. Trace of focal glomerulo-nephritis (4 secs.). Focal exudative infiltration of intertubular connective tissue. Foci of atrophied tubular cells. Inflammatory infiltration with lymphocytes. Some dilated tubules have casts; mild chronic interstitial nephritis.
Spleen: Mild congestion. Disorganized pulp. Typical of senile spleen. Thickened trabeculae (5 secs.).
Lung: Focal fibrosis. Reduction in number of expanded alveoli. Normal aged lung. Focal edema. Collection of lynphocytes around bronchioles.
Testes: Germinal cells present, but scarce. Senile, normal (4 secs.).
Genital gland: Focal abscess.

ATYPICAL MICROSCOPIC FINDINGS—1 PERCENT DL-MONOSODIUM GLUTAMATE GROUP (720-751 TEST-DAYS)

Liver: Pinpoint foci of inflammation around some central veins, involving some necrosis of parenchyma. Intensely stained nuclei (3 secs.).
Lung: Slight focal fibrosis, reduced number of alveoli as might be expected in aged lung. Areas of inflammation around bronchioles as evidenced by massive accumulation of lymphocytes. Reduced number of alveolar sacs. Focal fibrosis. 1 tumor, probably adenoma, benign. Some focal fibrosis with reduced number of alveoli. Typical of aged lung. No marked pathology (2 secs.).
Kidney: Pinpoint areas of inflammation in cortex as evidenced by accumulations of lymphocytes, and degenerating tubule cells. Many fibrotic glomeruli. Pelvis negative. Large, focal area of necrosis in pelvis. Cortex as described above. Pinpoint areas of interstitial inflammation in cortex involving glomeruli and tubules, also present in pelvis (4 secs.).
Spleen: Mild congestion. Red and white pulp not clearly demarcated. Trabeculae enlarged. Suggestive of aged spleen (4 secs.).
Testes: Reduction in number of germinal cells in tubules, as in aged or senile testis. No pathology (3 secs.).

ATYPICAL MICROSCOPIC FINDINGS—4 PERCENT DL-MONOSODIUM GLUTAMATE GROUP (727-752 TEST-DAYS)

Liver: Pinpoint areas of inflammatory reaction indicated by accumulation of lymphocytes around central vein, hepatic vein and arteries. Otherwise no pathology (4 sec.).
Lung: Focal fibrosis. Reduced number of alveolar sacs. Suggestive of aged lung with no real pathology. Inflammatory indications around bronchioles, in some areas extensive. Some fibrosis. Reduction in number of alveolar sacs (4 sec.).
Kidney: Pinpoint foci of interstitial inflammatory reactions, mostly collections of lymphocytes Extent of reaction is limited to a few fibrotic glomeruli Some necrosis in renal pelvis (3 sec.). Pinpoint foci of interstitial inflammatory areas around ducts. Capsular fat is characteristic of old fat cells and thickened capillary walls. Extensive inflammatory areas in cortex, involving interstitial tissue and tubules but not glomeruli (3 sec.).
Spleen: Mild congestion. Disorganized red and white pulp. Many giant cells. Suggests aged spleen (4 sec.).
Testes: Reduced population of germinal cells in tubules. No pathology. Senile testis (4 sec.).

ATYPICAL MICROSCOPIC FINDINGS—1 PERCENT L-GLUTAMIC ACID GROUP (752 TEST-DAYS)

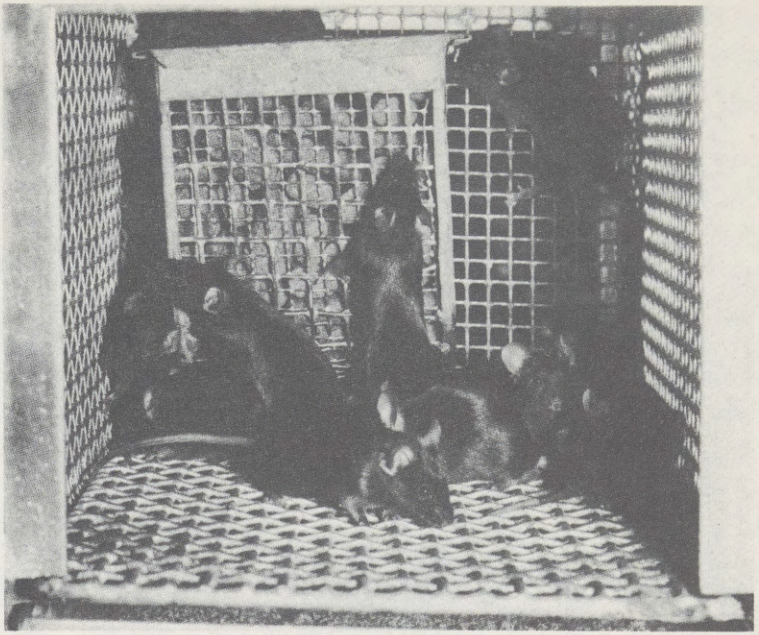
Lung: Inflamed bronchi. Thickened alveolar sacs (2 secs.). Inflamed bronchioles. Fibrosis (4 secs.).
Spleen: Mild congestion. Senile (9 secs.).
Liver: Giant nuclei in parenchyma. Some inflammation around blood vessels. Hyperchromatism and binucleates (3 secs.).
Kidney: Mild inflammatory areas in pelvis (3 secs.). Fibrosis of glomeruli.
Seminal vesicles: Epithelial disorganization (3 secs.).
Intestines: Focal destruction of epithelium lining. Epithelial area corroded.
Testes: Senile (3 secs.).

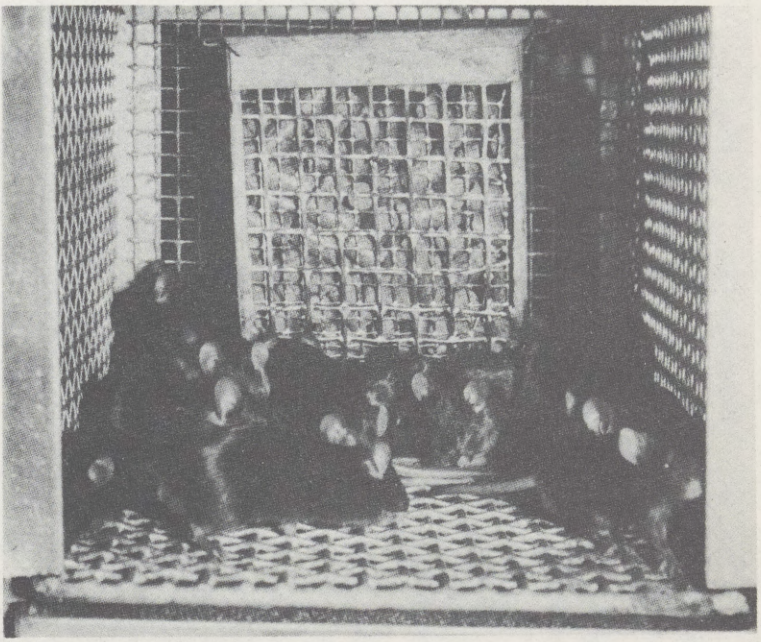
ATYPICAL MICROSCOPIC FINDINGS—4 PERCENT L-GLUTAMIC ACID GROUP (752 TEST-DAYS)

Lung: Inflamed bronchi (2 sections). Fibrosis (4 sections). Focal edema.
Spleen: Abscess. Mild congestion (3 sections).
Liver: Hyperchromatic nuclei (2 sections).
Kidney: Some necrosis in tubule cells of pelvis.
Testes: Sparse germinal cells.
Seminal vesicles: Area of corroded epthelium.

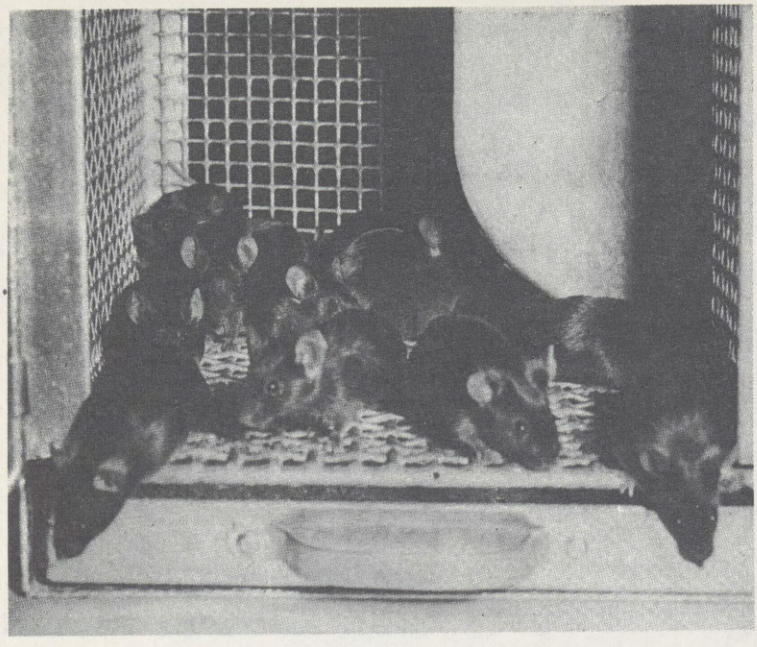
ATYPICAL MICROSCOPIC FINDINGS—CONTROL GROUP (729-757 TEST-DAYS)

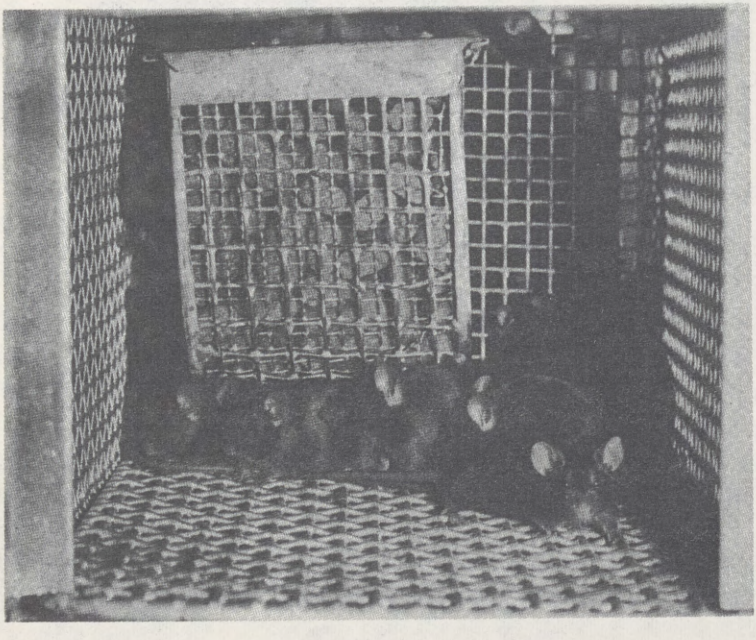
Liver: Pinpoint areas of accumulation of lymphocytes around veins (7 sections). Some hyperchromatism. 1 lobe shows general necrosis. Pinpoint areas of accumulated lymphocytes around hepatic veins.
Lung: Lymphocytic collections around bronchioles. Focal fibrosis. Reduced number of alveolar sacs. Slight effusion (8 sections). Lymph nodes around 1 bronchus inflamed. Otherwise no pathology (2 sections). Inflammation around bronchioles as evidenced by collections of lymphocytes. Otherwise no pathology.
Kidney: Some interstitial areas of inflammation indicated by collections of lymphocytes. Extent of effect only rarely affects glomerulus or renal pelvis. Scattered fibrotic glomeruli. Necrosis in distal medullary tubules in pelvis (2 sections). Glomeruli somewhat enlarged. Some dilated tubules. Some lymphocytic accumulation around proximal ureters. Focuses of interstitial inflammation in connective tissue around tubules. Some fibrotic and congested glomeruli.
Seminal vesicles: Some semisolid particles in lumen. Focus of extensive corrosion in epithelium.
Skin: Cyst in subcutis.
Bladder: Focus of collection of lymphocytes in epithelium.
Spleen: Mild congestion. Red and white pulp not clearly demarcated. Some thickening of trabeculae. Suggests aged spleen (8 sections).
Testes: Germinal cells reduced in number. Typical of senile testis (6 sections).



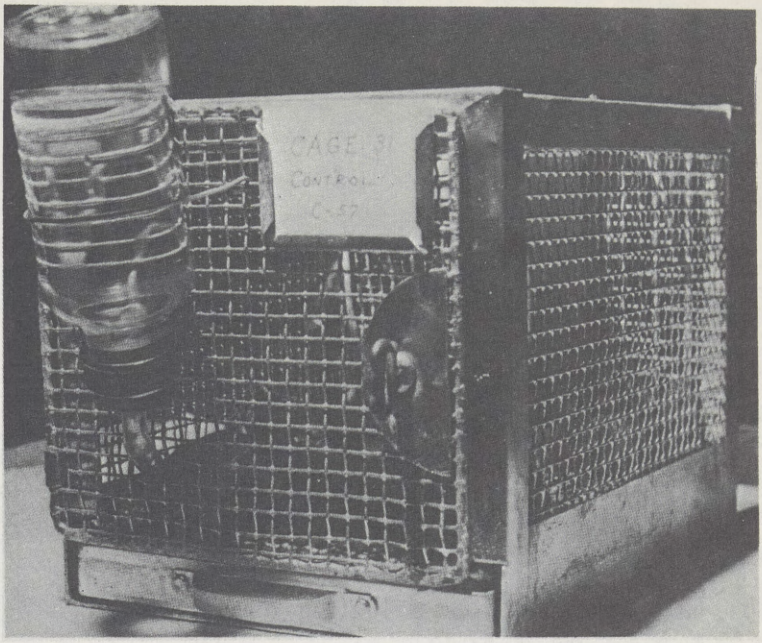


YOUNG C-57 BLACK MICE. SHOWS TYPE OF FEEDER USED.

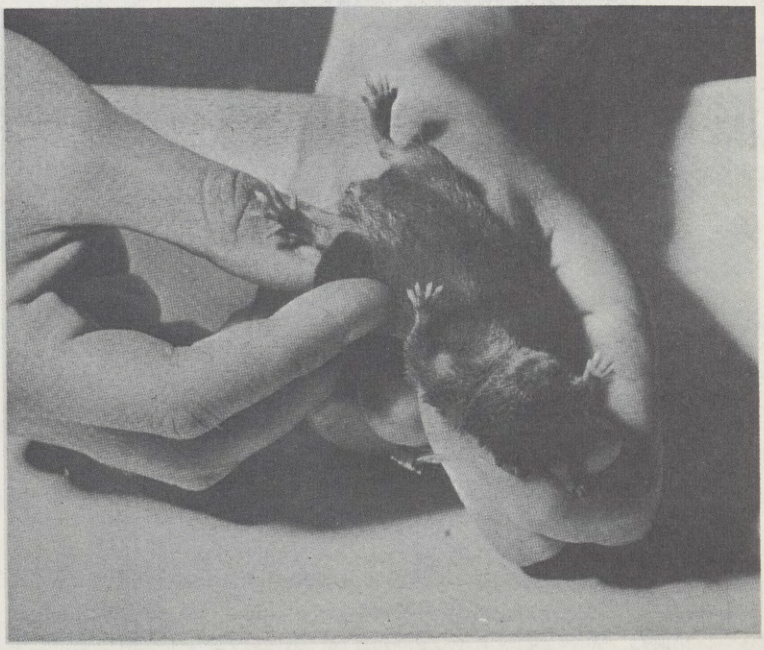




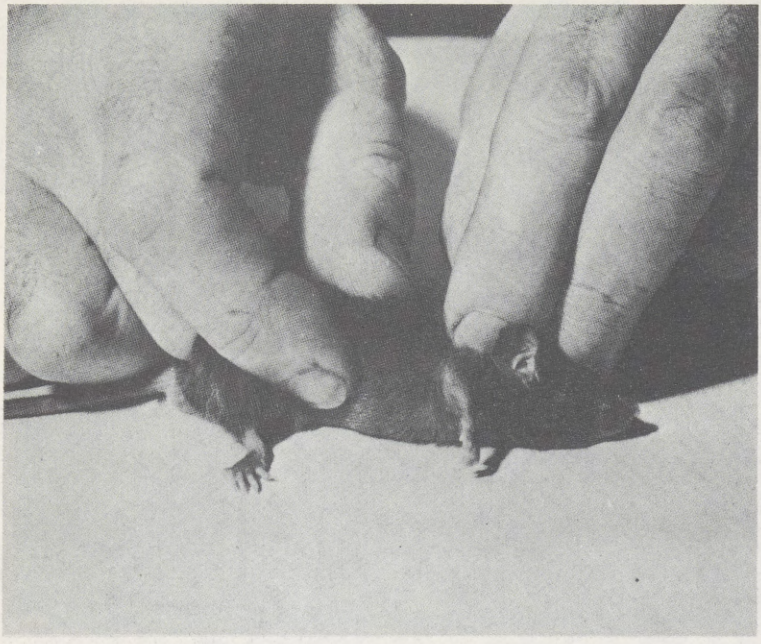
YOUNG C-57 BLACK MICE. SHOWS TYPE OF FEEDER USED.



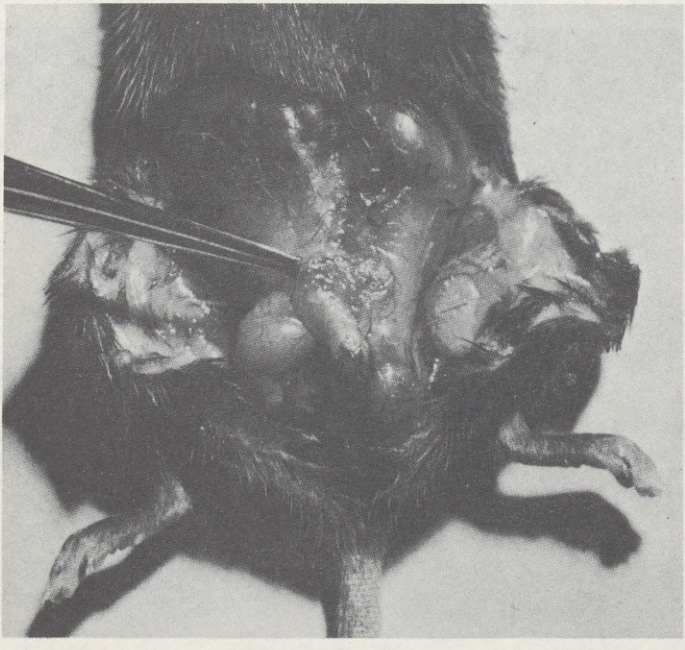
TYPE OF CAGE USED IN THIS WORK.



SHOWS METHOD OF PALPATING VENTRAL BODY SURFACES.



SHOWS METHOD OF PALPATING DORSAL BODY SURFACES.



NORMAL APPEARANCE OF PREPUTIAL (GENITAL) GLAND.

Dr. EBERT. It should be especially noted that the studies described today were all made on the basis of monosodium glutamate ingested orally, as the product is actually used, and not by subcutaneous injection or other routes foreign to normal use.

However, any report on glutamate has been, and is of interest to us. This includes reports claiming that MSG is the etiologic agent in the so-called Chinese restaurant syndrome. We are, therefore, sponsoring at a leading and highly respected university laboratory an extensive study in animals and humans on the possible role or MSG in these transient symptoms.

Mr. Mason?

Mr. MASON. Thank you, Dr. Ebert.

Mr. Chairman, distinguished members of the committee, that concludes our formal statement.

I want to thank you again for the opportunity to bring this information before this body. It is my corporation's position and philosophy that the effectiveness and safety of monosodium glutamate, or any of the other products the company sells, is a matter of primary and continuous concern.

In view of early testimony before this committee, IMC felt it had an obligation to users of the product, to our industry, to the scientific community, and to this committee to present to you research data on MSG safety which has not been refuted by recent studies.

May I thank you again for the opportunity to fulfill that obligation.

The CHAIRMAN. I thank you, Mr. Mason and Dr. Ebert. I think the questions that I would like to raise are primarily technical questions. Perhaps, Dr. Ebert, you may wish to respond to them, but we will leave that up to you gentlemen.

As you know, Dr. Olney conducted experiments in infant mice at the age of 10 days, which I understand is the equivalent of a 3- or 4-month-old infant. He used a dosage of 1.5 grams, 0.5 of a gram of MSG per kilogram of body weight. According to his studies he found brain damage in the mice with which he was experimenting.

Because some questions were raised about Dr. Olney's methods, particularly the subcutaneous feeding, he has advised the committee staff that he repeated those experiments, feeding the same dosage to mice of the same age orally, and got the same results. Again, he detected brain damage.

It is my further understanding that a 3- or 4-month-old child weighs on the average between 5 and 6 kilograms. Dr. Olney's dosage, therefore, would be equivalent of 2.5 or 3 grams of MSG for a baby. That is the amount of MSG that he found in baby foods, including the glutamic acid that was already present in the food and that which was added.

The amount he added, the 0.5 of a gram, brought it up to a level of 2.5 to 3 grams. In other words, he was trying to duplicate the same percentage of MSG in mice that would be present in the baby food that he examined.

On the basis of that he concluded that there was the strong probability of damage to infants in the present amount of MSG that baby foods that are currently on the market. Now in view of that situation I am wondering if you do not consider Dr. Olney's experiments to be credible.

Dr. EBERT. I am, first, surprised that Dr. Olney did not choose to present the oral administration data before this committee since our point was here, that this of course, is the normal route of administration. I think that the evidence is rather strong that we have a species effect here. We fed higher levels in our mouse studies, did not observe this effect and in the rabbit studies which duplicated the levels or went higher than what I understand Dr. Olney gave. Understand that I cannot comment on this too intelligently without seeing the data——

The CHAIRMAN. What he reported is that he had assumed before he conducted his original experiments that there would be no difference in terms of the impact on the mice between the subcutaneous feeding and oral feeding. But after his method was questioned, following his testimony here before this committee, he repeated the experiments orally and found the absorption rate the same and the results the same. There was no difference he could detect between MSG consumed orally as over against the subcutaneous method.

Dr. EBERT. I would refer Dr. Olney to a paper in JBC that demonstrated variation in glutamate metabolism with the route of administration, so this is indeed an important point. I would be curious in knowing the number of doses given, the length of time that it took to induce these effects that he observed, some more of the data.

My overall feeling here is that this appears to be a characteristic finding in this species.

The CHAIRMAN. Dr. Ebert, is it not true that the age of the animals used in these experiments is a critical factor? In other words, where you are trying to measure the impact of any ingredient on an infant, you would have to use an animal of comparable age in order to have a meaningful finding?

What were the ages of the animals and the experiments that you are citing in your testimony today?

Dr. EBERT. These animals were started at weaning and carried through 2 years, which is their anticipated lifetime.

The CHAIRMAN. What age?

Dr. EBERT. About 21 days.

The CHAIRMAN. What would that be in terms of a comparable age with a child?

Dr. EBERT. It is a very difficult question to answer, because we are talking about maturity here probably from a biochemical standpoint and trying to determine at what age does that animal or that child have a complete enzyme system. In the human we can talk about some enzymes being lacking for some months, others come on in a matter of days. So we are probably roughly extrapolating this information to a child of several months of age, I would guess.

It depends really on what you are specifically attempting to measure here.

The CHAIRMAN. I think that is really a critical point. It is Dr. Olney's conviction that a child of 3 or 4 months old would be the equivalent in terms of this physiological problem we are talking about to a mouse or a rate at the age of 10 days. In other words, to measure the impact of a particular ingredient on a 3- or 4-month-old child, you would have to experiment with a mouse or rats that were older than 10 days.

His experiments and his correspondence with us indicates that the difference in the results that he got as over against some of the studies you refer to, is in the age factor.

Dr. EBERT. I would refer him to the three reproduction and teratology studies where glutamate was fed to parents. Glutamate moves rapidly through the placenta. Placental as against blood glutmate ratios run about one, and I point out the lack of damage in the rabbits when the parents received the material, the embryo received the material and the animal from time zero received the material.

The CHAIRMAN. And there was no obvious damage or any damage that could be detected?

Dr. EBERT. No, sir.

The CHAIRMAN. I am not familiar with the point with reference to how your preserve glutamate in placenta, but the point as to age seems to me to be critical here. I wish you would comment directly as to the age of the mice or to the animals in the experiment. Is it not a fact that you would get a different result on a mouse or a rat or whatever the animal is beyond the 10-day period than you would get at the age of 10 days and is not Dr. Olney's point well taken that you would have to experiment with an animal at the 10-day period if you want to duplicate the probable effects on an infant of 3 or 4 months of age?

Dr. EBERT. Yes, indeed, that is why our studies include all the way from starting with the parents-to-be receiving the compound all the way through to the animal at weaning.

The CHAIRMAN. It seems to me the gap is in that period of the early days of the animal's life. You skip that period. You start in at the 20-day level.

Dr. EBERT. No, not if the ratio of glutamate in the parent and the child is one. In other words, you can be sure that the material that you give to the parent is going to get into the pup, and then you can be sure that the toxicological insult of the compound will start at the moment of conception of that animal.

That is, indeed, one of the problems with carrying out a reproduction and teratology study. You have to make sure that the material is going to get through the placental barrier into the pup to assert its effect. So a very important question here is does glutamate get through the placental barrier into the fetal circulation, and the answer is it does.

The CHAIRMAN. Senator Ellender?

Senator ELLENDER. There is a little conflict in the testimony, as I recall. I notice here on page 2 you state that this material is basically protein origin, that is, from natural foods. Would you be a little more specific?

Mr. MASON. Senator, all food, vegetable or animal or protein in nature has glutamic acid in it in its natural form. As we have tried to indicate this morning, we are adding on the average approximately 2 percent of what is already there I think there is an interesting question that if we took baby foods specifically and after extensive work, decided to remove MSG from it, what happens then when the baby is still getting glutamate in its natural form as protein in green beans or whatever baby food is being fed at considerably higher levels than anything that is being put into the baby foods now. Do we simply suggest the mother stop feeding the baby? That seems to be the ultimate choice.

Glutamate is there in its natural form. If you break the protein down and take out glutamic acid, which is the flavor-enhancing property of protein, that is monosodium glutamate.

Senator ELLENDER. That is some kind of salt?

Mr. MASON. I will let Dr. Ebert elaborate on that.

Dr. EBERT. Technically, it is salt, but the average person thinks of salt in terms of sodium chloride.

Senator ELLENDER. Are you prescribing any particular amount for children or persons of certain age or do you leave it to them to decide?

Mr. MASON. Senator Ellender, I have here some representative examples going back over some 10 to 15 years of the use levels that we have recommended for various types of food. I could specifically refer to the baby-food companies who testified a week ago yesterday and say that after hearing their testimony, we returned and contacted other people in the industry, analyzed our own records and were very interested to find that something in the neighborhood of 0.7 of 1 percent of the total monosodium glutamate produced annually in this country by everyone is being sold to baby-food companies.

That is no way means it is going into baby foods. For example, Heinz produces soups. It is also used in their soups. We are talking about a relatively small amount of the total annual output going to baby-food companies and not specifically to baby foods.

Senator ELLENDER. You stated the purpose of this additive was to improve the taste of the food.

Mr. MASON. Yes, sir; that is the only way we have ever promoted this product, to bring back the flavors that are lost through harvesting, processing, and storage in meeting our foods industry's big distribution channel needs in feeding the people in this country. That is how this product has found its place in the marketplace both with the consumer and the industrial side.

Senator ELLENDER. Would the use of this additive cause children, people to eat more than they ordinarily would?

Mr. MASON. No, sir. I can give you an example we lived with. The glutamate level is highest in its natural forms in such products as onions, sugar beets, wheat gluten, mushrooms—they have the highest levels naturally.

I think we often use the example that the reason onion soup as an appetizer has gained such acceptance and popularity is because the high glutamate level increases the mouth feel and sensitivity to flavor and the enjoyment of food.

Senator ELLENDER. Well, in French cooking I know that onions are the basis for much of the food taste.

Mr. MASON. And it is again one of the products that has the highest glutamate level in its natural form.

Senator ELLENDER. In French it is commonly known that L'oignon est le fond de la soupe de beau mangé. The onion is the foundation of good eating. In that respect you are using, I presume, this additive.

Mr. MASON. We use as the basis for our process the sugar beet industry.

Senator ELLENDER. Is that the basis of this salt extraction?

Mr. MASON. Of this product, yes, sir. In past years some companies have made it from wheat gluten, others have made it in the sugar process called cane sugar.

Today I believe Great Western Sugar makes their MSG from sugar cane. We start with a byproduct of the beet industry. There are other processes for making it.

Senator ELLENDER. Do you use any kind of chemicals in this process?

Dr. EBERT. Chemical in its broadest term, yes; keeping in mind we are all made up of chemicals.

Senator ELLENDER. I am talking about any particular concentrated chemicals.

Mr. MASON. We have maintained it is a natural food component and a natural food element coming from protein.

Senator ELLENDER. Extracted from food that we ordinarily eat; is that right?

Mr. MASON. Yes.

Senator ELLENDER. In presenting this additive to the public, I presume that you have gone through the regular process; the USDA has OK'd the use of this?

Mr. MASON. Senator Ellender, I think over a long period of time we could say quite honestly that we have found FDA a rather tough taskmaster.

Senator ELLENDER. They have found no difficulties with the use of it?

Mr. MASON. Not to our knowledge, sir; and everything we have in our files and what we are presenting here today is on file with the FDA and has been for a long period of time.

Senator ELLENDER. Thank you very much. I hope you have good luck in your Louisiana plant.

Mr. MASON. Thank you very much, Senator; I do too.

The CHAIRMAN. Senator Dole?

Senator DOLE. I have one specific question. As I understand, you have made a number of safety evaluation studies. Is this a continuing process as far as your company is concerned?

Mr. MASON. Senator Dole, we have been conducting research on this product since we got into the business in 1942. It has been of an ongoing nature where new scientific breakthroughs and new toxicological breakthroughs have been made and wherever doubt, either on our side of the fence or in the press or by other people, has been raised. I think Dr. Ebert eariler referred to the nice "pressy" name called Chinese restaurant syndrome, which first began in the scientific and lay press about 1968.

Following that a question had been raised. We didn't quite frankly place any emphasis on it based on what we knew to date on our own product. We contacted FDA. FDA said the question has been raised. They recommended at our request an outside unbiased independent organization that was reputable called the Albany School of Medicine, under FDA protocol and financed by our company with the findings to be submitted concurrently to FDA and IMC.

Following that, as the largest producer in this country, we wrote a letter to each of our fellow producers and said we are sure you have seen the publicity taking place on the Chinese restaurant syndrome. Please be advised that we have contacted FDA and have undertaken to finance a study at the Albany School of Medicine.

This information will be furnished to FDA and IMC, concurrently. Upon receipt, we will be more than happy to share this report with you. This study is to be completed—at the last estimate I heard

it was to take some 18 months, which would be approximately the spring, March, or April of 1970. This is taking place right now.

Senator DOLE. That is all I have.

Senator DOMINICK. Mr. Mason, welcome to the committee.

Mr. MASON. Thank you, I think.

Senator DOMINICK. I would like to ask you a couple of questions here to just try and see how your company interrelates in this. Do you sell to food processors or do you sell to retailers or what do you do?

Mr. MASON. The industry by its nature tends to break into three categories, the retail market or the homemaker; the institutional market which would be hotels, hospitals, schools, restaurants, the military, and so forth; the third category being either the industrial or the food processor category.

Our own sales, and I can't speak for the industry, approximately 16 percent of our annual output is sold to the homemaker. I wish this were larger.

A comparable 16 or 18 percent goes into the institutional area with the balance going to the food processor.

Senator DOMINICK. When you sell it to the homemaker, do they then add whatever they would like?

Mr. MASON. We have on our packages recommended use levels to bring out the best flavor based on the flavor panel work that we have done over the years. On beef, a certain amount is required, on poultry, a different amount, on vegetables, a different amount, and this is on our package for their instructions.

Senator DOMINICK. When you sell to the food processors, do the food processors add those amounts?

Mr. MASON. We have done work in our own company indicating what we believe to be the best level for maximum flavor improvement. Here are some samples over some 10 or 15 years of the levels we have recommended to them for maximum effectiveness of our product.

Senator DOMINICK. If it is not out of order as far as Mr. Mason is concerned, I think that might be interesting information to have in the record.

Mr. MASON. We have it here. We will be glad to submit it for the record and if additional information is needed, we will be glad to submit it.

Senator DOMINICK. Your third area was industrial. How does this fit into the industrial area?

Mr. MASON. The product has great application in the area of soups, canned vegetables. As we are all aware, we live in a changing society where we have gone from an agricultural to an urban, suburban, central city complex. If you take this example, many vegetables which are being consumed on the east coast are grown, harvested, processed, stored, shipped, and repeats at least part of this cycle on the east coast before they ever get to the homemaker.

Some amount, I can't quantify this—some amount of the natural glutamate level has disappeared and there is no more of the growing in the back yard and taking it directly to the table when it is at the peak of freshness. Our product has found its place in this country by filling that need.

It is the way to add MSG back to keep those flavors.

Senator DOMINICK. How do the use levels that you recommend compare to the use levels that were involved in testing, which Dr. Ebert was talking about?

Mr. MASON. I think Dr. Ebert is most qualified to answer that, sir.

Dr. EBERT. Briefly I will just say they are a small fraction of the high levels that were generally administered.

Senator DOMINICK. Are they considerably smaller than the amount Dr. Olney used in his experiments?

Dr. EBERT. By and large I think that the main points to be made from the Olney experiments that we have seen in the scientific literature would be the route of administration. We would have to learn more of this oral administration that apparently the chairman has referred to.

Senator DOMINICK. Specifically going to the baby foods which seems to be the crux of this particular review, how do the dose levels which you used in your experiments compare with the amounts that are recommended by you in your sales program in baby foods?

Dr. EBERT. They duplicate the levels we recommend.

Senator DOMINICK. Including the high level?

Dr. EBERT. We go much higher.

Senator DOMINICK. The experimental high level is higher than what is used in baby foods?

Dr. EBERT. Yes, sir; much higher.

Senator DOMINICK. This is the point I was trying to bring out. Based on your experimental work and your knowledge, and I will ask either Dr. Ebert or Mr. Mason this; is it your belief that MSG is or is not safe for babies?

Mr. MASON. Senator Dominick, based on everything and all the work we have done, we feel that our product is safe for its intended use as a flavor enhancer ingested orally.

Senator DOMINICK. I wanted to ask that question because it clearly brings out the problem the committee has been looking at and the problem, of course, you are faced with. For purposes of the record I thought we ought to have a very clear answer.

Your answer is basically yes, it is safe?

Mr. MASON. Yes, it is safe.

Senator DOMINICK. Thank you.

The CHAIRMAN. Mr. Mason, it seems clear to me that we have got an issue here where the committee is not competent to make a final judgment. We have either different experiments or else a difference in the interpretation of those experiments. It has to be one or the other.

We have had Dr. Olney making a judgment and we have what Senator Dominick just elicited from you, so he is either using a different set of criteria or he is interpreting it differently. What would you think of the Food and Drug Administration setting up a panel that would include Dr. Ebert, Dr. Olney, and perhaps someone named by the committee on nutrition of the American Academy of Pediatrics, to look at these questions that have been raised here and to make a judgment on it?

Mr. MASON. Senator McGovern, we would have no reservations about this at all, because it is our impression right now that you have two sides of an issue here. One is three or four men and the other side is

the industry and the balance of the scientific community. So if this would be helpful, we have no objections whatsoever and we would cooperate in every way.

Senator DOMINICK. Just as a matter of interest, I would like to ask a question of Dr. Ebert. Is there a difference in your testing procedure in your testing on mice or testing on rabbits, or is there a difference in the makeup of the two animals which would create a different result?

I gathered that the mice were used by Dr. Olney, the rabbits were used by you?

Dr. EBERT. We used mice and rabbits and the rabbits were specifically chosen, a New Zealand variety, because they are particularly sensitive to teratogenic insults and if you are going to have a problem with an adverse effect on reproduction teratology, this is the most sensitive species.

Senator DOMINICK. Fine, thank you.

The CHAIRMAN. The point is certainly clear that there is glutamic acid, as Mr. Mason has said, in all kinds of foods. Really the only question here is what level is safe, whether or not the additives are at a level now where they do raise some question about their safety. It seems to me this procedure that I suggested here is one that would be practical in trying to arrive at a judgment.

I think Senator Dominick would agree, we don't have the scientific competence on this committee to draw judgments when the scientists themselves are in dispute. I certainly have no reason to question Dr. Ebert and the scientists in your company any more than I would question Dr. Olney and others.

But there is a conflict here. I think in fairness to your company and in fairness to the consumer, that we ought to try to resolve this according to the best judgments we can bring to bear. I am sure that is what you want.

Mr. MASON. On behalf of IMC we have no objections and we will be perfectly happy to cooperate.

The CHAIRMAN. If the committee has no objection, I think we will pass on that suggestion to the Food and Drug Administration and discuss it with them and see if that isn't a practical way to try to bring about some resolution of this issue.

I think the same procedure might be followed with reference to the issue of the salt contents in baby foods that have been raised. I was interrogated about that on the "Today Show" the other morning as to whether I recommended, in view of the questions that have been raised before this committee, that mothers quit using baby foods until we can decide how much salt ought to be in it.

I don't think I am in a position to make judgments like that, but these questions have been raised by Mr. Nader and by some of the doctors who have appeared before the committee. I think we have some obligation not to leave those charges hanging in the air, but to try to bring about a resolution. We hope the Food and Drug Administration would take steps to give us the answers we need.

Do you have any thoughts on that, Senator Dominick, as to whether that procedure might be a way to approach it?

Senator DOMINICK. I have no objection to it from the point of view of clarifying the record. The only thing I think is troublesome about this is while these hearings are going on, questions are raised in the minds of the consuming public as to whether or not they ought to continue using baby foods now being fed to their babies by every mother in the country.

I just think we could go overboard on this, frankly.

The CHAIRMAN. The charges have been made and they have been made not only before this committee but, as you know, Dr. Ebert, they have been made in scientific papers. The word is out, regardless of what this committee does or doesn't do.

I think we have an obligation to evaluate those charges as best we can. When we reach a level where the committee can't make a final determination, we refer it to more competent authority. That would be my suggestion to try to refer the matter to the FDA with the suggestion they move in on it as quickly as possible.

I would see no reason why some kind of judgment could not be made on that in a few days' time.

Senator DOMINICK. In the meanwhile, I think this committee ought to take the position that we have no evidence one way or the other which is satisfactory to us as far as showing that any of these products are really dangerous.

The CHAIRMAN. I think that is the point. We have competent authority on both sides of the issue and we have to reserve any judgment on it until we can get a determination that is more convincing.

Senator DOMINICK. Mr. Chairman, I wonder if I could ask just one more question. I happen to be a devotee of Chinese food. Mr. Mason, or Dr. Ebert, I wonder if you could describe Chinese restaurant syndrome for the record?

Mr. MASON. I will pass that question to Dr. Ebert and let him describe the symptoms of this interesting phenomena, as it has been quoted in the press.

Dr. EBERT. I would say briefly that this is a transient neuromuscular episode that affects the muscles of the face. It is characterized by pressure under the eyes, through the temples, and around through the back of the neck that affects certain people when they eat in Chinese restaurants. According to the Schaumberg-Byck paper, they report that you can get this with a very small amount of Chinese food rich in glutamate.

I personally have taken large amounts, over 10 grams, of glutamate on an empty stomach and I do not suffer from it. There are several other interesting aspects. Onset is very rapid, duration is very short, and according to Schaumberg and Byck it is completely blocked by a little bit of food.

You have to have an empty stomach to get it. That is why they say the easy way to get it is to eat soup which contains glutamate.

Mr. MASON. It's been interesting to note that some of our Chinese restaurant customers lean a little bit to attributing this to martinis as opposed to won-ton soup.

Senator DOMINICK. I think you can attribute almost anything to martinis.

Mr. MASON. If it were possible, I would prefer that we direct it to martinis.

Dr. EBERT. One of the interesting aspects is that the Chinese restaurant syndrome is not known in the Orient.

Mr. MASON. In Japan the per-capita consumption is 1 pound per person and this phenomenon has never appeared there.

The CHAIRMAN. Thank you, Mr. Mason and Dr. Ebert, for your testimony today. We appreciate the time and effort that you people have put into this matter.

Mr. MASON. Thank you for the opportunity, Senator McGovern.

Dr. EBERT. Thank you, Senator.

The CHAIRMAN. The committee stands adjourned.

(Whereupon, at 11:10 p.m., the committee adjourned, to reconvene at the call of the Chair.)

APPENDIX

COMMITTEE CORRESPONDENCE FROM RALPH NADER AND HERBERT L. LEY, M.D.

SEPTEMBER 15, 1969.

Senator GEORGE MCGOVERN,
Chairman, Select Committee on Nutrition and Human Needs, Senate Office Building, Washington, D.C.

DEAR SENATOR MCGOVERN: The enclosed statement on the safety of Monosodium Glutamate raises a serious question about the competence of the FDA to carry on its task of protecting the nutritional quality and safety of the American food supply. In appearing before your Committee, the Agency cited as proof of MSG safety two studies that did not exist and two additional studies that have reached no conclusions. Such distortions require a serious and detailed examination of the Agency by your Committee or some other committee of the Senate.

In addition, it is quite important for you to be aware that the FDA is presently attempting to delete from the written record of their presentation at the hearing the gross error they made in claiming that excessive amounts of MSG were used in one private study suggesting that MSG might not be safe in baby foods. The Agency should not be allowed to delete its testimony. Every effort should be made to allow any correction of the error by addition to the record, but to allow a deletion of the lengthy exchange would be a distortion of what occurred in the hearing room and would deny those reading their record a thorough understanding of what occurred at the hearing.

Sincerely yours,

RALPH NADER.

REVIEW OF THE TESTIMONY ON MSG

One of the enduring characteristics of the food industry is its penchant to sell now and have someone else test later. In case after case, the sequence of doubt to risk to reasonable certainty of harm has been the burden of researchers outside the food industry. It comes as a highly disturbing disclosure that this sequence is emerging for the one area of food product in which most people hold greatest trust. I am speaking of baby food.

Competent nutritionists are showing growing concern over the amounts of salt, sugar, starch and monosodium glutamate in many baby foods . . .

The attraction of monosodium glutamate (85% of which is produced by Accent International) to the baby food producers is enhancing the flavor of these starchy foods for the benefit of the mother. There is no evidence that baby craves MSG. It was not until the late 1940's that large scale MSG production began in this country. Yet not until last year did the first report of the "Chinese restaurant syndrome"—a cluster of pathological reactions affecting some people who ate Chinese food—emerge. Typically, the report was not done by industry researchers, but by an independent physician. There still is no data on the tolerance of babies to MSG. It is known that MSG increases the sodium content of the food, that it has reacted in large doses, most seriously on mice and chicks, that the FDA has conducted tests on how much MSG is going into baby foods and that Campbell Soups is contracted for tests at Albany Medical College, N.Y. The question repeats itself—when the benefit is nil nutritionally and is commercially geared to the mother, why take the risk without studying the effects first?—Ralph Nader, to the Select Committee on Nutrition and Human Needs, July 15, 1969.

The efforts of the Food and Drug Administration and the President of the International Minerals and Chemical Corporation (makers of Accent which is pure Monosodium Glutamate) to explain away or refute the demand that MSG should be removed from baby food until it is proved to be both safe and nutritious not only fails but in fact brings to light a far more serious and disturbing situation than that which caused the original demand. Neither the FDA nor IMC attempted to establish that MSG has nutrient value, neither tried to refute the assertion made by several scientists that infants younger than four months have no taste discrimination. In short, neither organization offered any explanation for the inclusion of MSG in baby food, as either nutritionally important or necessary for palatability.

However, more serious and more shocking than the failure to establish a positive need for the use of MSG in baby food was the shoddy and misleading way in which the safety of the additive was defended. IMC combined reliance on a series of studies that had no direct relation to questions of infant consumption of MSG with a naive belief in the effectiveness of the Food and Drug Administration. The Food and Drug Administration misrepresented the results of four scientific studies establishing itself as grossly incompetent scientifically or cynically unconcerned about public welfare. In fact, the enormity of the distortion demands that a deep and searching examination be conducted into the ability of that Agency to handle problems of food, nutrition, and safety.

The Staff Paper on Monosodium Glutamate presented to the Select Committee on Nutrition and Human Needs by Dr. Herbert Ley, Commissioner of the Food and Drug Administration, on July 22, 1969, stated "When MSG was injected into fertilized eggs it caused no adverse effect on the embryo." In fact, prior to the appearance of Dr. Ley at the Committee hearing a meeting was held by the staff which conducted the test mentioned. In that meeting it was pointed out that only a limited number of eggs had been used in the test and "these results, based on such a limited number of eggs, are too preliminary for any conclusions to be drawn." (FDA Memo, May 7, 1969.) After the appearance of Dr. Ley the investigators who conducted the test indicated to their superiors in the FDA their displeasure with the use of the test findings. On August 1, 1969, Dr. Edwin L. Hove, the Acting Director of the Division of Nutrition, received a written memorandum pointing out the misuse of the data and saying in part "positive statement on findings with the chick embryo may not be warranted at this time. The investigators have requested that appropriate modification of this statement by the Commissioner be made." The investigators, who conducted the egg study relied on in part by the Commissioner to establish the safety of MSG, objected to its use both before and after the public appearance by Dr. Ley.

The second study cited by the Commissioner appears to have never taken place. The Staff Paper states "Another of the new tests has to do with cytogenic abnormalities, primarily in the indication of chromosome breaks in the cells of treated animals or bacteria. When MSG was subjected to these highly critical tests, no adverse reactions were noted." According to Dr. Marvin Legator (FDA cell biologist and expert on chromosome breakage) no FDA studies on MSG chromosome damage have ever been conducted.

The third study cited in the paper states "When fed to rats at levels of 30% of the diet, MSG has produced no adverse effects on growth." Dr. Hove has since notified the Commissioner that the actual figure should have been 30% of the protein in the diet, not 30% of the entire diet. More disturbing than the mistaken amount of MSG, however, is the failure of diligent effort to turn up any recollection of such a study among FDA investigators in the protein field.

Finally, the fourth study cited in the Staff Paper was incomplete at the time of the testimony. The paper stated "When fed to pregnant rats at a level of 10% of the diet (equivalent to 20 grams of MSG per kilogram of body weight), no adverse effect on the pregnancy occurred. The young born from those mothers were normal and developed normally." Dr. J. S. Adkins, FDA protein expert, was surprised that his study was cited since at the time rats involved in the test had not yet been sacrificed and therefore no complete test results were available.

These four tests were relied upon by FDA to convince the Committee of the safety of MSG. Two of the tests had apparently not been conducted at all and the other two were preliminary in nature. At the time FDA testified that they had found MSG safe, they had not conducted to completion any of the tests they cited as establishing that safety. Such misrepresentation and distortion is far more serious in its effect than the mere possibility that MSG has found its way

into baby food before its nutritional value and safety have been established. Such distortion brings into doubt the entire capability of the Food and Drug Administration to protect the public from any of the potentially harmful food additives presently in use in the American food supply.

The enormity of the situation was aptly underlined by the testimony of the President of International Mineral and Chemical before the Select Committee on Nutrition on August 5, 1969. He said, "I think over a long period of time we could say quite honestly that we have found FDA a rather tough taskmaster." It is clear that Mr. Mason and his company have been drawn into the belief that they can depend on the Food and Drug Administration as a back up to their activities in insuring the safety of MSG. It is equally clear from the FDA Staff Paper on MSG that such reliance is misplaced. Both Industry and the Consumer have been led to the belief that MSG is safe by FDA statements based on a series of nonexistent or incomplete studies.

Reliance upon inaccurate FDA assertions of safety by the Select Committee, the general public and industry illustrates an important and serious legal problem. Under the Food and Drug Law no substance which has not been proven to be safe can be placed in the food supply unless its safety has never been challenged. The safety of MSG has not only been challenged by the scientists who appeared before the Select Committee, but President Mason of IMC himself mentioned a 1966 paper "which claimed that glutamic acid was teratogenic of rabbits." Both Senator McGovern and Senator Dominick concluded that the evidence of safety or danger of MSG was inconclusive. The legal standard for adding chemicals to food requires a positive showing of safety. It has not been met.

When Senator Ellender asked "I presume that you have gone through the regular process, the USDA has OKed the use of this?" the answer he received was misleading. Mr. Mason referred to the FDA, which actually does the approving, as a "tough taskmaster." This implies a rigor on the part of FDA which was nonexistent. MSG was placed on the Generally Recognized As Safe list. The FDA required no formal testing of the chemical either inside or outside of its laboratories, conducted no thorough and in depth evaluation of any testing of the substance, and in fact merely assumed that chemical was safe since no doubts about it had been raised by reputable scientists. That situation is now changed and enough serious doubts have been raised by reputable scientists so that the safety of the chemical has been placed in doubt.

If a serious and formal review of the tests submitted by IMC had been conducted, a number of questions could have been raised. The rats used in the tumorgenicity study had a natural incidence of 41.1% "spontaneous tumors" suggesting that for best results different species of rats should have been used. Kidney lesions were noted in both the microscopic (page 75) and the pathological studies (page 63). Along with the tumor problems these suggest that further study might have been warranted. The result of the high incidence of tumors in the control species led to the dismissal of the finding that "a number of animals had developed tumors and a few had begun to show eye changes involving the cornea." Fertility studies were conducted but "it was difficult to determine the survival rate of the rat pups accurately." Again further study was suggested. For example, in the vitamin studies it was concluded that "the actual extent of the losses cannot be stated with exactness. However, it was apparent that no animal showed the effect of B_{12} avitaminoisis." Again further study was suggested. There are other questions about the studies which only serious and detailed review could clarify. Most basically, none of the studies were conducted on rats in age groups comparable to that of human infants.

All of the weaknesses or strengths in the various evaluations of MSG can only be resolved by a scientific debate within the scientific community. However, the law is quite clear that when a debate is in progress, such as the one being conducted over MSG, the chemical being debated cannot be legally added to the food supply. Only after safety has been conclusively shown should MSG be considered for addition to baby food. Even if MSG is finally proven to be safe the Select Committee on nutrition should still question the addition to baby food of a non-nutritious substance which serves no purpose.

It is quite important to emphasize that the failure of the FDA to conduct thorough and rigorous evaluation of all studies on MSG and its misrepresentation of the extent and depth of its own studies on MSG raise a question more serious than the safety of MSG. For example, the serious problems connected with the treatment of food by radiation escaped the notice of FDA, while thousands of pounds of the food were fed to American soldiers under FDA sanction, because

the Agency failed to thoroughly review the studies on radiation conducted by private researchers. In addition, a very serious controversy is presently being waged in the scientific community over the safety of the artificial sweetener cyclamate. This chemical, like MSG, is currently on the FDA Generally Recognized As Safe list. The misrepresentations and distortions presented by the FDA in answer to serious questions about the safety of MSG raise serious doubts about the Agency's ability to resolve problems of food nutrition and safety.

RALPH NADER.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE,
Washington, D.C., September 22, 1969.

Hon. GEORGE MCGOVERN,
Select Committee on Nutrition and Human Needs,
U.S. Senate,
Washington, D.C.

DEAR SENATOR MCGOVERN: Mr. Nadar has identified an error in the Staff Paper on Monosodium Glutamate (MSG) which we submitted to your Committee on July 22, 1969. In that Staff Paper, the following statement appears:

> Another of the new tests has to do with cytogenic abnormalities primarily in the area of chromosome breaks in the cells of treated animals or bacteria. When MSG was subjected to these highly critical tests no adverse reactions were noted.

The facts are that this statement was made on the basis of long time use of MSG in growth media for tissue cultures of cells in which chromosome breaks are studied (glutamic acid is a necessary component of growth media for this purpose and MSG is a convenient means of providing this). Cells grown in media containing MSG exhibit the normal background of 1 to 3% chromosome breaks.

Since the testimony was given, Dr. Legator, during August 4 through 8, 1969, has made a purposeful study of the effect of MSG in causing chromosome breaks. At levels as high as 1000 ppm (0.1%) MSG only normal background breakage occurred.

Although the statement has been confirmed by subsequent experience, its use in the July Staff Paper was unjustified. We regret that this occurred. Steps have been taken to avoid repetition of this kind of incident.

The important point from a public health standpoint is that MSG does not cause chromosome breaks. The error in the Staff Paper is inexcusable, and I regret that it was not called to my attention earlier.

In regard to the remaining three studies, the facts are these:

Study 1—Toxicity of MSG in incubating chicken eggs.—A study was conducted with 180 eggs which indicated no appreciable toxicity at dosage levels of 0.5 mg/egg to 10 mg/egg. No teratology was observed in non-surviving embroyos. The investigator noted death of two chicks (1.0 mg/egg) shortly after hatching, but no such mortality at higher dose levels (up to 10 mg/egg). This study is continuing. The investigator considers that at least 1000 eggs must be studied before any conclusions can be reached. At this point, no significant adverse effects have been identified.

Study 2—Effects of feeding MSG to weanling rats.—The reference for this "non-existant study" is: Hepburn, F. N. and Bradley, W. B. "The Glutamic Acid and Arginine Requirements for High Growth Rate of Rats Fed Amino Acid Diets," Journal of Nutrition *84*:305–312 (1964). FDA scientists were the source of my information about the study which is why I cited it in testimony. Neither I nor Dr. Hove were aware of any error in reporting the level of feeding until Mr. Nader stated that the reference should have been feeding levels of "30% of protein in the diet" instead of "30% of the diet." Since the study does exist, apparently Mr. Nader was able to check it and bring this error to our attention. Moreover, studies of this same general nature were in progress at FDA at least a month before I testified and are continuing now.

Study 3—Effects of feeding MSG to pregnant rats.—In challenging the fourth study, Mr. Nader assumes that no observation can be made until the animals are sacrificed and examined under a microscope. The pratice of reporting on significant stages of studies in which observations of behavior and growth can be made is a necessary part of any animal feeding study. My report on this study was correct at that time. I would report the same today on the study which is still

underway. In the study of pregnant rats and their offspring, a number of observations were made including (1) litter size, (2) birth size, (3) alertness of the offspring, and (4) gross development of the weanlings. No deviations from the normal range of development, as compared with controls, were observed.

In view of this information a revised copy of the Staff Paper is enclosed. After reviewing this area again, I do not believe that the issues raised about scientific facts justify removing MSG from the GRAS list at this time. Nevertheless, because of the questions raised by your Committee, I have asked the Academy to examine the data on which we have arrived at our conclusion and also any other information known to them. In the process of this review I would expect the Academy to examine FDA's evaluation of the data as well.

Sincerely yours,

HERBERT L. LEY, Jr., MD.,
Commissioner of Food and Drugs.

STAFF PAPER

MONOSODIUM GLUTAMATE

The Problem

Monosodium glutamate (MSG) has been generally recognized as safe with no limitations. A number of recent reports suggest that a new look at the safety of this widely used condiment should be taken.

Production and Use

Prior to World War II MSG was almost entirely used as a protein hydrolysate called soy-sauce for flavoring of Chinese food. Its production as a relatively pure substance has increased steadily up to an output of 46 million pounds in 1966 in the United States. In addition to the sodium salt, lesser amounts of the potassium and ammonium salt are used. All of these compounds are on the GRAS list. They are added to baby foods, candy, baked goods, meats, pickles, and soups. The highest level of use appears to be in soups where it may occur at about 0.4% of the fluid weight or about 3% on the dry basis. Medically, MSG is used for lowering high blood ammonia in liver failure diseases. The therapeutic dose is about 25 grams infused intravenously over a period of one or more hours.

FDA has developed two methods for the assay of MSG in Foods. One is colorimetric and will be proposed as Official, First Action, for adoption by the Association of Official Analytical Chemists. The other uses the Amino Acid Analyzer. Many baby foods declared MSG on the label; some representative samples have been analyzed, and found to range from 0.02 to 0.42% free MSG determined as glutamic acid.

Toxicity Reports

Recent reports on the Chinese Restaurant Syndrome in man indicated that some people experience flushing, dizziness, constriction about the chest and temples, weakness, headaches or nausea after eating Chinese food. Dr. Schaumburg, et al., reporting in Science, and Dr. Ambos and co-workers reporting in the New England Journal of Medicine, claim that the reaction is due to MSG used in Chinese foods. Most of the people subjected to their tests were found to be susceptible to pure MSG intakes of between two and eight grams. They reacted equally to free L-glutamic acid. The symptoms are usually of short duration lasting from a few seconds to 30 minutes. It might be assumed that when an individual has reacted to food in a Chinese Restaurant that he would tend to refuse to eat in such places in the future, but in most cases this does not happen.

Dr. J. W. Olney reported in a recent issue of Science that when new-born mice were injected with MSG subcutaneously, necrosis of several regions of the developing brain occurred. The doses were 0.5 to 4.0 grams per kilogram body weight. Other unpublished work by Dr. Olney indicates that similar lesions were observed after oral treatment of weanling mice and rats with doses of 0.5 to 1.0 gram of MSG per kilogram of body weight. He also noted similar results in one baby Rhesus monkey after injection of MSG. Earlier reports by others (Cohen, American Journal of Anatomy *120*:319, 1967; Lucas and Newhouse, AMA Archives of Ophthalmology *58*:193, 1957) had indicated lesions in the eyes of glutamate injected mice. Such studies indicate that MSG is toxic for young rodents. Glutamic acid is one of the 18 to 20 amino acids that occur naturally in food proteins. Each of the amino acids is toxic at some level. Glutamic acid is no exception.

The FDA has developed refined toxicological indicator methods that frequently show evidence of adverse effects of food chemicals even when the classical battery of toxicological tests show no adverse effect. One of the new tests has to do with the teratology of the incubating chicken egg. Very preliminary work in FDA laboratories, using 180 fertile eggs, showed no toxicity of MSG when doses as high as 200 parts per million (of egg) were injected at 0 hours or 96 hours of incubation. A definitive answer to the question of whether MSG is teratogenic must await the outcome of further experiments, because the investigator considers observation of at least 1,000 embryos necessary to arrive at a reliable answer, unless a high incidence of such effects should occur earlier. Another of the new tests has to do with cytogenic abnormalities, primarily the indication of chromosome breaks or growth inhibition of cells from tissue cultures. When MSG was subjected to these highly critical tests no adverse reactions were noted at levels as high as 1,000 parts per million. When fed to rats at levels of 30% of the protein in the diet (10% of the total diet) glutamic acid produced no adverse effects on growth. This observation confirms results reported by Hepburn and Bradley, Journal of Nutrition *84*:305 (1964), who noted that glutamic acid, at 30% of the amino acid mixture in the diet, permitted normal growth. An equivalent amount of MSG appeared to give a slightly diminished growth rate, although the efficiency of food utilization was not impaired.

Recent studies in the FDA laboratories have shown that L-glutamic acid fed to young rats at 25% of the total diet resulted in a reduction of growth rate of about 50% as compared with controls. This growth inhibition was partially prevented by the addition of 2% argenine to the diet, and the efficiency of food utilization was restored to normal. Young rats fed L-glutamic acid at 50% of the total diet survived for the duration of the test (about 4 weeks), but they did not grow.

When commercial MSG was fed to pregnant rats at a level of 10% of the diet (equivalent to 20 grams of MSG per kilogram of body weight) no adverse effect on the pregnancy occurred. Observations were made of litter size, birth size, alertness of the offspring, and gross development to weaning. No deviations from the normal range of development, as compared with controls were observed. Additional behavorial, biochemical, and histological studies will be conducted as the animals mature.

Other Considerations on MSG

The average normal dietary intake of glutamic acid in American adults is about 15 to 20 grams per day as supplied in food protein. It is difficult to understand why certain individuals should react to levels of glutamic acid as low as two grams per day.

The reports on the reaction of humans to Chinese food and on toxicity to developing nervous system require a new and thorough look at the safety of this widely used condiment.

MSG is widely used as a flavoring in dehydrated and canned soups, where it may be present at a level of 3% dry basis. During the two decades that such soups have been on the market we have been aware of no complaints of adverse reactions.

Several years ago there were reports that high levels of glutamic acid fed to children with low mental competence brought about an increase in the I.Q. scores. In the several years following this report in the 50's, many attempts to confirm this finding were made. The original claim could not be confirmed by everyone, and the subject is still controversial. However, it is to be noted that among hundreds of children who received large doses of glutamic acid (i.e. 10gm/day for several months or more as MSG) during these tests, there was a consistent absence of harmful side effects.

In short, the fact that we are taking a new look at monosodium glutamate should not cause alarm. Our scientists are familiar with the studies that have been mentioned before this Committee. We have seen no convincing evidence of a significant health problem in this area.

Partial Translation of a Paper Entitled "Observations of Pharmacological Actions and Toxicity of Sodium Glutamate, With Comparisons Between Natural and Synthetic Products"

Saburo Hara, Takeshi Shibuya, Koji Nakakawaji, Meitestu Kyu, Yukio Nakamura, Hideo Hoshikawa, Takako Takeuchi, Taijiro Iwao, and Hideki Ino

Journal of the Tokyo Medical College, Volume 20(1), 1962

II. MATERIALS AND METHODS

The experimental sample, MSG was provided by Ajinomoto Company. Natural L-sodium glutamate was designated as NL, synthetic L-sodium glutamate as SL, and synthetic D-sodium glutamate as SD. The chemical formula is shown in Figure 1. The concentrations of solutions tested were 0.2%, 2% and 20%. Figure 1 shows the chemical formula of MSG. The experimental animals used were goldfish, frog, Wister male rat, rabbit, cat and dog. Plant parts were used for study of the effect on plants, and for an experiment in taste, the human tongue was used. All other experimental methods will be described in Experimental Results Section.

III. EXPERIMENTAL RESULTS

A. Studies on the toxicity of various MSG

For toxicity studies by forced feeding of test material in rats, it is very important to observe the details of general phenomena in addition to the growth curve for the materials which are expected to give a very small amount of toxicity. In order to obtain a most suitable growth curve it is desirable to use immature and healthy animals. Therefore, we used the 120 g Wister male rat. Many times the required number of these animals were grown for two weeks under control conditions and better or healthier animals were selected for this experiment. The feeding was done by a type of constant temperature feeding box, at temperature of 22° C±1°. Five animals per cage per group and 10 groups were used. This is shown in Drawing 1. The feed, Oriental NMF, was used (Table 2). Three drops of vitamin B complex was added to drinking water. Water was changed daily. Fresh vegetables were given weekly.

For testing material NL, SL and SD at concentrations of 0.2 percent, 2 percent and 20 percent solution were divided into three and given to rats at 1 cc per 100 g per day for 90 days at a set time in day according to the Zonday(?) method of forced feeding. In addition, for control experiments 20 mg of sodium chloride per Kg was force fed to rats. This amount represents the corresponding equivalent amount of MSG per 50 Kg body weight(?).

Body weights were measured daily at a certain time using an automatic balance with 0.5 g sensitivity. At the same time the feed consumption and water consumption were both recorded. In addition the motion of the animal, the appearance, the hair growth, nose breathing or not, change in appearance of eyes and other general phenomena were also made and recorded. Moreover during forced feeding, if the compounds were pushed into the lung by mistake these animals were removed from the experiment. After 90 days of forced feeding the rats were sacrificed immediately by bleeding and the weight and volume of intestinal organs were measured and compared with the control. The various intestinal organs were preserved in formalin solution and pathological studies were made.

1. The growth experiments of rat by forced feeding of various MSG.

(1) Control experiment: Average body weight 190 g prior to start of experiment. Experimental animals after 90 days weighed 336.2 g and showed good daily body weight gains. This growth curve was used for the standard and the general conditions as well as water and feed consumption. Condition of feces and urine was all recorded in detail, and compared with other experimental animals.

(2) The forced feeding experiment with NL:

(i) With the basic amount of NL at 20 mg/Kg, the body weight of rats increased after forced feeding. Average body weight at the start was 115 g; after 90 days it had increased to 319.6 g. No abnormal appearance of general conditions were observed during this period and no differences were observed when compared to the control (Table 4 a,b and Table 13).

(ii) With 10 times amount of the basic NL (200 mg/Kg) the body weight after forced feeding still continued to increase and increased smoothly. That is, the body weight curve increased linearly and was not different from controls. The average body weight at the beginning, 160.2 g, reached 336.6 g after 90 days. (Table 5 a,b and Table 13). The water and feed were all normal and the hair growth appeared normal.

(iii) With 100 times that of NL basic amount (2000 mg/Kg) the body weight of the rats increased from 156.8 g to 302.6 g after 90 days. During that period no abnormal symptoms were seen, the appetite of the animals was the same as controls, the appearance of the hair was normal. No differences were observed in the eyes, nose. However, after 5 days feed in some cases a sudden increase in body weight was seen and in other cases slight suppression in the rat of body increases were shown after 60 days. However, from average values of growth curves no meaningful differences were observed (Table 6 a,b and Table 13).

(3) SL Feeding:

(i) With the basic amount of SL (20 mg/Kg) the body gain increases were normal from an average of five animals of 131.8 g the body weight reached 306.2 g after 90 days. No differences can be made when compared with control (Table 7 a,b and Table 13). During this period a temporary decrease in body weight for 5 rats was observed but this was found to be due to the leaking in the water supply. General conditions of the animal, behavior, hair growth, eye appearance and skin condition were normal.

(ii) With 10 times that of basic SL (200 mg/Kg), the body weight of the rats increased daily. The average weight of the rat at the beginning was 155.2 g and increased to 334 g after 90 days. During this time, general conditions were excellent and appeared to be superior to that of the basic amount of SL (20 mg/Kg). No differences were observed when compared with control (Table 8 a,b and Table 13).

(iii) With 100 fold that of basic SL (2000 mg/Kg) feeding the body weight of the rats increased daily from 158.4 g average to 288.4 g after 90 days. The general conditions of the rats were good during this time. No abnormality was observed with regard to eyes, nose, or any sign of sickness. However, after 13 days, a slight and temporary loss in body weight was observed due to the water loss. This was however recovered after 15–20 days and normal growth rate was observed until 90 days (Table 9 a,b and Table 13).

(4) SD force feeding experiment:

(i) At 20 mg/Kg feeding the body weight increased from 126.8 g to 298.3 g in 90 days. During 60 days some weight loss was observed and some animals showed reduced growth development but no abnormality (any symptom) was shown when compared with the control experiment. No meaningful differences were recognized. (Table 10 a,b and Table 13).

(ii) Feeding at 200 mg/Kg, the body weight increased from 145 g to 305.4 g in 90 days. No abnormalities were found and hair growth conditions, activities and appetites were normal. No symptoms were observed (Table II a,b and Table 13).

(iii) Feeding at 2000 mg/Kg the body weight increased from 165 g to 287.8 g after 90 days. During this period the activity and the hair growth were normal. No change in eye appearance and no nose breathing phenomena were seen. No abnormal symptoms were observed in skin. Some reduction in body weights were seen when compared to that of control group. However, a meaningful difference cannot be obtained when compared with the control group (Table 12 a,b and Table 13).

2. *Studies on the effect of feeding on the weight and volume of intestinal organs in rats.*—After 90 days continuous feeding all the rats were sacrificed by bleeding. Their organs, that is, brains, heart, lung, stomach, kidney, liver and spleen (were removed) and weight and volume of various organs were measured and recorded. The results were shown in Table 14 a, b, c. No differences were seen between control group and experimental group. Also, no differences were seen between the experimental groups.

3. *Pathological studies.*—After the organs were preserved in formalin solution, the pathological studies of the organs were performed by hematoxylin-eosin staining. The results show that in stomach the complete and normal gland structure was seen and the upper epidermic tissue cells and tissue structure were normal. Similarly, the tissues and gland structure of the small and large intestine were normal and no swelling or abnormality were seen. In the intestinal structure (the layer of viscous (mucous) membrane) no increase in free cells were recognized in the tissues under the mucous, and no swelling or blood clotting symptom were recognized. In liver, no abnormal fatty liver tissue or other abnormality was seen. The perfect normal liver structure was maintained. In spleen, no abnormal cell number or blood clotting or tissue fattening phenomenon were observed. In kidney, no abnormality was observed in tissues or cells. Others such as the brain tissue, heart and lung were also studied but no abnormalities were seen.

4. Small Conclusion (?)

B. Studies on the general pharmacological reactions

1. *Toxicity against various animals by force feeding of large amount of samples.*—One to 10 g per Kg were force fed to dogs and cats. No abnormal symptoms appeared. Vomiting occurred when large amounts were fed to dog. However, when large amounts of sample were mixed with small amounts of rice and vegetable or Miso and cooked, no vomiting was shown. Feeding of 0.5 to 1 g or higher per Kg to rabbits for two weeks by intravenous injection showed no abnormal effect.

2. *Effect on plant seed germination.*—The seed of the "plenem partens" (?) were studied at room temperature for 8 days. These experiments were based on the Hara method by using 40 to 520 times concentrated (?). The results are shown in Figures 15–17 (Tables). At lower concentration, stimulation on the germination and development were seen by NL, SL and SD forms. However, differences between the effects by NL, SL and SD were not seen.

3. *Effect on small fish.*—Three fishes per group of 5 centimeters length were used in solutions containing 0.01% to 10% of NL, SL and SD. Goldfish were placed in the solutions. General phenomena were observed during 24 hours. Table 18 shows the result of this experiment. The fish in the NL solution increased their mobility at the concentration of 0.05% The fish mobility slightly increased in SL and SD solution at 0.01%. At 0.1 to 3% the motion stopped after the increased activity. At the concentration above 4%, spasm-like motions were observed immediately and (the fish) floated to the top and stopped moving after a while. After 10 hours those fish are dead. Therefore this kind of phenomena increased when the concentration increased and the time required for this type of phenomena decreased on increased concentration. Moreover, the SD form showed greater effect when compared with NL and SL forms.

4. *Studies on the taste by human tongue.*—The NL and SL both have taste—no difference. SD. does not have taste or flavor.

5. *Studies of effect on isolated frog heart.*—0.1% to 1% MSG solution were perfused into the isolated frog heart. No reactions were shown with NL, SL and SD. At 10% an apparent reduction in the pulse and temporary pulse stoppage was observed. This probably is due to the overconcentration of MSG which caused some physical damage.

6. *Effect on respiration and blood pressure in rabbit.*—Urethane-treated rabbits were used for respiration and blood pressure studies. Intravenous injection at 1 mg/Kg showed no effect with NL, SL and SD. At 10 mg/Kg with SD, the respiration slightly increased. At 100 mg/Kg, NL, SL and SD all show some slight increase in respiration rate, and increase in blood pressure. At 500 mg/Kg increase in respiration and blood pressure were observed but respiration did not stop at 800 mg/Kg.

7. *Effect on smooth muscle.*—Isolated rabbit intesting was used. The Magnus method was used. No effect was seen at 0.01%. At 0.05% only SD showed some decrease in tension. At 5%, NL, SL and SD all showed slight temporary decreases in tension and decreases in pulse.

8. *Small Conclusion.*

C. Effect on the brain nerve pulse. (EEG?)

Cat of 2.5 to 3 Kg body and Wister male rats of about 300 g weight were used. (See Methodology)

1. Study in cat.

2. Cats were used for neurological tests (experimental detail is omitted).
3. Neuropotential study by injection of MSG solution into skull (Detail omitted).
4. Conclusions.

D. Effect on metabolism

Effect on blood sugar metabolism and blood electrolytes, sodium, potassium, calcium, chloride and protein metabolism, total blood protein, protein fraction changes, and lipid metabolism (blood cholesterol) were measured. The experimental animal was the mature male rabbit weighing 2.5 Kg. We have already described the general pharmacology reactions at 100 mg and 500 mg/Kg. Injection of MSG was intravenous into urethane treated rabbits. Respiration and blood pressure raises and these amounts are the minimum required to induce this reaction(?). Therefore at these doses, or dosed continuously for 10 days, injection was made and the metabolic changes were studied(?).

1. *Blood sugar studies.*—Sugar was measured by the Somogyi method. SD, after intravenous injection of 100 mg/Kg, a slight increase in blood sugar was seen and this started to decrease after 45 minutes. With SL, after 60 minutes from injection, the blood sugar increased slightly and showed no difference from that of NL. Both SL, NL and SD showed slightly decreased blood sugar after 120 minutes, when 500 mg/Kg were injected. Similar phenomena of sugar decrease was observed with SD after 50 minutes. With SL, the blood sugar increased and reached a maximum at 60 minutes but showed a similar effect to that of 100 mg/Kg. With the NL solution, similar results are obtained.

2. *Blood electrolyte studies.*—Fluorometric analysis was used for sodium, potassium, calcium. The Sharles and Sharles method was used for chloride determination. The change in electrolyte concentration was obtained by measurement of electrolytes before and after the injection.

In the case of 100 mg/Kg dosage, injection of SD showed an increase of sodium and chloride, calcium decreased after 15 minutes but sodium increased after 30 minutes. Potassium decreased at 15 and 30 minutes but after 120 minutes recovered to normal. Both calcium and chloride recovered to normal value after 120 minutes but sodium increased at the rate of 5% for 240 minutes. With SL sample, the tendency of increase of sodium and chloride was slightly less than SD, calcium and potassium changes were similar to that of SD sample (Figure 10). With 500 mg/Kg sodium, calcium and chloride increased immediately after injection with SD. The increase of sodium became more pronounced at 120 minutes which gives the increased rate of 10%. The decrease in potassium became more profound than that of 100 mg/Kg and the rate of decrease reached about 13% after 120 minutes and apparently had an opposite effect to that of sodium. The rate of calcium increase was next to sodium. After 240 minutes a 5% increase still appeared. The change in chloride was very small and recovered to normal after 120 and 240 minutes. The effect of SL is similar to that of SD, in that sodium, calcium and chloride increased but potassium decreased.

3. *Blood cholesterol.*—Blood cholesterol was determined by Zak's method. In the case of a single intravenous injection of 100 mg/Kg there was an immediate decrease of blood cholesterol, with NL, SL and SD. The decrease of cholesterol was more profound with SD and reached 18% after 30 minutes, and continued until 240 minutes. The effects of SL and NL are similar but a 10% decrease was maintained for 240 minutes. At 500 mg/Kg dosage, SD and SL both caused a rapid decrease of cholesterol, at the rate of 20% at 15 minutes, but temporarily showed some increase in cholesterol at 60 minutes but after that showed a decrease again. With NL, the decrease of cholesterol was not rapid. The rate of decrease however reached maximum at 60 minutes. After that slight tendency of increase in cholesterol was shown. All three MSG samples showed decrease of cholesterol up to 240 minutes.

4. *Blood protein.*—500 mg/Kg was continuously injected for 10 days. The blood protein fractions were studied.

1. Total blood protein.—The protein content before injection was 6.25 to 6.6 g/100 ml. Injection of NL, SL and SD did not effect the total protein level. Sometimes however, there was a slight increase.

2. Blood protein fractions.—Paper electrophoresis was used for protein fractionation. Decrease in albumin fraction was shown with NL, SL and SD and at the eleventh day, 0.43 to 0.60 g/100 ml decrease was shown. The alphaglobulin fraction tended to increase with NL and SD. SD showed a slightly higher increase rate but no change was seen with SL. Little

change in beta-globulin fraction was noticed with NL, SL and SD. Increase in gamma-globulin fraction was seen with NL, SL and SD and reached 0.2 to 0.3 g/100 ml at the end of feeding. The increase was highest with SD. Therefore the common effect of these forms of MSG would suppress the albumin formation and tend to increase the alpha-globulin and gamma-globulin and have no effect on beta-globulin formation. Therefore, a decrease in albumin and increase in globulin resulted in reversed value of A/G ratio.

5. *Effect of continuous intravenous injection on the body weight.*—The body weight and general condition after injection with 5 mg/Kg of NL, SL and SD showed very little difference in the increase of body weight among the three groups. After 11 days injection, a 5 to 7% increase in body weight was seen and no evidence was shown that injection of relatively large amounts of MSG decreased body weight.

Conclusions and Summary omitted.

Effects of Some Salts of Glutamic Acid on Pregnant Rabbits and Their Fetuses

Recently it has become an issue that thalidomide has something to do with developmental defects of fetuses. S. Tugrul has attempted an experiment, using rabbits, to see of glutamic acid and the related substances have the same effect as thalidomide on animals and she has demonstrated that the amino acid evoked teratogenic effects. We have also made the same kind of experiments on rabbits to examine whether or not glutamic acid hydrochloride (Glu-HCl) and monosodium glutamate (Na-Glu) might induce teratogenic effects.

MATERIAL AND METHOD

Twenty-four cases of pregnant rabbits were prepared and divided into two groups; that is, one group which consists of 15 cases administered Glu-HCl in dose of 25 mg/kg orally once a day for 15 days, and the other group of 9 cases, administrated Na-Glu in the same dose and method as in the former.

On the other hand, 11 cases were prepared as control, given saline solution. These rabbits (only female) were palpated carefully to diagnose status of pregnancy on lower abdomen every three days after 11 days of copulation. (Fig. 1) After delivering, each group was divided into two more groups: in one group, mother rabbits and their litter were autopsied within post-portum three days; in the other group only litter were autopsied after being nursed for 30 days. (Fig. 2) For an observation of skeletal characteristics in fetuses, the skeletal system was stained with alizarin red after clearing way of soft tissue with potassium hydroxide.

RESULTS

1. Conception rate was presented statistically the same pattern in the treated group as in control.

2. Abnormal cases of pregnancy.—The majority of gravid animals were presented pregnancy to be maintained normally. On the other hand, some abnormal changes of gestation were observed with similar insidence in all groups as follows:

In the group administrated Glu-HCl, 6 cases among 15, at the incidence of 21%, presented more or less abnormal status: abortion (one case), resorption of all fetuses (one case) and some portion of fetuses (two cases) and death of mother animal (two cases).

In the group administered Na-Glu, 2 cases among 8, incidence of 25%, presented abnormality: abortion of all fetuses on 26th day of pregnancy (one case) and death of mother animal (one case).

In control group 3 cases among 11, incidence of 27%, presented abnormality: abortion (one case) and resortion (two cases). We have never seen external and skeletal malformation in any aborted fetus of each group.

3. Littersize and nursing.—Nursing rates of each group were presented in Fig. 3. Mean littersize were 8.1 ± 2.21 (SD) in Glu-HCl-treated group, 7.2 ± 2.23 in Na-Glu-treated group, and 7.5 ± 2.27 in control group. There was not significant difference among these groups. ($P < 0.05$) The change of littersize during nursing

term of post-portum 30 days was almost similar pattern in all groups. The nursing rate in all groups fell finally to the level of 40% (equivalent to 3 youngs).

4. Aspects of fetuse's external and skeletal form.—The results obtained are summarized in table 2–4 and plate 1–12. In any group, we could not recognize external and skeletal malformation in fetuses.

5. Average body weight of youngs in each group and weight of main visheral organs of both youngs and mothers were shown in table 5. The former means average weight of youngs in each group and the litter, average relative value to body weight.

There existed not so severe difference of body weight of litter between the treated group and the control thought that in the former group was generally rather lower than that in the later. The weight of visheral organs, of youngs that is, testis ovary, and adrenal gland, was not different between treatment and control group, either in 3 day old or 30 day old. While, that of mothers, that is, overy, adrenal gland, liver, kidney, spleen, where not different between those two groups.

CONCLUSION

In the results of the experiment in which either Glu-HCl or Na–Glu was given orally to pregnant rabbits, it was recognized that there were no adverse effects to be caused by these substances, that is, as to the rate of conception, mean littersize and nursing rate, there was no difference between in the treatment group and in control.

In the young, there was not any abnormality in aspects of the gros, skeletal formations and visheral organ.

On the other hand, some abnormal changes of gestation such as abortion or resorption of fetuses were observed.

However, incidence of these cases were almost similar in both treatment and control group.

Gross and skeletal malformation in the aborted fetuses was not observed after inspection.

From the aspects mentioned above, the results of our present experiment were contradicted with that of S. Tugrul's.

However, our conclusion was that neither Glu–HCl nor Na–Glu had any influence upon pregnant rabbits and their youngs in our experiment.

Fig. 1. Time Schedule during Pregnancy

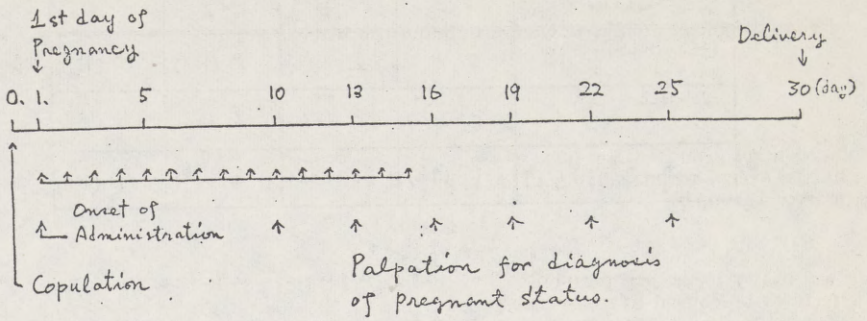


Fig. 2. Time Schedule after Delivery

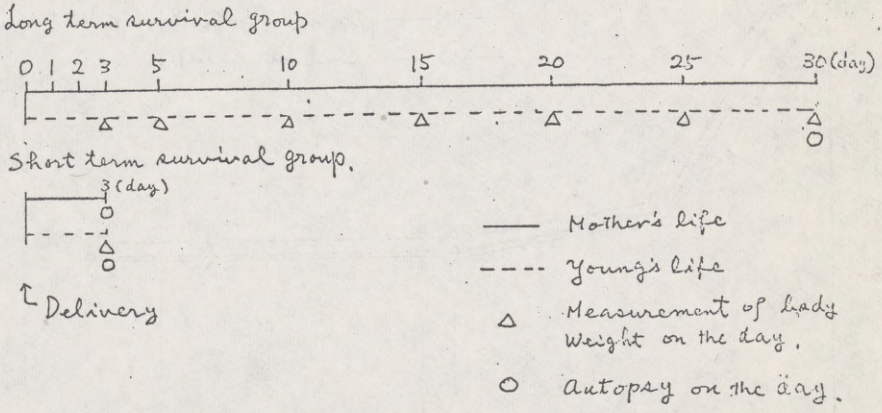


Table. 1. Distribution of conception rate in serviced female rabbit of each group.

Group \ No. of cases / Conception rate ※		1/4	1/3	1/2	1/1
Glu-HCL treated group	15	0	2 (13%)	2 (13%)	11 (73%)
Na-Glu treated group	9	1 (11%)	2 (22%)	2 (22%)	4 (44%)
Control	11	1 (9%)	1 (9%)	2 (18%)	7 (64%)

※ Frequency of gestation / Frequency of service

Fig. 3. Changes in Nursing rate of Three Group

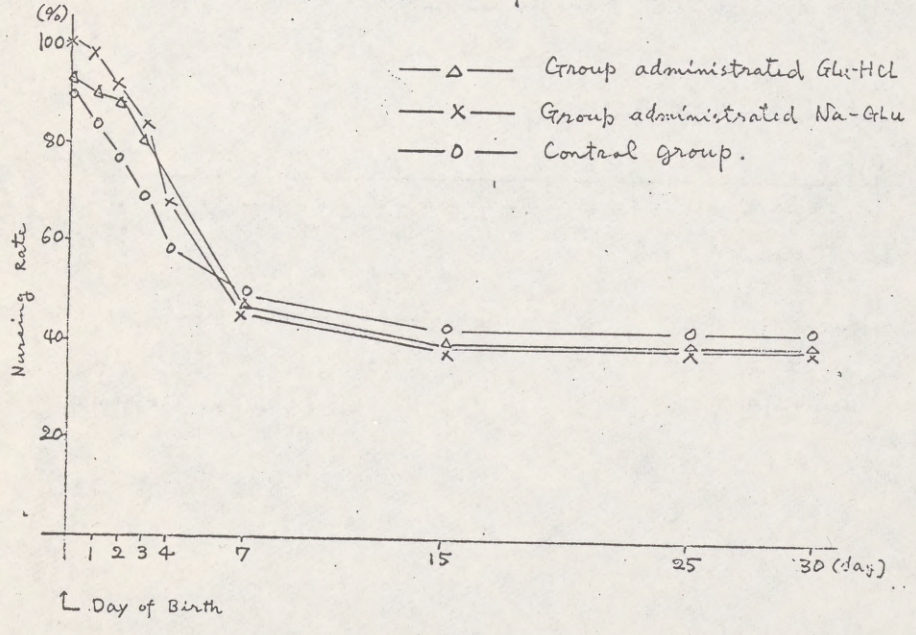


Table. 2.

Results of Observation in Youngs in Glu-HCl Treated Group.

Mother No.	Young No.	Observation Schedule of Youngs after Delivery (△ ···· External Inspection; ○ ···· Autopsy; ⊗ ···· Posthumous Inspection)									Results of Observation for Malformation											
											External				Skeletal							Visceral Organs.
											Face											
		0 (day)	1	2	3	4	5 ~ 10	11 ~ 20	21 ~ 29	30	Nose	Eye	Ear	Other Part	Cranial Bone	Vertebrae	Ribs & Sternum	Limbs	Occipital	Pelvis	Tail	
4.	1.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	2.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	3.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	4.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	5.				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	6.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	7.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	8.				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	9.				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–
	10.			△⊗							–	–	–	–	–	–	–	–	–	–	–	–
	11.	△⊗																				
	12.	△⊗																				
21.	1				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	2				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	3				△				△⊗		–	–	–	–	–	–	–	–	–	–	–	–
	4				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	5				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	6				△	△⊗					–	–	–	–	–	–	–	–	–	–	–	–
	7				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	8				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
22.	1				△	△⊗					–	–	–	–	–	–	–	–	–	–	–	–
	2				△				△⊗		–	–	–	–	–	–	–	–	–	–	–	–
	3				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	4				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	5				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	6				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	7				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	8				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
	9				△					△○	–	–	–	–	–	–	–	–	–	–	–	–
3.	1				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	2				△				△⊗		–	–	–	–	–	–	–	–	–	–	–	–
	3				△⊗						–	–	–	–	–	–	–	–	–	–	–	–
	4				△	△⊗					–	–	–	–	–	–	–	–	–	–	–	–
	5				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	6			△⊗							–	–	–	–	–	–	–	–	–	–	–	–
	7			△⊗							–	–	–	–	–	–	–	–	–	–	–	–
	8	△⊗																				
	9	△⊗																				
7.	1				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	2				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	3				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–
	4				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–
	5				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–
	6				△⊗						–	–	–	–	–	–	–	–	–	–	–	–
	7				△⊗						–	–	–	–	–	–	–	–	–	–	–	–
	8				△⊗						–	–	–	–	–	–	–	–	–	–	–	–

Table. 2. (Continue)

Results of Observation in Youngs in Glu-HCl Treated Group.

Mother No.	Young No.	Observation Schedule of Youngs after Delivery: △ External Inspection, ○ Autopsy, ⊗ Posthumous Inspection									Results of Observation for Malformation											
											External				Skeletal							
											Face											Visceral Organs
		0 (day)	1	2	3	4	5~10	11~20	21~29	30	Nose	Eye	Ear	Other Part	Cranial Bone	Vertebrae	Ribs & Sternum	Limb	Digital	Pelvis	Tail	
4	1				△○						—	—	—	—	—	—	—	—	—	—	—	—
	2				△○						—	—	—	—	—	—	—	—	—	—	—	—
	3				△○						—	—	—	—	—	—	—	—	—	—	—	—
	4				△○						—	—	—	—	—	—	—	—	—	—	—	—
	5				△○						—	—	—	—	—	—	—	—	—	—	—	—
	6				△○						—	—	—	—	—	—	—	—	—	—	—	—
	7				△○						—	—	—	—	—	—	—	—	—	—	—	—
	8	△⊗									—	—	—	—	—	—	—	—	—	—	—	—
25	1				△○						—	—	—	—	—	—	—	—	—	—	—	—
	2				△○						—	—	—	—	—	—	—	—	—	—	—	—
	3				△○						—	—	—	—	—	—	—	—	—	—	—	—
25	4				△○						—	—	—	—	—	—	—	—	—	—	—	—
	5				△○						—	—	—	—	—	—	—	—	—	—	—	—
32.	1				△○						—	—	—	—	—	—	—	—	—	—	—	—
	2				△○						—	—	—	—	—	—	—	—	—	—	—	—
	3				△○						—	—	—	—	—	—	—	—	—	—	—	—
	4				△○						—	—	—	—	—	—	—	—	—	—	—	—
	5				△○						—	—	—	—	—	—	—	—	—	—	—	—
	6				△○						—	—	—	—	—	—	—	—	—	—	—	—
	7				△○						—	—	—	—	—	—	—	—	—	—	—	—
	8				△⊗						—	—	—	—	—	—	—	—	—	—	—	—
33.	1				△○						—	—	—	—	—	—	—	—	—	—	—	—
	2				△○						—	—	—	—	—	—	—	—	—	—	—	—
	3				△○						—	—	—	—	—	—	—	—	—	—	—	—
	4				△○						—	—	—	—	—	—	—	—	—	—	—	—
	5	△⊗									—	—	—	—	—	—	—	—	—	—	—	—
	6	△⊗									—	—	—	—	—	—	—	—	—	—	—	—
34.	1				△○						—	—	—	—	—	—	—	—	—	—	—	—
	2				△○						—	—	—	—	—	—	—	—	—	—	—	—
	3				△○						—	—	—	—	—	—	—	—	—	—	—	—
	4				△○						—	—	—	—	—	—	—	—	—	—	—	—
	5				△○						—	—	—	—	—	—	—	—	—	—	—	—
	6				△○						—	—	—	—	—	—	—	—	—	—	—	—
3.	1				△○						—	—	—	—	—	—	—	—	—	—	—	—
	2				△○						—	—	—	—	—	—	—	—	—	—	—	—
	3				△○						—	—	—	—	—	—	—	—	—	—	—	—
	4				△○						—	—	—	—	—	—	—	—	—	—	—	—
	5		△⊗								—	—	—	—	—	—	—	—	—	—	—	—
	6				△○						—	—	—	—	—	—	—	—	—	—	—	—
	7				△○						—	—	—	—	—	—	—	—	—	—	—	—
	8		△⊗								—	—	—	—	—	—	—	—	—	—	—	—
	9				△○						—	—	—	—	—	—	—	—	—	—	—	—
	10				△○						—	—	—	—	—	—	—	—	—	—	—	—
Total	89	82/89	80/89	77/89	72/89	29/46	19/46	16/46	16/46	16/46												
Nursing rate %		92.1	89.9	87.7	79.5	71.5	46.8	39.5	39.5	39.5												

Table. 3.

Results of Observation in Youngs in Na-Glu Treatment Group

Mother No.	Young No.	Observation Schedule of Youngs after Delivery: △ External Inspection; ○ Autopsy; ⊗ Posthumous Inspection									Results of Observation for Malformation												
											External				Skeletal								Visceral Organs
											Face												
		0 (day)	1	2	3	4	5~10	11~20	21~29	30	Nose	Eye	Ear	Other Part	Cranial Bone	Vertebrae	Ribs & Sternum	Limb	Diaphragm	Pelvis	Tail		
12.	1				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	2				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	3				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	4				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	5				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	6				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	7				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	8				△		△⊗				–	–	–	–	–	–	–	–	–	–	–	–	–
14.	1				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	2				△					△○	–	–	–	–	–	–	–	–	–	–	–	–	–
	3				△			△⊗			–	–	–	–	–	–	–	–	–	–	–	–	–
	4				△			△⊗			–	–	–	–	–	–	–	–	–	–	–	–	–
	5				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
	6				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
	7				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
	8				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
9.	1				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
	2				△⊗						–	–	–	–	–	–	–	–	–	–	–	–	–
	3				△		⊗				–	–	–	–	–	–	–	–	–	–	–	–	–
	4				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
	5				△	⊗					–	–	–	–	–	–	–	–	–	–	–	–	–
28	1				△					△	–	–	–	–									
	2				△					△	–	–	–	–									
	3				△⊗						–	–	–	–	–	–	–	–	–	–	–	–	–
	4			△⊗							–	–	–	–	–	–	–	–	–	–	–	–	–
23	1				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	2				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	3				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	4				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	5				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	6				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	7		△⊗								–	–	–	–	–	–	–	–	–	–	–	–	–
	8			△⊗							–	–	–	–	–	–	–	–	–	–	–	–	–
12.	1				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	2				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	3				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	4				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	5				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	6				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	7				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	8				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	9				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
	10				△○						–	–	–	–	–	–	–	–	–	–	–	–	–
Total	43	43/43	42/43	40/43	38/43	15/25	13/25	11/25	11/25	11/25													
Nursing rate(%)		100	97.2	90.2	83.2	67.0	45.2	38.3	38.3	38.3													

Table. 4.

Results of Observation in Youngs in Saline Control Group.

Mother No.	Young No.	Observation Schedule of Youngs after Delivery (△ External Inspection, ○ Autopsy, ⊗ Posthumous Inspection)								Results of Observation for Malformation												
										External				Skeletal								
										Face												Urinary and Org.
		0 (day)	1	2	3	4	5~10	11~20	21~29	30	Nose	Eye	Ear	Other Part	Cranial Bone	Vertebrae	Limbs. Sternum	Limbs.	Digital	Palus	Tail.	
10.	1				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	2				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	3				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	4			△⊗							−	−	−	−	−	−	−	−	−	−	−	−
	5		△⊗								−	−	−	−	−	−	−	−	−	−	−	−
	6		△⊗								−	−	−	−	−	−	−	−	−	−	−	−
	7		△⊗								−	−	−	−	−	−	−	−	−	−	−	−
11.	1									△○	−	−	−	−	−	−	−	−	−	−	−	−
	2									△○	−	−	−	−	−	−	−	−	−	−	−	−
	3						△⊗				−	−	−	−	−	−	−	−	−	−	−	−
	4									△○	−	−	−	−	−	−	−	−	−	−	−	−
	5				△⊗						−	−	−	−	−	−	−	−	−	−	−	−
	6				△⊗						−	−	−	−	−	−	−	−	−	−	−	−
18.	1									△○	−	−	−	−	−	−	−	−	−	−	−	−
	2									△○	−	−	−	−	−	−	−	−	−	−	−	−
	3							△⊗			−	−	−	−	−	−	−	−	−	−	−	−
	4									△○	−	−	−	−	−	−	−	−	−	−	−	−
	5									△○	−	−	−	−	−	−	−	−	−	−	−	−
	6							△⊗			−	−	−	−	−	−	−	−	−	−	−	−
	7									△○	−	−	−	−	−	−	−	−	−	−	−	−
	8									△○	−	−	−	−	−	−	−	−	−	−	−	−
9.	1									△○	−	−	−	−	−	−	−	−	−	−	−	−
	2									△○	−	−	−	−	−	−	−	−	−	−	−	−
	3									△○	−	−	−	−	−	−	−	−	−	−	−	−
	4									△○	−	−	−	−	−	−	−	−	−	−	−	−
	5									△○	−	−	−	−	−	−	−	−	−	−	−	−
	6						△⊗				−	−	−	−	−	−	−	−	−	−	−	−
6.	1				△○						−	−	−	−	−	−	−	−	−	−	−	−
	2				△○						−	−	−	−	−	−	−	−	−	−	−	−
	3				△○						−	−	−	−	−	−	−	−	−	−	−	−
	4				△○						−	−	−	−	−	−	−	−	−	−	−	−
	5				△○						−	−	−	−	−	−	−	−	−	−	−	−
	6				△○						−	−	−	−	−	−	−	−	−	−	−	−
	7				△○						−	−	−	−	−	−	−	−	−	−	−	−
	8				△○						−	−	−	−	−	−	−	−	−	−	−	−
	9			△⊗							−	−	−	−	−	−	−	−	−	−	−	−
	10				△⊗						−	−	−	−	−	−	−	−	−	−	−	−

Table. 4. (Continue)

Results of Observation in Youngs in Saline Control Group

Mother No.	Young No.	Observation Schedule of Youngs after Delivery: 0 (day)	1	2	3	4	5 ~ 10	11 ~ 20	21 ~ 29	30	Results of Observation for Malformation: External — Face: Nose	Face: Eye	Face: Ear	Face: Other Part	Skeletal: Cranial Bone	Skeletal: Vertebrae	Skeletal: Ribs & Sternum	Skeletal: Limb	Skeletal: Digital	Skeletal: Pelvis	Skeletal: Tail	Visceral Organs
7.	1				△⊗						−	−	−	−	−	−	−	−	−	−	−	−
	2				△⊗						−	−	−	−	−	−	−	−	−	−	−	−
	3				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	4				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	5				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	6				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	7		△⊗								−	−	−	−	−	−	−	−	−	−	−	−
6.	1				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	2				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	3				△		△⊗				−	−	−	−	−	−	−	−	−	−	−	−
	4				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	5				△		△⊗				−	−	−	−	−	−	−	−	−	−	−	−
29.	1	△⊗									−	−	−	−	−	−	−	−	−	−	−	/
	2	△⊗									−	−	−	−	−	−	−	−	−	−	−	/
	3	△⊗									−	−	−	−	−	−	−	−	−	−	−	/
	4			△⊗							−	−	−	−	−	−	−	−	−	−	−	−
	5			△⊗							−	−	−	−	−	−	−	−	−	−	−	−
	6	△⊗									−	−	−	−	−	−	−	−	−	−	−	−
	7				△	⊗					−	−	−	−	−	−	−	−	−	−	−	−
	8				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	9				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
	10				△			△⊗			−	−	−	−	−	−	−	−	−	−	−	−
	11				△			△⊗			−	−	−	−	−	−	−	−	−	−	−	−
	12				△					△○	−	−	−	−	−	−	−	−	−	−	−	−
9"	1				△○						−	−	−	−	−	−	−	−	−	−	−	−
	2				△○						−	−	−	−	−	−	−	−	−	−	−	−
	3				△○						−	−	−	−	−	−	−	−	−	−	−	−
	4				△○						−	−	−	−	−	−	−	−	−	−	−	−
	5				△○						−	−	−	−	−	−	−	−	−	−	−	−
	6				△○						−	−	−	−	−	−	−	−	−	−	−	−
	7				△○						−	−	−	−	−	−	−	−	−	−	−	−
	8			△⊗							−	−	−	−	−	−	−	−	−	−	−	−
	9	△⊗									−	−	−	−	−	−	−	−	−	−	−	−
21.	1	△⊗									−	−	−	−								
	2		△⊗								−	−	−	−								
	3	△⊗									−	−	−	−								
	4		△⊗								−	−	−	−								
	5				△⊗						−	−	−	−								
Total		75	68/75	62/75	57/75	51/75	35/51	31/51	21/51	29/51	29/51											
Nursing rate (%)			89.7	82.9	76.2	68.5	58.3	49.4	42.7	42.7	42.7											

Table. 5. Details of mean Values on mothers and youngs for each experimental group.

Group	No. of Pregnant Rabbits	Mean Litter Size	Average Body Weight in Youngs		Mean relative Value of Organ Weight to Body in Youngs						Mean relative Value of Organ Weight to body in Mother Rabbits				
					3 Day Old			30 Day Old.							
			3 day old	30 day old	Testis	Ovary	Adrenal gland	Testis	Ovary	Adrenal gland	Ovary	Adrenal Gland	Liver	Kidney	Spleen
Glu-HCl treated	15	8.1 ±2.21	69.5 ±11.2	352.0 ±92.1	6.72 ±0.90	3.40 ±1.13	4.50 ±1.16	7.90 ±1.67	2.08 ±0.38	5.03 ±0.92	1.30	5.4	3.21	2.4	6.0
Na-Glu treated	8	7.2 ±2.23	76.7 ±12.1	340.0 ±32.7	6.20 ±0.87	2.98 ±0.58	4.04 ±0.71	7.90 ±0.71	2.36 ±0.29	4.67 ±0.61	1.40	4.0	3.59	3.1	4.9
Control	11	7.5 ±2.26	77.7 ±13.5	463.0 ±68.9	7.08 ±1.23	4.08 ±0.48	5.31 ±1.06	7.17 ±1.03	2.09 ±0.49	4.91 ±1.72	1.39	6.4	3.38	3.4	5.3

HAZLETON LABORATORIES, INC.,
Falls Church, Va., November 3, 1966.

Sponsor: International Minerals & Chemical Corp.
Material: Monosodium Glutamate
Subject: Final report. Reproduction study—Rabbits. Project No. 466–103.

INTRODUCTION

The purpose of this study was to characterize and evaluate, in adult albino rabbits, the toxicity of monosodium glutamate following short-term (six to seven weeks) dietary feeding; the effect upon reproduction after two to three weeks ingestation of monosodium glutamate; and the teratogenic potential of monosodium glutamate.

MATERIAL

The samples of monosodium glutamate which were used in this study were received from International Minerals & Chemical Corporation on January 19, 1966, May 2, 1966, and May 12, 1966. They were submitted by the sponsor as routine commercial production samples, labeled ACCENT brand monosodium glutamate, fine crystalline grade. The materials were white powders with no discernible odor. For the purpose of this study the compound was considered to be free of impurities and was used as received.

METHODS

One hundred and eighteen healthy proven breeding does and 64 healthy proven breeding bucks, all of the New Zealand white variety, were used in the study. Each animal was known to have produced or sired at least one litter prior to the test. Initial body weights ranged from 2.6 to 4.4 kg. for the females and from 3.0 to 4.7 kg. for the males. The animals were randomly divided into the following five groups:

Group No.	Number of animals		Dietary level	
	Females	Males	Percent	Mg./kg.
1 (negative control)	24	16	0	0
2 (positive control)	22	0	----------	[1] 100
3 (low level)	24	16	0.1	----------
4 (middle level)	24	16	.825	----------
5 (high level)	24	16	8.25	----------

[1] From day 8 to day 17 of the gestation period.

The animals were acclimated to laboratory conditions and to a basal diet of ground Purina Rabbit Chow for one to two weeks prior to the start of the study. After acclimation, both the negative and positive control animals were maintained on the basal ground diet. For the test animals, MSG was incorporated into the basal diet on a weight/weight basis and thoroughly mixed in a twin-shell blender to provide the desired dietary levels. Fresh diets were prepared twice weekly. Apart from Group No. 2, the appropriate diet and water were available to all male and female animals until sacrifice.

After a two to three week feeding period, each doe in Groups No. 1, No. 3, No. 4, and No. 5 was mated with a breeding buck from the corresponding group; mating was repeated on the following day to ensure fertilization. Each doe in Group No. 2 was also mated in the same manner; however, bucks from the supplier's breeding colony were used and then returned. An equal number of does (eight) from each group were bred at three different times, within a period of one week; eight of the bucks in each group were used at both the first and the third breeding

intervals. From the eighth through the 16th day of the gestation period (calculated from the second mating) each doe in Group No. 2 received Thalidomide at a dose of 100 mg/kg of body weight per day. The material was mixed in the ground food during this time; on the 17th day, these animals were returned to the untreated basal diet.

From the eighth through the 16th day of the gestation period, individual body weights and food consumption were recorded daily for the animals in Group No. 2. Otherwise, individual body weights were recorded weekly and food consumption was measured and recorded three times weekly. The animals were observed for gross toxic signs and general appearance and behavior daily throughout the study.

On the 29th or 30th day of gestation, all does were sacrificed by intravenous air embolism and the young immediately delivered by Caesarean section. All litters were very carefully examined for stillbirths and possible malformations. Individual weights (in grams) and length (in centimeters) were recorded for all fetuses. The uteri of all does were carefully examined for sites of fetal attachment and resorption. Each fetus was sacrificed by chloroform, examined grossly, and then placed in 10% formalin. At this time each male animal was also sacrificed by intravenous air embolism and necropsied. At necropsy, gonads from representative male animals in each group, as well as any grossly abnormal organs from either sex were placed in 10% formalin. These tissues are being stored at Hazleton Laboratories, Inc., for possible future reference.

After fixation, approximately one-third of the fetuses from each litter were inspected for external and visceral abnormalities and prepared for skeletal clearing and staining as follows: each fetus was skinned, eviscerated, and then totally immersed in a 2.0% solution of KOH for maceration; after a period of three to four weeks, depending on fetal size, the fetuses were transferred to a solution of Alizarin Red S for staining; and after complete staining, the fetuses were cleared in glycerin and held in this solution for observation of skeletal malformations and abnormalities. Bone structure development evaluations included the cranial and facial aspects of the skull, pectoral girdle, anterior limbs, sternum, and posterior limbs. These fetuses, as well as the ones which were not cleared or stained, are being held at Hazleton Laboratories, Inc.

RESULTS

The mean weekly body weights, weight ranges, and food consumption, as well as the amount of compound consumed on average mg/kg/day basis are presented in Table No. 1. The positive control females (Group No. 2) are not included in this table since they received compound only from the eight through the 16th gestation day.

In general, body weight gains and food consumption were comparable among all groups. Slight body weight losses and decreased food consumption were noted during the transient periods when signs of respiratory and/or intestinal infection were noted in a few of the animals. A marked body weight loss (note low 1575 gram range in Table No. 1 for 0.1% females) in the animal that died was observed. Except for the interval (eighth through the 16th day) when Thalidomide was administered and food was restricted (100 grams/animal/day) to assure complete compound consumption, the body weight gains and food consumption for the positive control animals were comparable with the negative control animals.

General appearance and behavior

At the 0.1% level, one animal of each sex (female Rabbit No. 66–809 and male Rabbit No. 66–900) died during the third or sixth week of the study; gross signs prior to death (depression, labored respiration, bloating, mucoid diarrhea, and body weight loss) and necropsy findings indicated mucoid enteritis, a coincidental disease not related to oral ingestion of the compound. Gross signs indicating

mucoid enteritis were also noted in one high level male during the last week or two of the study.

One positive control animal aborted on the 19th gestation day and was therefore sacrificed at that time. Doe No. 66–839 (0.825% monosodium glutamate level) was sacrificed on the 25th gestation day due to a moribund condition, and one negative control animal was sacrificed on the 27th gestation day after one fetus was found in the cage.

Apart from these findings, and except for transient signs of wheezing and/or a nasal discharge and soft feces observed in both control and test animals, all animals seemed normal in appearance and behavior throughout the study.

Gross pathology—parents

One negative control male animal showed apparent atrophy of one testis. The following necropsy findings were noted among the female negative control animals: friable, mottled, and granular liver (one animal); parasitic areas on the liver, parasitic cysts on the mesentery, and fluid in the peritoneal cavity (one animal); and no grossly visible right uterine horn (one animal).

At the 0.1% level, the male animal that died showed marked autolytic changes, congested lungs, and ruptured stomach; the female animal that died showed congested lungs, parasitic areas on the liver, and hardened fecal material in the cecum. Watery cysts were noted in the uterine wall of one female animal at necropsy following sacrifice.

At the 0.825% level the entire right lung of the animal sacrificed on the 25th day was consolidated and abscessed. One 8.25% male animal showed pitted, congested, and tough kidneys, gelatinous intestinal contents, and slight intestinal inflammation. One nonpregnant high level female showed uterine inflammation, and one pregnant high level female showed watery cysts throughout the renal cortex. No other gross necropsy findings were noted in any of the control or test animals.

Breeding data

The breeding data, which include days of gestation, method of delivery (Caesarean or natural), number of implantation and resorption sites, number of live young and stillbirths, and mean litter weights (in grams) and lengths (in centimeters) for control and test animals are presented in Table No. 2.

NEGATIVE CONTROL

Twenty-one of the 24 does in this group became pregnant. Apart from the Caesarean section performed on the 27th day after one fetus was expelled, Caesarean deliveries were performed on the 29th or 30th day. The uteri of the three nonpregnant animals did not show any evidence of fetal implantation or resorption. Total implantation sites in the pregnant does of this group averaged 8.0 and ranged from one to 14. Of the 168 fertilized ova implanted, 19 were resorbed, 132 were born alive, 17 (including the one expelled) were dead, and five showed gross abnormalities. One of the live pups from Doe No. 66–771 showed collapsed lungs and an incomplete formation of the diaphram with adhesions between liver tissue and thoracic tissue. Two of the live pups from Doe No. 66–760 showed milky abdominal fluid and intestinal adhesions. The one expelled fetus from Doe No. 66–754 showed incomplete skin formation over the anterior part of the body, including the head, no grossly visible bone formation over the cranial area, a small, twisted left front paw, and a turning down of the right forepaw. One dead pup from Doe No. 66–761 showed a mottled liver, pale-appearing intestines, and a small amount of fluid in the thoracic cavity. The dead fetuses varied in size, depending on the stage of development prior to death, and only three were comparable to the live fetuses in size. No other gross abnormalities were observed among the other fetuses.

POSITIVE CONTROL

Eighteen of the 22 does in this group became pregnant; however, Doe No. 66–787 aborted nine small embryos on the 19th gestation day, and the uteri

of Doe No. 66–786 showed, when sacrificed on the 29th gestation day, six apparent implantation sites which could not be accounted for. Possibly this doe aborted sometime during the gestation period and devoured the young. The uteri of the four nonpregnant animals did not show any evidence of fetal implantation or resorption.

Total implantation sites, including the six unaccounted for sites noted above, in the pregnant does of this group averaged 8.0 and ranged from three to 12. Of the 148 fertilized ova implanted, eight were resorbed; 25, including the nine aborted on the 19th day, were born dead; 109 were born alive; and six were unaccounted for. Eight of the young, seven live ones and one dead one, showed gross abnormalities.

One of the dead fetuses from Doe No. 66–782 showed apparent umbilical strangulation. One of the live young from Doe No. 66–778 showed a watery-appearing cyst and incomplete skin formation over the sacrum and displayed very little use of the hind limbs. Six of the remaining live young, two from Doe No. 66–785 and one each from Does No. 66–791, No. 66–794, No. 66–795, and No. 66–796, showed gross abnormalities of the left or right forepaw; a bent or club-like appearance was observed and one pup walked on the radial-carpal joint. The one pup from Doe No. 66–794 also showed a diaphragmatic hernia resulting in a portion of the intestines present in the thoracic cavity, collapsed lungs, and the absence of a right kidney. The dead fetuses varied in size, depending on the stage of development prior to death, and none were comparable to the live fetuses in size. No other gross abnormalities were observed among the other fetuses.

0.1 PERCENT LEVEL

Nineteen of the 24 does in this group became pregnant. The uteri of the five nonpregnant does, including the one that died, did not show any evidence of fetal implantation or resorption. Total implantation sites in the pregnant does of this group averaged 9.5 and ranged from six to 13. Of the 181 fertilized ova implanted, 12 were resorbed, nine were born dead, and 160 were born alive. Two of the does (Does No. 66–816 and No. 66–823) delivered live pups prior to scheduled Caesarean sections. One of the pups from Doe No. 66–816, natural delivery, showed what appeared to be subcutaneous hemorrhage in the cranial area. No other gross external or internal abnormalities were observed in any of the live or dead fetuses. The dead fetuses varied in size, depending on the stage of development prior to death, and none were comparable to the live fetuses in size.

0.825 PERCENT MSG

Twenty of the 24 does in this group became pregnant. For Doe No. 66–839 pregnancy was terminated on the 25th gestation day due to a moribund condition; Doe No. 66–832 delivered naturally before scheduled Caesarean section. The uteri of the four nonpregnant animals did not show any evidence of fetal implantation or resorption.

Total implantation sites in the pregnant does of this group averaged 8.6 and ranged from three to 11. Of the 173 fertilized ova implanted, 14 were resorbed, eight were born dead, and 151 were born alive. No gross internal or external abnormalities were observed in any of the live or dead fetuses. The dead fetuses varied in size, depending on the stage of development prior to death, and only two of them were comparable to the live fetuses in size the litter delivered on the 25th gestation day was slightly smaller in size than those obtained on the 29th and 30th days.

8.25 PERCENT MSG

Eighteen of the 24 does in this group became pregnant. The uteri of the six nonpregnant animals did not show any evidence of fetal implantation or resorption. Total implantation sites in the pregnant does of this group averaged 9.3 and ranged from 7 to 11. Of the 168 fertilized ova implanted, eight were resorbed, 16 were born dead, and 144 were born alive. The dead fetuses varied in size, de-

pending on the stage of development prior to death, and only one of these was comparable in size to the live fetuses of the same litter. One of the five young from Doe No. 66–852 showed a malformed forepaw and walked on the radial-carpal joint. No gross internal or external abnormalities were observed in any of the other fetuses.

SKELETAL STAINING

Individual bone changes for all control and test pups which were cleared are presented in Table No. 3.

Clearing and staining was performed on 47 negative control pups, 42 positive control pups, 53 of the 0.1% test pups, 48 of the 0.825% test pups, and 49 of the 8.25% test pups.

After staining, the bone structure was evaluated for any gross or comparative difference in size, location, atypical formation, and incomplete ossification, and for the abnormal absence or presence of bone structures.

In the negative control group, skeletal abnormalities noted in three of the pups included marked fusion of ribs on the left side in the lumbar region (one live pup), and slight or moderate spinal curvature in the thoracic region (two dead pups). Other apparently spontaneously occurring findings found in these control animals as well as in control animals from previous studies included missing or small fiifth sternebrae, small sixth sternebrae, and small 13th rib.

In the positive control group, no skeletal abnormalities, apart from those frequently found in negative control animals, were found in any of the pups cleared.

At the 0.1% test level, bone changes were comparable to those found in the negative control animals; however, ribs 8–9 of one pup showed a swollen area in the central portion. At the 0.825% test level, no skeletal abnormalities were found in any of the pups cleared, bone changes were comparable to those occurring spontaneously in control pups. At the 8.25% test level, three live pups from Doe No. 66–855 showed retarded closure of the cranial sutures. Since these latter changes were found in a single litter and not in others at this dosage, it is not considered to be compound-induced but probably due to genetic alteration. Retarded suture closure is not a frequent spontaneous anomaly in this strain of rabbits. No other skeletal abnormalities other than those also occurring in the control animals, were noted in any of the pups cleared.

SUMMARY

Oral ingestion of monosodium glutamate for six to seven weeks at dietary feeding levels of 0.1, 0.825, and 8.25% did not produce, in adult male and female albino rabbits, any toxic effects which could be attributed to compound. Transient signs of respiratory and intestinal infection were noted in both control and test animals. At the 0.1% level, one animal of each sex died during the study; gross signs prior to death and necropsy findings indicated intestinal mucoid enteritis. One 0.825% doe sacrificed on the 25th gestation day in a moribund condition showed lung consolidation and abscessation. At termination one high level male showed gross signs of mucoid enteritis and gelatinous intestinal contents as necropsy. Body weight gains and food consumption were comparable in all groups. The test males and females were fed monosodium glutamate two to three weeks prior to mating, and were mated to animals within the same group. The positive control animals received 100 mg. of Thalidomide per kg. of body weight from the eighth through the 16th gestation day only and were maintained on ground Purina Rabbit Chow during the remainder of the study, while the negative control animals received the ground basal diet during the entire study. Conception occurred in 21/24 negative control does, 18/22 positive control does, 19/24 0.1% test does, 20/24 0.825% test does, and 18/24 8.25% test does.

The gross internal and external abnormal findings and number of resorption sites per total number of implantation sites are summarized below.

Group	Gross internal abnormalities		Gross external abnormalities		Resorptions
	Live fetuses	Dead fetuses	Live fetuses	Dead fetuses	
Negative control	3/132	1/17	1/132	1/17	19/168
Positive control	1/109	0/16	7/109	1/16	8/14
0.1 percent MSG	0/160	0/9	1/160	0/9	12/181
0.825 percent MSG	0/151	0/8	0/151	0/8	1/173
8.25 percent MSG	0/144	0/16	1/144	0/16	8/168

The total number of dead positive control fetuses used in the above summary does not include the fetuses aborted on the 19th day since they were too small for gross examination, nor the six unaccounted for implantation sites in the one doe. The one abnormal live fetus in the 0.1% MSG group was delivered naturally and showed, what appeared to be, subcutaneous hemorrhages in the cranial area. The gross external abnormalities noted among the seven live positive control fetuses and the one live 8.25% MSG fetus were malformed forepaws. The gross internal abnormalities noted in the live negative control fetuses included diaphragmatic hernia and collapsed lungs; and milky abdominal fluid and intestinal adhesions. One live positive control fetus also showed a diaphragmatic hernia. In one dead negative control animal (aborted on the 27th day) the gross external abnormalities consisted of malformed forepaws, incomplete skin formation over the anterior part of the body, and no apparent bone formation in the cranial area. In the one dead positive control animal, the gross external abnormalities consisted of umbilical strangulation. The gross internal abnormalities in the one dead negative control fetus included a mottled liver, pale-appearing intestines, and a small amount of fluid in the thoracic cavity. The average litter weight of the live pups from each group ranged from 38 to 44 grams and the average length from 9.9 to 10.3 centimeters.

The type and incidence of skeletal abnormalities noted in all groups were consistent with the control experience of this laboratory for the rabbit strain used in this study.

CONCLUSION

Dietary feeding of monosodium glutamate to adult male and female albino rabbits at levels of 0.1, 0.825, and 8.25% for two to three weeks prior to mating and during the subsequent 29 to 30 days produced no apparent effect in either sex. Body weight gains, food consumption, general appearance and behavior, survival, breeding performance, and all litter data (total number, number of live young, number of dead young, number of resorptions, gross internal and external abnormalities, and skeletal staining) were comparable among negative control and test animals. The incidence of grossly appearing malformed forepaws in the positive control (Thalidomide) animals was higher than in the other groups; however, skeletal staining did not confirm this finding and the effect was apparently not due to a bone abnormality.

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TABLE No. 1—Mean weekly body weights, weight ranges, food consumption, and average compound consumption on an mg/kg/day basis for male and female albino rabbits which served as negative controls or received Monosodium glutamate at the indicated dosage levels.

TABLE 1

GROUP NO. 1—NEGATIVE CONTROL

Week No.	Body weight in grams				Mean food consumption (grams)		Compound consumption (mg/kg/day)	
	Mean: Males	Range: Males	Mean: Females	Range: Females	Males	Females	Males	Females
0	3,779	3,026–4,504	3,386	2,610–4,358				
1	3,800	2,970–4,470	3,406	2,814–4,496	771	783		
2	3,756	2,951–4,380	3,374	2,677–4,370	699	697		
3	3,808	2,951–4,525	3,492	2,857–4,496	871	892		
4	3,813	2,971–4,444	3,542	2,807–4,624	851	888		
5	3,845	2,969–4,486	3,676	2,963–4,927	818	952		
6	3,852	2,918–4,548	3,736	3,007–4,798	764	803		
7	3,816	2,900–4,450	3,699	3,113–4,218	797	936		

TABLE 1.—Continued

GROUP NO. 3—0.1 PERCENT MONOSODIUM GLUTAMATE

Week No.	Body weight in grams: Mean: Males	Range: Males	Mean: Females	Range: Females	Mean food consumption (grams): Males	Females	Compound consumption (mg/kg/day): Males	Females
0	3,697	3,363–4,200	3,479	2,677–4,440				
1	3,698	3,440–4,252	3,425	2,526–4,343	672	769	26.0	31.8
2	3,664	3,322–4,218	3,470	2,022–4,306	519	766	20.1	31.7
3	3,736	3,441–4,310	3,523	1,575–4,454	893	886	34.5	36.2
4	3,764	3,420–4,341	3,718	2,985–4,579	875	936	33.3	36.9
5	3,791	3,443–4,501	3,839	2,991–4,865	805	963	30.4	36.4
6	3,814	3,402–4,460	3,893	3,023–4,912	834	890	31.3	32.9
7	3,946	3,533–4,470	3,839	3,102–4,944	815	1,109	30.6	41.0

GROUP NO. 4—0.825 PERCENT MONOSODIUM GLUTAMATE

0	3,645	3,014–4,475	3,129	2,673–3,927				
1	3,699	3,100–4,472	3,204	2,654–4,123	677	840	217.0	313.0
2	3,614	2,977–4,243	3,223	2,471–4,076	512	767	165.0	281.0
3	3,644	3,131–4,339	3,320	2,512–4,125	830	985	270.0	355.0
4	3,712	3,188–4,463	3,475	2,713–4,262	808	1,015	259.0	352.0
5	3,730	3,134–4,500	3,608	2,760–4,396	817	999	259.0	332.0
6	3,742	3,116–4,462	3,688	2,854–4,298	737	926	232.0	299.0
7	3,480	3,098–4,134	3,674	2,784–4,149	757	1,151	247.0	368.0

GROUP NO. 5—8.25 PERCENT MONOSODIUM GLUTAMATE

0	3,713	2,980–4,671	3,300	2,674–4,411				
1	3,748	2,985–4,643	3,322	2,752–4,375	799	798	2,520.0	2,840.0
2	3,696	3,127–4,466	3,292	2,699–4,177	689	774	2,180.0	2,760.0
3	3,809	3,333–4,694	3,393	2,907–4,291	900	922	2,830.0	3,250.0
4	3,813	3,397–4,584	3,499	3,095–4,298	910	930	2,810.0	3,180.0
5	3,841	3,482–4,515	3,605	3,201–4,550	826	960	2,540.0	3,185.0
6	3,877	3,452–4,580	3,692	3,236–4,767	783	858	2,390.0	2,770.0
7	3,823	3,511–4,551	3,789	3,426–4,744	982	1,060	3,010.0	3,340.0

TABLE No. 2.—Summary of breeding data for albino rabbits which served as negative or positive controls or received Monosodium Glutamate at the indicated dietary levels. See text for details.

TABLE 2

GROUP NO. 1—NEGATIVE CONTROL

Doe No.	Delivery	Gestation day	Implantation sites	Live births: Number of fetuses	Mean weight	Mean length	Stillbirths: Number of fetuses	Mean weight	Mean length	Resorption sites
66–754	Caesarean	27	8	6	30	9.4	[1] 2			0
66–755	do	29	12	11	46	11.3	1	[2]	4.0	0
66–756	do	29	4	2	55	7.5	0			2
66–757	do	29	8	2	36	9.0	0			6
66–758	do	29	10	8	44	10.2	2	34	9.5	0
66–760	do	29	8	8	39	10.4	0			0
66–763	do	29	5	3	30	10.0	1	[2]	4.0	1
66–764	do	29	8	5	47	10.5	2	14	7.0	1
66–765	do	29	14	10	32	9.5	3	[3] 18	5.7	1
66–766	do	29	8	7	46	11.3	1	[2]	2.0	0
66–770	do	29	12	9	41	10.1	2	[2]	3.5	1
66–771	do	29	3	2	45	10.0	0			1
66–772	do	29	8	8	39	9.9	0			0
66–773	do	29	12	12	40	9.7	0			0
66–761	do	30	6	4	55	10.9	1	46	11.0	1
66–767	do	30	7	5	43	10.3	1	[2]	1.0	1
66–768	do	30	11	9	47	10.3	1	14	7.0	1
66–769	do	30	7	6	46	10.2	0			1
66–774	do	30	1	1	70	13.5	0			0
66–775	do	30	9	9	44	10.1	0			0
66–777	do	30	7	5	56	11.8	0			2
66–759	Not pregnant									
66–762	do									
66–776	do									

TABLE 2.—Continued

GROUP NO. 2—POSITIVE CONTROL—100 MG/KG/DAY THALIDOMIDE

Doe No.	Delivery	Gestation day	Implantation sites	Live births: Number of fetuses	Live births: Mean weight	Live births: Mean length	Stillbirths: Number of fetuses	Stillbirths: Mean weight	Stillbirths: Mean length	Resorption sites
66-787	Early abortion	19	[4] 9							
66-778	Caesarean	29	10	9	36	9.3	1	15	7.0	0
66-780	do	29	8	8	39	9.3	0			0
66-782	do	29	9	6	45	10.3	2	[3] 16	4.8	1
66-783	do	29	7	6	43	9.6	0			1
66-784	do	29	3	1	58	11.0	0			2
66-785	do	29	8	8	39	9.3	0			0
66-786	do	29	[4] 6							
66-788	do	29	11	10	40	10.7	1	14	7.5	0
66-790	do	29	8	4	37	10.1	4	[3] 23	5.6	0
66-791	do	29	8	6	34	9.8	1	([2])	5.0	1
66-792	do	29	12	9	41	10.1	2	5.3	5.8	1
66-793	do	29	10	9	37	9.9	1	([2])	2.5	0
66-794	do	29	11	9	35	10.2	2	20	6.5	0
66-795	do	29	9	7	40	10.6	0			2
66-796	do	29	6	6	39	9.9	0			0
66-797	do	29	8	6	47	10.7	2	([2])	5.3	0
66-799	do	29	5	5	50	11.5	0			0
66-779	Not pregnant									
66-781	do									
66-789	do									
66-798	do									

GROUP NO. 3—0.1 PERCENT MONOSODIUM GLUTAMATE

66-802	Caesarean	29	9	7	48	11.4	0			2
66-803	do	29	7	7	56	12.0	0			0
66-805	do	29	6	5	37	9.5	0			1
66-806	do	29	9	9	38	10.1	0			0
66-808	do	29	13	10	31	8.5	2	[3] 20	5.3	1
66-810	do	29	9	5	36	9.6	0			4
66-811	do	29	10	8	37	10.4	2	4.8	5.3	0
66-812	do	29	10	7	39	9.5	3	([2])	3.2	0
66-814	do	29	10	10	33	10.1	0			0
66-815	do	29	11	11	40	9.9	0			0
66-818	do	29	10	9	28	8.7	1	([2])	2.0	0
66-820	do	29	10	9	35	9.3	0			1
66-807	do	30	12	12	35	9.5	0			0
66-813	do	30	10	9	39	9.9	1	11	6.5	0
66-817	do	30	9	9	41	9.7	0			0
66-821	do	30	8	7	45	11.3	0			1
66-822	do	30	8	7	29	8.8	0			1
66-823	Natural	29	11	11	39	9.6	0			0
66-816	do	30	9	8	39	9.6	0			1
66-809	Not pregnant (died).									
66-804	Not pregnant									
66-819	do									
66-824	do									
66-825	do									

GROUP NO. 4—0.825 PERCENT MONOSODIUM GLUTAMATE

66-839	Caesarean	25	10	8	18	7.8	2	20	7.5	0
66-826	do	29	10	7	33	10.3	0			3
66-827	do	29	8	8	44	10.7	0			0
66-828	do	29	9	6	42	10.4	0			3
66-829	do	29	11	10	37	9.7	0			1
66-830	do	29	11	9	45	10.2	0			2
66-835	do	29	7	6	34	10.1	0			1
66-836	do	29	5	5	38	10.3	0			0
66-837	do	29	7	5	42	9.9	2	([2])	5.3	0
66-838	do	29	9	9	41	10.5	0			0
66-842	do	29	9	6	30	9.1	1	([2])	1.0	2
66-843	do	29	11	11	35	9.5	0			0
66-831	do	30	8	7	47	10.4	0			1
66-833	do	30	9	8	42	10.1	1	10	6.0	0
66-834	do	30	3	2	53	11.3	1	([2])	1.0	0
66-845	do	30	9	9	43	11.1	0			0
66-847	do	30	10	10	34	9.2	0			0
66-848	do	30	9	9	44	11.1	0			0
66-849	do	30	9	8	33	9.9	1	([2])	3.0	0
66-832	Natural	30	9	8	47	10.0	0			1
66-840	Not pregnant									
66-841	do									
66-844	do									
66-846	do									

TABLE 2.—Continued

GROUP NO. 5–8.25 PERCENT MONOSODIUM GLUTAMATE

Doe No.	Delivery	Gestation day	Implantation sites	Live births: Number of features	Live births: Mean weight	Live births: Mean length	Stillbirths: Number of fetuses	Stillbirths: Mean weight	Stillbirths: Mean length	Resorption sites
66–850	Caesarean	29	10	10	31	10.2	0			0
66–852	do	29	10	10	37	10.6	0			0
66–853	do	29	11	11	37	9.6	0			0
66–855	do	29	10	6	32	10.3	4	[2]	6.1	0
66–856	do	29	11	10	45	10.9	1	23	9.0	0
66–857	do	29	10	8	44	10.7	1	25	8.5	1
66–858	do	29	11	9	36	10.2	1	27	9.5	1
66–859	do	29	7	6	46	11.1	1	1.5	4.0	0
66–861	do	29	10	7	43	10.6	0			3
66–862	do	29	8	8	42	9.9	0			0
66–863	do	29	9	9	40	9.7	0			0
66–865	do	29	7	7	34	9.3	0			0
66–866	do	29	11	8	37	9.1	3	[2]	3.5	0
66–868	do	29	7	7	40	9.8	0			0
66–869	do	29	8	6	41	9.9	2	[3] 11	4.3	0
66–864	do	30	7	6	46	10.3	0			1
66–872	do	30	10	7	50	11.3	2	[3] 22	6.3	1
66–873	do	30	11	9	48	11.2	1	[2]	2.0	1
66–851	Not pregnant									
66–854	do									
66–860	do									
66–867	do									
66–870	do									
66–871	do									

[1] 1 fetus expelled prior to caesarean section.
[2] No weight obtained due to small size.
[3] Weight of 1 fetus only; others too small to weigh.
[4] 9 small dead embryos aborted; 6 unaccounted for implantation sites.

TABLE No. 3—Incidence of skeletal variations in rabbit fetuses from groups serving as negative or positive controls (Thalidomide) or receiving Monosodium Glutamate; expressed as a percentage of number of fetuses showing variations/number of fetuses examined. Numbers in parentheses indicate total number of fetuses examined.

TABLE 3

[In percent]

Skeletal variations	Group No. 1, negative control		Group No. 2, positive control		Group No. 3, 0.1 percent		Group No. 4, 0.825 percent		Group No. 5, 8.25 percent	
	Alive (46)	Dead (9)	Alive (36)	Dead (6)	Alive (49)	Dead (5)	Alive (45)	Dead (3)	Alive (46)	Dead (3)
Sternebrae:										
Missing:										
No. 1				17	2	40				
No. 2				17		20				
No. 3					2					
No. 4					2	20				
No. 5	9	22	3	50	6	20	20	33	20	67
No. 6	2			33	6	40	2	33	2	67
All (Nos. 1 to 6)		44		33				33		
Small:										
No. 1								33		
No. 2		11	3		12	20	4	67	13	33
No. 3						40		33		33
No. 4						20		33		
No. 5	57	11	58	17	82	80	56	33	72	33
No. 6	4	22	3		4	20	7		11	
Additional: No. 7	2									
Fusion:										
Nos. 1, 2, and 3	2									
Nos. 4 and 5			3		2					
Atypical structure:										
No. 5	2				2					
No. 6	4	11								
Ribs:										
Thickened areas:										
No. 7		11								
Nos. 8 and 9					2					
All (Nos. 1 to 12)	4									
Additional: No. 13	54	22	17		45	60	31	33	54	67
Small:										
No. 1			3			20		33		
No. 2	2									
Atypical structure:										
No. 11			3							
No. 13										4
Fusion: All (Nos. 1 to 12 on left)	2									
Ossification incomplete:										
Skull		33		50		60		67		13
Mandible		33								
Palate		33		17						
Teeth		11								
Cervical and thoracic vertebrae		33		17						
Lumbar vertebrae		33								
Sacral vertebrae		11		17		40		33		
Caudal vertebrae				17		40		33		
Carpus		22		67		60		67		33
Pelvis		33								
Tarsus		22		67		60		67		33
Phalanges		33		33		20				
Cranial sutures									7	
Ossified material not visible:										
Teeth		33		67		40		33		
Sacral vertebrae		33		33						
Caudal vertebrae		44		50		40				
Carpus		22		17						
Tarsus		22		17						
All sternebrae: Covered with additional ossified material									2	
Rib cage: Surrounded by wave-like material (not bone related)	20	11								
Spinal curvature: In thoracic region		22							2	
Lumbar disc: Atypical structure of one	2								2	

HAZELTON LABORATORIES, INC.,
TRW LIFE CENTER,
July 18, 1969.

Sponsor: International Minerals & Chemical Corporation.
Material: Monosodium Glutamate.
Subject: Addendum to final report.—Reproduction Study—Rabbits. Project No. 466–103.

SUMMARY

Microscopic examination was performed on hematoxylin- and eosin-stained sections of brain tissue from rabbit pups of Project No. 466–103, removed by Caesarean section on Gestation Day 29 or 30. Ten of the pups (five male and five female, Path No. 47–738 to Path No. 47–747) were removed from does which had been fed monosodium glutamate at a level of 8.25% for two to three weeks prior to mating and during the subsequent 29 to 30 days prior to Caesarean section. The 10 control pups (five males and five females) were obtained from does which were maintained on the basal laboratory diet. Transverse sections of the brain were examined at the level of the hypothalamic nuclei and pituitary gland. Artifactual distortion of the brain was occasionally noted in sections from pups of both treated and control does. Evidence of neuronal necrosis or other pathologic alteration was not apparent in the sections examined.

In conclusion, there was no discernible difference in the histologic appearance of brain sections from pups obtained from control does or those receiving monosodium glutamate at a level of 8.25% of the diet.

RICHARD W. VOELKER, Jr.,
D.V.M., Ph. D., Staff Pathologist.

PRESS REPORTS ON THE BANNING OF CYCLAMATES

[From the Washington Post, Sept. 13, 1969]

SWEETENER IS LINKED TO CANCER

Animal evidence of a potential cancer hazard from cyclamate, the most widely used form of artificial sweetener, was reported yesterday by Food & Drug Administration researchers.

Dr. Marvin Legator, leader of the research team, told a reporter it's always hazardous to relate animal results to humans when dealing with genetic experiments. But he added:

"Unless you can show differences between how animals handle a given material—such as that used in these experiments—and how it would be handled in man, you must allow the animal results to stand unless and until refuted."

Legator, amplifying on a technical report published in Science magazine, said chromosome breaks were produced in both bone-marrow cells and reproductive cells of male rats receiving injections of a chemical called cyclohexyamine, a metabolic breakdown product of cyclamate.

He said appreciable numbers of breaks resulted in animals given doses as small as 5 milligrams per kilogram of body-weight, or an amount equivalent to that which might be consumed by a human in drinking "several bottles of a diet soft drink a day."

[From the Wall Street Journal, Sept. 15, 1969]

FDA EXPERIMENTS WITH CYCLAMATE RAISE NEW QUESTIONS OVER SAFETY OF SWEETENER

(By Richard R. Leger)

NEW YORK.—Experiments at the Food and Drug Administration's laboratories are raising new questions about the safety of cyclamate, the most widely used artificial sweetener in the U.S.

Four FDA scientists reported that in tests on rats a chemical related to the cyclamates had produced significant breaks in the chromosomes of cells that form sperm and in bone marrow cells. The significance of the study, however, was challenged by at least one cyclamate maker.

Scientists aren't certain what the effect of broken chromosomes really are but some worry they may lead to cell mutations and eventually to birth defects, cancer or other conditions.

The experiments were based on the fact that the human body sometimes converts the artificial sweetners into a related chemical called cyclohexylamine, or CHA. The CHA was injected into the pertioneal, or body cavity of the rats in weights ratios ranging from five to 250 milligrams per 2.2 pounds of body weight.

The increase in chromosome breaks was directly related to the increase in dosage of CHA given the rats, said Marvin S. Legator, one of the four scientists. Mr. Legator is chief of the cell biology branch of the Bureau of Science of the FDA and also is professor of microbial genetics at George Washington University School of Medicine. The mean percent of sperm cells with chromosome breaks ranged from 4.4%up to 19.2% and for bone marrow cells from 4% up to 16.3%. In control rats, which weren't given CHA, cells with the chromosome breaks average 1.8% in sperm cells and 2.7% in bone marrow cells.

DOSE-RELATED EFFECT REPORTED

"It's extremely important in the study that we have a dose-related effect," said Mr. Legator in a telephone interview. "We've shown that the heavier the dose, the greater number of breaks. So far this hasn't even been shown in LSD studies over which most of the 'chromosome-break' arguments are being waged."

Mr. Legator said the study on rats, published in the current issue of Science, also was significant in that it was the first such research "using animals and not test tubes to demonstrate chromosome breaks." Science is a weekly journal published by the American Association for the Advancement of Science.

The scientist said about one-third of the humans who use cyclamate convert the sweetener in their bodies into CHA. Why some people do and some don't isn't known, he said. He indicated that there could be a serious risk for such humans using cyclamate even in moderate amounts. "The levels where we got significant breaks were well within terms of intake related to body weight for some individuals using cyclamates," he said.

The FDA last April proposed a suggested maximum daily intake for humans of 50 milligrams of cyclamate per 2.2 pounds of body weight. Mr. Legator said his group's study on rats wasn't completed or considered when the FDA made its proposal on maximum amounts of cyclamate that could be safely consumed.

He argued that the new study indicates some people, if they's taking close to 50 milligrams of cyclamate per 2.2 pounds of body weight are past the "zero safety margin. Whenever we find a toxic product, we usually insist on at least a tenfold safety margin between actual use and degree of toxicity."

USED IN DIET SOFT DRINKS

Cyclamates are the most widely used of artificial, noncaloric sweeteners. Major producers of cyclamates include Abbott Laboratories, Chicago, Chas. Pfizer & Co., New York, and Miles Laboratories Inc., Elkhart, Ind. Well-known soft drinks using cyclamates include Diet-Rite, made by Royal Crown Cola Co., Columbus, Ga., Tab and Fresca, made by Coca-Cola Co., Atlanta, and Diet-Pepsi, produced by Pepsi Co. Inc., New York.

The soft-drink companies declined comment on the study by the FDA scientists. The soft-drank industry is believed to be the biggest user of the chemical. The cyclamate content of most artificially sweetened soft drinks ranges from 0.3 to 0.9 gram per 12-ounce bottle.

An Abbott Laboratories spokesman said his company questioned "the importance" of the study by the FDA researchers. He said Abbott Laboratories sponsored a study for the past two years in which rats were fed "massive doses of cyclamates." There was "no adverse effect upon the ability of rats to reproduce or upon the offspring of the rats," he said.

A spokesman for the FDA commented that any regulatory action on cyclamates "would have to be based on more than the work of one group of scientists. It's still in the basic research area and shoud be considered in that light," he said.

Some 17 million pounds of cyclamates were produced last year, with a value of some $9 million at a price of more than 50 cents a pound. Sales of the highly concentrated sweetener could reach 21 million pounds next year, one producer predicted.

[From the Washington Post, Sept. 27, 1969]

ERROR ON FOOD ADDITIVE CONCEDED BY FDA CHIEF

(By Morton Mintz)

Dr. Herbert L. Ley Jr., Commissioner of the Food and Drug Administration, has conceded that he erred in testimoney about the safety of a chemical additive in processed baby foods and is asking for a new review by the National Academy of Sciences-National Research Council.

In July, Dr. Ley told the Senate Select Committee on Nutrition and Human Needs of four scientific studies that, he said, established the safety of the chemical, monosodium glutamate (MSG), which enhances flavor.

Last week, in testimony at a House hearing and in a letter to Committee Chairman George C. McGovern (D-S.D.), Ralph Nader charged that two of the four studies did not exist and that two others were preliminary.

The commissioner acknowledged an "inexcusable" error in an FDA staff paper that claimed that no adverse reactions were noted in "highly critical tests" for chromosome breaks in animals and bacteria treated with MSG. Nader charged that there had been no tests for such breaks, which could affect the genes that transmit inherited characteristics.

Dr. Ley said the statement was made on the basis not of tests, but of routine, long-time use of MSG for laboratory investigation of cells in which chromosome breaks occur.

But not until after he had testified, he said, did the FDA undertake "a purposeful study of the effect of MSG in causing chromosome breaks." That study, he told the senator, showed that even with very high levels of MSG "only normal background breakage occurred," and that his original testimony—even though originally "unjustified"—now has been confirmed.

Nader charged that a second "non-existent" study challenged Dr. Ley's testimony that MSG "produced no adverse effects on growth" when fed to baby rats "at levels of 30 per cent of the diet."

[From the Baltimore Sun, Oct. 8, 1969]

FINCH CRITICIZES CYCLAMATE CASE—SCORES VARIANCE IN FDA'S JUDGMENTS ON SWEETENER

WASHINGTON, October 7.—Robert H. Finch, the Secretary of Health, Education, and Welfare, criticized a unit of his own department today for its handling of safety questions about the widely used artificial sweetner cyclamate.

Mr. Finch said that it was "inevitable" that there would be "some rather substantial reorganization of procedures and personnel in the Food and Drug Administration.

VARYING ASSESSMENTS

The secretary was critical of what he termed varying assessments made by the government agency about possible health hazards associated with cyclamate use.

He singled out a recent experiment made by the food and drug agency—one widely reported on national television—which demonstrated a 15 percent incidence of birth defects after cyclamate injection into chicken eggs.

Mr. Finch said in an interview, "Some have been overzealous, saying 'Sure, this may not be final or conclusive . . . but we still ought to run up the flag and sound the bugle.' And others have gone too far the other way."

NO INDIVIDUALS NAMED

He declined to mention any individuals but was apparently referring to Dr. Jacqueline Verrett, the government scientist who conducted the chick experiment, and to Herbert L. Ley, Jr., the commissioner of the Food and Drug Administration. Dr. Verrett has been quoted as advising pregnant women to exercise care with cyclamates unless all doubts about their use are removed.

Dr. Ley has emphasized that the findings are tentative from the cyclamate studies on animals.

The sweetener, used by an estimated 175 million Americans, is found in diet foods and diet drinks, as well as in frozen desserts, children's vitamins, bacon, canned fruits and many other non-diet foods.

[From the Washington Post, Oct. 18, 1969]

FINCH WILL RECALL ARTIFICIAL SWEETENER

(By G. C. Thelen, Jr.)

Robert H. Finch, Secretary of Health, Education and Welfare, will announce today severe restrictions on use of the artificial sweeteners called cyclamates.

Finch decided on the strong step against the sweetener, widely used in diet drinks and foods, after new laboratory evidence this week disclosed that cyclamates produced cancer in rats.

It is understood that scientists are not convinced that the substance causes cancer in man.

Finch's action will include a phased recall of foods containing the substance now on store shelves, it was learned.

The recall of substances containing cyclamates will take place over a matter of weeks—as will the substitution of other sweeteners for cyclamates.

In New York City, Canada Dry Corp. said it would stop selling all of its products, such as diet soda, that contain the artificial sweetener.

An independent laboratory reported this week that very large doses of cyclamates fed to rats over a long period of time produced cancer in the animal's bladders.

The findings were immediately turned over to a National Academy of Sciences panel already doing a hurry-up study of health dangers from cyclamates. The panel recommended the strong action against cyclamates be taken immediately.

Finch acted because statutes require the withdrawal from the government's safe list of compounds any substance that has been proven to cause cancer in animals. He also decided to act because he believed prudence required it.

Finch has scheduled a 9:30 a.m. press conference today in which he will announce his decision.

The ban on cyclamates will not be total. People with health problems requiring extreme limits on sugar intake will still be able to obtain food products containing cyclamates.

The bulk of cyclamates—approximately 70 per cent—are found in diet soft drinks. The substance is also contained in diet foods and such nondiet foods as bacon, canned fruits and vegetables, children's vitamin tablets and oral medications.

Doubts about cyclamates were first raised last October by a government scientist who found that a metabolic breakdown product of cyclamates caused shattering of genetic material in rat cells. Similar chromosome breaks in man have been linked to cancer and birth defects.

Another government scientist has found that cyclamates injected into chicken eggs produces a 15 percent incidence of birth defects in chicks. Following the second study, the Food and Drug Administration came under mounting criticism from Capitol Hill consumer advocates, led by Sen. Warren Magnuson (D-Wash.), to provide safety precautions regarding use of the substance.

Seven days ago, Finch reacted strongly to the Food and Drug Administration's handling of studies on the artificial sweetener, saying it could lead to reorganization of the agency.

"We have appeared to waffle on it," he said. "Some have been overzealous, saying, "Sure, this may not be final or conclusive . . . but we still ought to run up the flag and sound the bugle,' and others have gone too far the other way."

The Secretary referred to an experiment conducted by Dr. Jacqueline Verrett, an FDA scientists, which showed 15 per cent of chicks hatched from eggs injected with cyclamates had birth defects.

Washington Post staff writer Morton Mintz reported earlier yesterday:

Limits recommended by the Food and Drug Administration for daily intake of cyclamates, widely used artificial sweeteners, should be observed "until it has been conclusively shown that there is no significant hazard," the Medical Letter says in its new issue.

What intake limits should be for pregnant women, the aged and persons with certain diseases "is not known," the Medical Letter said.

"The FDA has recommended a maximum intake of 23 milligrams per pound of bulk weight. Under pending recommendations, labels of products containing cyclamates would state that the maximum daily intake by an adult should not exceed 3,500 mgs., and by a child 1,200 mgs. A bottle of soft drink may contain between 300 and 1,000 mgs."

[From the New York Times, Oct. 18, 1969]

FINCH IS REPORTED READY TO BAN CYCLAMATES USED IN DIET DRINKS

(By the Associated Press)

WASHINGTON, October 17.—Secretary of Health, Education, and Welfare Robert H. Finch will order cyclamates, an artificial sweetener, removed from the market tomorrow, the National Broadcasting Company said in a news report today.

The broadcast said that Mr. Finch did not make the announcement today because of the impact the news could have made on the stock market, which is closed on weekends.

In the broadcast, N.B.C. said Mr. Finch planned to meet tomorrow with manufacturers of foods containing cyclamates so they can announce future plans.

There was no immediate confirmation of the broadcast from Health, Education, and Welfare.

N.B.C. also said: "Finch acted after a study showed that malignancies, or cancers, appeared in animals after they were given big dose levels of cyclamate. The Department of Health, Education, and Welfare has no evidence that cyclamates have produced cancer in human beings.

"Finch believes that he is taking a prudent course, rather than responding to an emergency.

"Seventy per cent of cyclamates now in use appear in diet soft drinks.

"Finch's order means that as of next week manufacturers can no longer put cyclamates in diet foods. To provide for an orderly phase-out of diet drinks and other dietary foods containing cyclamates now on store shelves, they can be sold until the first of next year.

Canada Dry, the soft drink manufacturer, announced here yesterday that its products containing cyclamate as an artificial sweetner would be removed from markets throughout the world, according to Reuters.

The action was being taken in view of public concern over the possible ill effects of artificial sweeteners, said a statement by James De W. Blyth, president of the company.

It was being done in "the public interest," said Mr. Blyth, who added that the removal of products that contained cyclamate would begin immediately and extend from manufacturing plants to store shelves through the world.

[From the New York Times, Oct. 19, 1969]

GOVERNMENT OFFICIALLY ANNOUNCES CYCLAMATE SWEETENERS WILL BE TAKEN OFF MARKET EARLY NEXT YEAR

(By Harold M. Schmeek)

WASHINGTON, October 18.—Robert H. Finch, Secretary of Health, Education and Welfare, announced officially today that the widely used artificial sweeteners called cyclamates will be withdrawn from general use by early next year.

He has ordered them removed from the list of substances recognized as safe for use in foods largely because some rats that were fed heavy doses of the artificial sweeteners during most of their lifespan developed bladder cancers.

Mr. Finch and high officers of his department emphasized, however, that there is no evidence, at present, to link the artificial sweeteners with cancers in man.

The withdrawal of products containing cyclamates will be done in phases.

The use of cyclamate in the production of general purpose foods and beverages has been ordered discontinued immediately.

Recall of soft drinks containing the sweeteners is to be completed by Jan. 1.

All other artifically sweetened food products using the substances are to be phased out of the market by Feb. 1.

"I should emphasize also that my order does not require the total disappearance from the market place of soft drinks, foods and non-prescription drugs containing cyclamates." Mr. Finch said. "These products will continue to be available to persons whose health depends upon them, such as those under medical care for such conditions as diabetes or obesity."

But the impact of the Government decision is certain to be great. The National Academy of Sciences has estimated that about three-quarters of the population

consumes some of the artificial sweeteners. The industry that produces and provides them for human use is an enterprise of at least a billion dollars a year.

About 70 per cent of the use of cyclamates is in the form of soft drinks such as Tab, Diet Pepsi, Diet Cola, Fresca, Like, Wink and others.

Mr. Finch said the beverages were singled out for most rapid action because they are so widely used and because they contain relatively large quantities of the sugar substitutes.

Frequently the highest concentrations are in dry beverage mixes, such as Kool-Aid.

In the news conference at which the announcement was made, the Secretary said his action should not be interpreted as an emergency measure, but a matter of prudence and legal necessity.

Federal law requires that any food additive must be removed from the market if it has been shown to cause cancer when fed to humans or animals.

In the case of cyclamates, the department has taken action within days of receiving evidence that is considered scientifically valid.

A reporter asked him how the government could move so fast against these products when it has been impossible for years to obtain anything beyond warning label requirements for cigarettes.

Mr. Finch said he has no jurisdiction over cigarettes, over which the Federal Trade Commission has authority.

Many specialists consider the scientific evidence to be overwhelming that cigarette smoking can lead to lung cancer. Indeed, it is the official position of the Department of Health, Education, and Welfare that cigarette smoking is the major cause of lung cancer.

Dr. Jesse L. Steinfeld, the department's Deputy Assistant Secretary for Health and Scientific Affairs, said the decisions announced today were based on the discovery of bladder tumors in rats that had been fed cyclamates all their lives in amounts about 50 times as great as the maximum previously proposed for human consumption by the National Academy of Sciences.

The key item of evidence was that six of 12 rats given the highest doses of sugar substitute developed bladder cancers in an unusual part of the order. None of the control animals developed bladder cancers. Thus, even though the numbers involved were small, the evidence pointed strongly to a cause and effect relationship.

There has also been some other recently acquired evidence in laboratory animals, but Dr. Steinfeld indicated it is less persuasive.

Within the last few days the new data has been reviewed by specialists of the National Cancer Institute and a special committee of the National Academy of Sciences.

Mr. Finch said he expected that cyclamate products, in the future, would be labeled as drugs to be consumed on the advice of a physician. The secretary said he was meeting today with representatives of the affected industries and consumer groups to determine the most effective methods of offering the products for use on a restricted basis and for developing new and safe formulations without cyclamates.

The orders announced at the news conference this morning in the H.E.W. north building here do not affect saccharin, a chemically different artificial sweetener that has been in use for well over a century. Saccharin is often used, in smaller amount, in combination with cyclamates. It has 500 times the sweetening capacity of sugar, but for some persons, it leaves a bitter aftertaste. Cyclamates are considered 30 times as powerful as sugar in producing a sweet taste.

Much of the research on which today's decision was based was done under non-government auspices. Indeed, some of it was sponsored by Abbott Laboratories, principal American manufacturer of cyclamates. This pharmaceutical company brought its information to the attention of the National Cancer Institute last Monday.

Further evidence was compiled and reviewed during the rest of the week by government and non-government scientists. By Friday, they reached the unanimous opinion, Dr. Steinfeld said, that cyclamate induces cancer of the bladder in rats, using the dosages and under the conditions of the experiments.

"This was not observed in previous experiments, probably because the urinary bladders of the test animals were never examined," Dr. Steinfeld said today. "There was no reason to suspect damage to that organ system until last summer when Abbott scientists first learned that implantation of pellets of cyclamate and cholesterol in the bladder cavity did indeed cause bladder tumors in mice."

He said that the National Academy of Sciences—national research, council subcommittee on cyclamate safety confirmed the Government scientists' views yesterday and recommended that cyclamates be removed from the list of approved food substances for general human use.

Dr. Herbert L. Ley, Jr., Commissioner of Food and Drugs, said today his agency plans a thorough re-evaluation of all of the approximately 100 other items on that list.

The government spokesman said there is no evidence that cancers of the human bladder are increasing in any significant degree.

[From the New York Times, Oct. 19, 1969]

DIET FOOD INDUSTRY WILL BE HARD HIT BY CYCLAMATE BAN

WASHINGTON, October 18.—The Government's ban on the artificial sweeteners called cyclamates is going to sour a billion-dollar-a-year diet food and drink industry and force a change in American eating habits.

The restriction on the public's use of cyclamates and their elimination from food products early next year were announced today in a news conference by Robert H. Finch, Secretary of Health, Education, and Welfare.

The use of cyclamates in the production of general purpose foods and beverages has been ordered discontinued immediately, with recall of products now on the market to be accomplished in phases. Soft drinks with cyclamates are to be off the market completely by Jan. 1, and all other food products using the substance to be removed by Feb. 1.

Since the calorie-counting craze started in the United States a decade ago, the production of the chemical cyclamates has grown from almost nothing to about 10,000 tons a year, enough sugar substitute to sweeten 50 billion cups of coffee.

About 250 products of American food counters contain small amounts of cyclamate, which is blended into soft drinks, canned fruits, ice cream, salad dressings, powdered fruit drinks, gelatin desserts, dessert topping, drugs, cakes, and even bacon. Cyclamates have been used instead of sugar in curing some bacon to avoid caramelizing and burning when it is fried.

Dr. Roger Q. Egeberg, Assistant Secretary for Health Affairs of the Department of Health, Education and Welfare, pointed out that the use of cyclamate has been of direct medical benefit to a tremendous number of persons suffering from diabetes and hypertension who are forbidden sugar in their diets.

"Cyclamates and artificial sweeteners have probably saved or prolonged a lot of lives in recent years by helping people keep their weight down," Dr. Egeberg said at the news conference announcing the ban on cyclamate. He added that "dentists say the artificial sweeteners may have saved a lot of teeth."

Mr. Finch told the news conference that he expected that some diet foods will be relabeled as drugs and will be available to "persons whose health depends upon them" and will be available "to be consumed on the advice of a physician."

Such products, presumably, would be available in drug stores in the future, rather than food markets.

But today's order will mean the virtual elimination from the household of such popular brand name products as Metrecal, Diet Pepsi, Fresca, Tab, Kool-Aid, Hawaiian Punch and Gatorade, unless their manufacturers reconstitute the brands using sugar, saccharin or some other sweetener.

Attempts to reach some of the larger soft drink bottlers and food processors were unsuccessful late today.

Several drug companies are known to have been working on a new substitute for the sugar substitute cyclamate, whose major manufacturers are Abbott Laboratories in Chicago, Chas. Pfizer & Co., Inc., of New York, and the Union Starch and Refining Company; which is a division of Miles Laboratories Inc., Elkhart, Ind.

A spokesman for Abbott Laboratories would not comment on reports that research was being conducted on a new chemical sweetener. He would only say that "artificial sweetener products represent approximately 4 percent of Abbott's annual sales volume and less than 3 percent of annual earnings." Last year, Abbott had sales of $351-million and earnings of $36.1-million.

One possibility is that either sugar, or saccharin, or a combination of the two, would be used to replace cyclamate in diet products.

Many, if not most, of the diet preparations using artificial sweeteners now contain combinations.

An average 10-ounce bottle of low-calorie cola, for example, contains about one-hundredth of an ounce of cyclamate. A one-pound can of diet peaches might contain twice as much.

The Food and Drug Administration recommended two years ago that adults should not use more than 3,500 milligrams of cyclamate a day. This is about equivalent to 10 10-ounce bottles of artificially sweetened soda pop. The limits for children then were set at about one-third that amount.

At the time, the drug administration reported that the ingestion of large quantities of cyclamates, such as about two ounces a day, could cause diarrhea. There also are at least eight cases on medical records of cyclamate users suffering allergic reactions to sunlight.

Cyclamate had been on the market for 16 years in the United States when two Japanese scientists discovered in 1966 that a metabolic product of cyclamate named cyclohexylamine could cause severe skin irritation in some persons.

The full impact of the cyclamate ban on the food industry could not be immediately assessed.

A report on artificial sweeteners made public two years ago by Arthur D. Little Inc., a Boston management consultant company, noted that when cyclamate drinks became popular in the mid-nineteen-sixties their popularity did not affect the market for sodas containing sugar.

In fact, said the Little report, sugar soft drink sales rose.

This has worried some scientists who believe that while the consumption of cyclamate sodas has been relatively modest for most Americans, a small percentage have been drinking too much.

[From the Washington Post, Oct. 19, 1969]

Halt Ordered in Making of Cyclamates

(By Morton Mintz)

The federal government yesterday ordered an immediate halt to the production of cyclamates, the artificial sweeteners used in soft drinks and food found in an estimated 75 percent of American households.

The Department of Health, Education and Welfare took the action on the basis of newly reported evidence of cancer of the bladder in rats treated with the chemicals in doses about 50 times normal.

The soft drink industry said it would "immediately suspend production" of low calorie soft drinks containing cyclamates.

Tom Baker, executive vice president of the Soft Drink Association, reported the decision after a meeting with HEW Secretary Robert H. Finch.

Finch, announcing the government ban, emphasized "in the strongest possible terms that we have no evidence at this point that cyclamates have indeed caused cancer in humans."

Finch said he was "required" to act under an 11-year-old law saying that a food additive that causes cancer in either humans or animals "must be removed from the market."

But he also said that he invoked the law, whose principal sponsor was Rep. James J. Delaney (D-N.Y.), "because it is imperative to follow a prudent course in all matters concerning public health."

The action does not affect other synthetic sweeteners like saccharine. However, producers of soft drinks and artificially sweetened foods, which commonly are used by diabetics, have shunned saccharine because it leaves a bitter aftertaste in the mouths of some users.

When a cyclamate or other non-nutritive sweetener is used, the maker is required to specify it on the labeling.

Sen. Warren G. Magnuson (D-Wash.), chairman of the Senate Appropriations subcommittee for HEW, said that he now expects Finch to request funds to review a list of more than 10 food additives generally recognized as safe—as the cyclamates have been until now—but which have not been demonstrated to be free of hazards. Magnuson promised "careful attention" to such a fund request if Finch makes it.

The Secretary said that a "conservative" estimate by an industry source put annual sales of products sweetened with cyclamates—mainly beverages—at $1 billion.

REPORT BY ABBOTT

The first report to HEW on the rat studies was made by Abbott Laboratories, the leading producer of cyclamates, on Tuesday. That was two days before a special cyclamates subcommittee of the National Academy of Sciences-National Research Council began a two-day meeting.

To effect an "orderly withdrawal" of cyclamate-sweetened beverages now in distribution pipelines, Finch set a deadline of Jan. 1 for suppliers to complete a recall from retailers. He set Feb. 1 as the deadline for a recall of foods, which contain lower levels of the chemicals. All of the products will remain available for use on advice of a physician.

While permitting diabetics and others with special diet problems to enjoy foods that otherwise would be denied them, the cyclamates are not believed to have any purely medical utility.

Dr. Roger O. Egeberg, Assistant Secretary of HEW, said that the cyclamates have "probably saved and prolonged a number of lives by helping people keep their weight down." Told of a report in The Medical Letter that persons on cyclamates "commonly compensate by excessive consumption of other foods," Dr. Egeberg conceded that he was speaking entirely from personal experience.

CONSUMPTION NOT DOWN

The view of the highly regarded Medical Letter is backed by statistics showing that since the early 1960s, when cyclamates began to win wide popularity, the consumption of sugar per person has not gone down.

The Food and Drug Administration had requested the NAS–NRC to evaluate studies of cyclamates, particularly those made by FDA research scientist Jacqueline Verrett.

She produced severe deformities in about 15 percent of 4,000 chicken embryos treated with normal doses. In an additional 10,000 chick embryos, derivatives of cyclamates created by body metabolism caused deformities at rates approaching 100 percent.

The NAS–NRC subcommittee confirmed the new study showing cancer of the bladder in rats. But Dr. Jesse L. Steinfeld, Deputy Assistant Secretary for Health and Scientific Affairs, told the press conference that Dr. Verrett's studies cannot be extrapolated to humans.

Another FDA scientist, Dr. Marvin Legator, found in test tube studies that cyclamates could cause breakage of rat chromosomes. These contain the genes, which transmit hereditary characteristics.

[From the Washington Post, Oct. 20, 1969]

SWEETENER ACTION STIRS CONTROVERSY—BARB BY FINCH EMBITTERS FDA AIDE

(By Morton Mintz)

Because of a strong personal criticism made in public of a Food and Drug Administration researcher, the handling of the artificial sweetener episode is leaving a bitter aftertaste.

The criticism was made by Robert H. Finch, Secretary of Health, Education and Welfare, of Dr. Jacqueline Verrett, whose studies of chicken embryos given normal doses of cyclamates revealed deformities at a rate of about 15 percent. Derivatives of cyclamates created by body metabolism caused deformities at a rate approaching 100 percent.

Her conclusions were simply that studies should be undertaken in other animals and that pregnant women should not ingest the chemicals—or others—without consultation with a physician. Such advice has been given for years by HEW and the American Medical Association, among others.

NOT RELATED TO FINDINGS

Finch criticized Dr. Verrett at the Saturday press conference at which he announced an order halting production of soft drinks and foods containing cycla-

mates. The order was based entirely on the new discovery of cancer in the bladders of rats which had been given heavy doses of cyclamates and was in no way related to Dr. Verrett's findings.

Accusing Dr. Verrett of "not acting in a very ethical way," the Secretary said that she "chose to go directly" to news media—she appeared on an NBC–TV telecast Sept. 30—without clearing her appearance with her superiors at FDA.

SECOND FOR FINCH

This was Finch's second public criticism of the scientist. The first was on Oct. 8, when he told the Associated Press he was unhappy about her appearance on NBC.

Dr. Verrett said that before giving the NBC interview she had obtained clearance from her boss, Dr. Keith Lewis, head of FDA's Bureau of Science, and from two agency press officers, Milton Wisoff and Judith S. Bublick. Permission also was obtained from Deputy Commissioner Winton B. Rankin, she said.

Even before this, Dr. Verrett told a reporter, she had given an interview to Jean Carper for a syndicated newspaper column Miss Carper writes with Sen. Warren G. Magnuson (D-Wash.). The interview was released to clients before the telecast was aired.

In a statement Saturday, Magnuson came to Dr. Verrett's defense. Even if not surprising, this is of special significance because he heads the Senate Appropriations subcommittee with jurisdiction over Finch's department.

MADE "WHIPPING POST"

Magnuson praised Dr. Verrett's "fine research contributions" and protested that simply by giving factual replies to questions about her studies she has been made into "a whipping post."

At the press conference, Finch—and, for that matter, FDA Commissioner Herbert L. Ley Jr.—said that they had not known of Dr. Verrett's findings and television interview until they saw her on NBC.

Yet, it turns out that Dr. Verrett had spoken of her studies last December in a memo addressed to Dr. Ley. At that time she says, her conclusion of a cause-effect relation between cyclamates and deformities in chick embryos was "very firm" even though her studies were less extensive.

On Saturday, Dr. Ley acknowledged a serious "communications gap" in FDA and said he is trying strenuously to correct it. He indicated the memo apparently became stalled in agency channels and did not reach him.

Magnuson said that Dr. Verrett "was in no way attempting an end run around her superiors even though they had not given a great deal of attention to her work."

[From the New York Times, Oct. 21, 1969]

U.S. CURB ON SWEETENERS TRIGGERS FRANTIC TRADING—PAPER PROFITS' LOSSES SOAR TO HUNDREDS OF MILLIONS OF DOLLARS AS SPECULATORS UNLOAD DIET ITEMS FOR SUGAR STOCKS

(By Terry Robards)

Hundreds of millions of dollars in paper profits and losses were recorded in the stock market yesterday as a result of the Government's ban on soft drinks and foods containing cyclamates, an artificial sweetener.

Heavy selling flowed into the shares of those concerns dependent on the sale of diet drinks or foods using the chemical, while speculative buying surged into the stocks of sugar companies or other companies that make artificial sweeteners without cyclamates.

Wall Street's brokerage houses sped news flashes to branch offices via their internal communications systems, advising the sale of some securities and the purchase of others. Officials of some of the involved companies issued statements.

The net effect was near-chaos in more than a dozen issues traded on the New York Stock Exchange. Ten failed to begin trading on time and three of these did not open until the noon hour.

Abbott Laboratories, the largest chemical producer in the cyclamate market, opened at 10:46 A.M. at 67½, down 6½ points from Friday's closing price. The

paper loss in this single issue amounted to about $87-million, before it rallied to finish the session down 2⅛.

Royal Crown Cola, which derives about 25 per cent of its sales from Diet-Rite Cola containing a cyclamate, was off 3¼ at the opening and closed with a loss of 2½ at 16. Pepsi-Co. finished the session down 2⅝ at 48, while Coca-Cola closed down only ¾ at 77⅜ after being down 2⅝ at the opening.

Stokely-Van Camp, the distributor of Gatorade, a new soft drink said to have unusual attributes, was one of the session's biggest losers. It closed with a loss of 4 at 29⅛.

Sugar stocks moved in the opposite direction, apparently on the theory that the market for drinks containing real sugar would expand in relation to the anticipated contraction in the diet drink market.

Gains of 2 points or more were scored by Amalgamated Sugar, American Crystal Sugar, American Sugar and Holly Sugar. MacAndrews & Farbes, disclosing that it might be able to produce an artificial sweetener without cyclamates, leaped 5⅝ to 28⅛ at the close.

Bache & Co. one of the largest brokerage houses, washed a series of items on its news wire, suggesting at one point that the initial impact on Abbott Laboratories had been too great and that buying was warranted. Bache estimated the adverse impact of the ban to be about 7 cents a share on Abbott earnings.

Bache foresaw little or no impact on the earnings of Chas. Pfizer and Miles Laboratories, the other cyclamate producers. The firm called Cocoa-Cola a buy and advised holding Pepsi-Co. It suggested selling Royal Crown on strength.

Another big wire house also recommended selling Royal Crown in trading accounts. But it said any "severe" near-term weakness might represent a long-term buying opportunity, since the company no doubt eventually would shift to some other sweetener.

[From the New York Times, Oct. 21, 1969]

Risks and Benefits: Job for a Doctor

(By Harold M. Schmeek, Jr.)

Washington, October 20.—The question before the average American family now is what to do with that six-pack of diet soft drink in the refrigerator. The safest answer, if the drink contains cyclamate appears to be: Throw it out. But this applies only to the person who has no particular medical need to be taking the artifical sweetener instead of sugar. For the diabetic, or other persons on a strict diet for health reasons, the apparently small risk from the cyclamate is probably less than the risk of the disease condition that calls for its use.

These points are implicit in the Government's actions on the artificial sweeteners.

The Department of Health, Education and Welfare has ordered an immediate halt in production, a recall of existing supplies of cyclamate-containing beverages by Jan. 1, other foods by Feb. 1 and drugs by July 1.

At the same time, legal officers of the Food and Drug Administration are trying to work out, with manufacturers, labeling that will allow diet products containing cyclamates to be sold without prescription.

WARNINGS ON LABELS

The labels must be so worded as to give the prospective buyer a sufficient warning of the hazards and an admonition to use the products only on doctor's advice.

William W. Goodrich, the department's assistant general counsel for food and drugs, said today that no decision had yet been made on whether cyclamate-containing products would be available without prescription after the recalls are effective. He said it was hoped that they would be available without prescription.

The gist of the matter is that the Food and Drug Administration has ruled that cyclamates can no longer be regarded as "generally recognized as safe for use in food."

Yet there is no direct evidence that the cyclamates have harmed human beings. The new evidence cited against them is that they appear to have caused some bladder cancers in rats fed massive doses of the artificial sweetener over long periods of time.

Thus, the decision for or against using such products should be made by weighing the potential risks against the potential benefits—presumably a job for the physician.

Dr. Jesse L. Steinfeld, Deputy Assistant Secretary for Health and Scientific Affairs, said the Department would make an effort to acquaint physicians with the details of the new evidence on the cyclamates.

Meanwhile, one officer of the department, who is a physician, said his personal inclination would be to throw out any household stocks of cyclamate-sweetener soft drinks.

Another officer a nutritionist, said he had not come to any firm conclusion on that issue, although he doubted that reliance on artificially sweetened food and drink made much sense in ordinary efforts at weight control.

For the general public it appears that the only available non-caloric alternative to cyclamates will again be saccharin, at least for the immediate future. Officers of the Food and Drug Administration said that they knew of nothing else available.

Several alternatives are being or have been, studied in laboratories throughout the country. Some are several hundred times more potent than sugar as sweetners, but none of these has yet been approved by the F.D.A.

How long it would take to get approval depends on how much toxicity research has been done to date. This information is not available. For some substances, the F.D.A. approval would seem to be years away.

One alcohol sugar called sorbitol is already used in making sugar-free candy, but it is only 60 per cent as sweet as ordinary sugar. Furthermore it is rated as the same caloric content—four calories a gram, although it may be differently utilized by the body.

Saccharin itself is expected to get further scrutiny to see whether its clean bill of health can be maintained. A year ago it was thought that the cyclamates could not cause cancer production. Indeed a report by the National Academy of Sciences last November said long-term studies in several species, including the rat showed no evidence of any cancer danger through use of cyclamates.

At that time, a government spokesman said, it had not been considered that the posibility of bladder cancer needed to be studied in detail.

Now that this effect is known, research workers have one more clue with which to screen out potentially dangerous products in the future.

Several other ingredients in food or beverages have been recalled in the past after new evidence showed they could not be labeled as safe.

[From the New York Times, Oct. 21, 1969]

ADVERTISING: A "CYCLAMATIC" DAY AT AGENCIES

(By Philip H. Dougherty)

"This has been cyclamates day in the agency business," Edward H. Meyer, president of Grey, said yesterday. He was obviously right, too, since most advertisers and agencies with products containing that artificial sweetener (soon to be banned) were getting ready to roll with alternate advertising.

There appeared to be two strategies developing. If you have a product that comes in two versions, cyclamate and noncyclamate, promote the noncyclamate. If you have just a cyclamate-containing product, announce that you are reformulating and a new product is on the way.

Pepsi-Cola did just that yesterday in a full-page ad in this paper. The ad, in preparation for six weeks, will be appearing in about 25 major markets across the country. "Cyclamates? Diet Pepsi can do better without them," says the head. The ad shows a new six pack with the "New! Better tasting" and "Sugar added—no cyclamates!" on the package.

General Foods bumped one of its spots off the "Mayberry R.F.D." series on NBC–TV last night to make way for a stand-up announcer telling the consumer that its regular Kool-Ade, to which sugar is added, is absolutely cyclamate free and safe for the kiddies. The spot will go on "Julia" on the C.B.S. network tonight and by tomorrow they should be ready with the same commercial that Danny Thomas is expected to go on down in New Orleans today.

By the end of the week, Canada Dry's Wink is expected to be out with ads headlined, "Wink, Great (no cyclamates)."

Maybe the only silver lining in Saturday's Department of Health, Education and Welfare announcement as far as soft drink companies and their agencies are concerned is that it came at a fairly slack season for advertising.

The heavy times are the late spring, the summer and between Thanksgiving and Christmas. Right now, too, the companies are between the last and the next advertising campaigns.

Royal Crown, for example, has no advertising running for its Diet-Rite, and is awaiting the unveiling of the new Wells, Rich Greens effort to bottlers on Nov. 1.

A Coca-Cola spokesman said "of all the complexities involved, advertising was the least complex." He said there was no national print or broadcast to worry about for either Tab or Fresca, but some bottlers had local advertising running.

"All media involved have been very cooperative," he said.

His company has already announced that it had new formulas for its drinks.

"There will be a couple of weeks hiatus" in advertising and promotion while the new advertising is prepared, the spokesman said, "then we'll be back in with advertising and packaging to match."

Coke plans to do research on the consumers' reaction to the Government ban, and Pepsi is already in the field doing the same.

Pepsi said it would withhold national advertising until it has got the new formula throughout the marketplace but would use local advertising as each area is supplied.

What it looks like right now is that soft-drink agencies, which would normally find billings rather slack at this time of year, will find a little more action through noncyclamate advertising.

The running back from Southern Cal has already signed contracts with Chevrolet and ABC–TV.

[From the New York Times, Oct. 21, 1969]

INDUSTRY WAS READY WITH NEW PRODUCTS

(By Douglas W. Cray)

The nation's diet food and soft drink manufacturers rushed out more new-product announcements yesterday, indicating they had been prepared for the Government's ban on the use of the artificial sweetener cyclamate in general-purpose food products.

The Government's action was announced on Saturday. By nightfall yesterday, a number of leading soft drink manufacturers and others involved in the $1-billion low-calorie market had reported they were ready to market new cyclamate-free beverages and other products within a matter of days or a few weeks at the most.

The Pepsi-Cola Company, for example, began serious work on the new diet drink it announced over the weekend as long as a year ago. John Scully, director of new product development for the company, said yesterday: "It's just a question of prudent management. Any alarm, even though not supported, has to be considered. We did start work on this as much as a year ago."

Charles W. Adams, senior vice president of the Coca-Cola Company in Atlanta, emphasized the same degree of preparedness or, in his words, "taking out insurance."

Along with Pepsi, the Coca-Cola company has announced its readiness to introduce new formulations containing no cyclamates, in its Fresca soft drink. "We've been working with artificial sweeteners since the early sixties," Mr. Adams said yesterday, "and we went to work in earnest on these new formulations earlier this month when Dr. Herbert L. Ley, Jr., Commission of Food and Drugs, requested another formal study of cyclamates."

Among the others joining the new-product parade yesterday was John Cott, president of the Cott Corporation, who announced that his company will have low-calorie diet beverages with no cyclamate or sugar added available this week.

No-Cal Corporation, a wholly owned subsidiary of Kirsch Beverages, Inc., will have a new line of No-Cal drinks on the market in about two weeks. A com-

pany spokesman said they will contain saccharin and a small amount of sugar, adding about 10 to 14 calories to the drinks.

Business action was immediate. Abbott Laboratories, the major producer of cyclamate, and the other two producers, Miles Laboratories and Chas. Pfizer & Co., have discontinued production. Cyclamate-oriented shares on the New York Stock Exchange were down yesterday in the wake of the Government action.

LITTLE EFFECT AT REYNOLDS

Elsewhere, reaction was less hectic. Hawaiian Punch, produced by R. J. Reynolds Foods, promptly announced it was halting manufacture of its one-low-calorie item. The rest of its line, accounting for over 90 per cent of its sales of canned and frozen fruit beverages, does not contain cyclamate and is not affected.

Abbott Laboratories sources indicated yesterday they had no plans for development work on other cyclamate-free sweeteners. But G. D. Searle & Co., another leading drug manufacturer, said that its development of a new type of low-calorie sweetening agent is proceeding favorably. Searle has been at work on this for several years and hopes to have the necessary medical data ready to submit to the Food and Drug Administration by the middle of next year.

The A. E. Staley Manufacturing Company announced it was introducing new low-calorie versions of its "Wagner Breakfast Drink Line" containing no cyclamates. Alberto-Culver Company reported that "we made a prudent decision months ago to develop a reformulation of our product (a sugar substitute called Sugartwin) without cyclamate content. This we have done and will begin distribution of the reformulated product before the Government deadline."

JANUARY 2 DEADLINE

Products containing cyclamates that are already on the market were ordered by the Department of Health, Education and Welfare to be phased out by next Jan. 2 and Feb. 1. The action was taken on the basis of research on a group of rates, some of which developed bladder cancers after being fed large quantities of cyclamates over long periods. It was emphasized on Saturday that there was no evidence at present linking cyclamates to cancer in man.

The Searle Company said it had no idea at this point when its new product, so far unnamed, would be commercially available. The sweetening agent is based on two naturally occuring amino acids and the company reports that to date all animal feeding studies have shown the new sweetener to be without effect on the test animals.

[From the Wall Street Journal, Oct. 21, 1969]

SOME CONSUMERS RETURN CYCLAMATE FOODS; OTHERS HOARD THEM; MANY STORES SIT TIGHT

(A Wall Street Journal News Roundup)

Many anxious consumers across the nation are demanding refunds for soft drinks and other food products artifically sweetened with cyclamates.

But some others, ironically, are busily buying up stocks at their stores, apparently in fear they won't be able to acquire sugar-free substitutes after the Federal Government's ban on the artificial sweetner takes effect next year.

Stores, for their part, are generally making refunds to any customers who request them, a survey by The Wall Street Journal finds. Some soft-drink makers and food processors are, in turn, taking back the rejected stocks.

A number of merchants and manufacturers, though, are sitting tight with their existing supplies. Some stores are continuing to display cyclamate-sweetened products. Many manufacturers are urging retailers to hold off on abrupt returns.

Louis Sherry Inc., for one, is telling its customers to "keep your pants on until the consumers make their minds up," says Clifford Spiller, president of the Garden City, N.Y., food processing company. "We have a feeling that consumer demand will decline, but not to the point that we'll have to do anything about the stuff already on the shelves." Louis Sherry, however, isn't shipping anymore cyclamate-sweetened foods.

The initial consumer response yesterday, the first full shopping day after the Government's Saturday announcement, was widely varied.

LOTS OF QUESTIONS

"We're going crazy giving money back on the stuff," exclaims one supermarket manager near Pittsburgh. "They're giving us a headache, asking questions about the stuff."

In Dallas, however, the manager of a Tom Thumb Stores Inc. outlet says he has sold a "huge quantity of cyclamate products."

Few of the stores are pulling cyclamate foods off their shelves, unless the manufacturer offers credit or a merchandise swap. "Don't forget," observes a spokesman for Food Fair Stores Inc., a Philadelphia-based chain, "we're still selling cigarets, and people are still buying them."

A number of manufacturers are withdrawing their cyclamate-sweetened products in advance compliance with the Government's deadline of Jan. 1 for soft drinks and Feb. 1 for other food products.

ALLEGHENY TO CONTINUE SELLING

General Foods Corp., White Plains, N.Y., says it is withdrawing a number of products immediately and replacing them in store inventories with cyclamate-free products that have been on the market for years. For Pre-Sweetened Kool-Aid Mix, for instance, General Foods offered its regular Kool-Aid Soft Drink Mix. For its Good Seasons low calorie Italian salad dressing mix, General Foods offered in exchange the regular-calorie version. Such products, the company said, accounted for about $48 million in sales last year, or about 2.5% of its annual volume.

Privately owned Atlanta Coca-Cola Bottling Co. says it has already started picking up retailer stocks of Tab and Fresca, two cyclamate-sweetened drinks, and is replacing them with comparable sizes of Coca-Cola, Sprite and Fanta.

In Baltimore, however, Allegheny Beverage Corp., which owns 80% of Allegheny Pepsi-Cola Bottling Co., asserts it plans to keep selling its cyclamate products from its inventories as long as permitted by law.

Barton's Candy Corp. is speeding up deliveries. Steven Klein, chairman and president of the Brooklyn, N.Y., candy maker, says the company has had to make special shipments to several stores because customers who normally buy one box of low-calorie chocolate suddenly want five. Mr. Klein says he reacted the same way himself: He went out Sunday night and bought two dozen bottles of cyclamate-sweetened Fresca.

More companies, meanwhile, are announcing new products that will satisfy Government regulators and diet needs of weight-watching and diabetic consumers.

Cott Corp., New Haven, Conn., a soft-drink manufacturer and bottler, says it will have cyclamate- and sugar-free beverages on the market in a few days. Alberto-Culver Co., Melrose Park, Ill., says it has come up with a new cyclamate-free formulation for its sugar substitute, Sugartwin. A. E. Staley Mfg. Co., Decatur, Ill., promotes new low-calorie versions of Wagner Breakfast Drink.

Not that those and similar announcements calmed investors in their securities trading. Stock prices of food companies with dietetic products generally eased yesterday. Securities of cyclamate makers also fell. But securities of sugar companies and makers of other sugar substitutes rose in anticipation of increased volume. (See page 39 for further details.) World sugar prices also rose on commodity markets (see page 32).

Some of the apparent gainers, though, minimize the impact of the Government order on their sales.

Raymond Guth, secretary of American Sugar Co., says in New York, "We expect some increase, but it won't have a substantial impact on volume."

At another sugar processor, an official proclaims, "I certainly don't see it as a bonanza for the sugar companies."

Makers of soft-drink bottles also scoff at suggestions that they'll be in for a windfall. As explained by an executive of Brockway Glass Co., Brockway. Pa., all soft-drink bottlers will have to discard their stocks of returnable diet soda bottles, which have their labels permanently affixed to the glass. But he says many bottlers, possibly in anticipation of the Governments decision, have been switching from returnable to nonreturnable bottles, which avoid the relabeling chore. "When you spread the available business out through the giant industry, I can't see where it would be critical to any of us," says the official.

Makers of saccharin, a sugar substitute, wasn't affected by the Government ruling and expects to be clear gainers on the move.

"I've booked 100,000 pounds of orders today" says John Drumheller, marketing manager for organic chemicals at Sherwin-Williams Co., Cleveland. "That's a little better than a month's business as a rule."

[From the Washington Post, Oct. 21, 1969]

CYCLAMATES—SWEET HABIT

(By Elinor Lee)

With the federal government's ban on cyclamates, an American habit almost as deeply ingrained as cigarette smoking went up in smoke.

About 17 million pounds of cyclamate (a salt of cyclamic acid about 35 times as sweet as sugar) were produced last year, according to Dr. J. D. Taylor of Abbott Laboratories, which manufactures more than half the cyclamate used in this country.

An estimated 70 to 75 percent of the people in the United States use some form of cyclamate.

With about 50 million Americans counting calories and trying to lose weight, it isn't surprising that production of non-nutritive sweeteners has zoomed.

Until the action Saturday by U.S. Department of Health, Education and Welfare, hundreds of artificially sweetened foods and beverages were being purchased by consumers.

These products included not only low-calorie soft drinks but all kinds of dietetic canned fruits, puddings, canned fruits, puddings, candy, jams, salad dressings, liquid meal substitutes, sugar substitutes to sweeten tea and coffee, sugar-coated and chewable aspirins and vitamins for children, ice creams and many other products.

The number of such products on the market has doubled in production over the last 10 years. The diet and low calorie segment of the grocery business was expected to top $1 billion this year.

Now what happens?

One mother of five said she would stop buying low calorie bottled drinks and packaged beverages "but I expect all the kids will lose their teeth or get cavities with all that sugar now."

Another woman to whom I talked claimed artificial sweeteners had become a way of life in her family. "We'll all become obese now and die of too many calories," she added.

But Dr. Jean Mayer, the President's adviser on nutrition and health, says if he could issue one warning to the mothers of the country it would be to cut down on the calories in everything from unnecessary desserts to soft drinks. The human race survived very well until only a few years ago without soft drinks, declared Dr. Mayer. "What's wrong with tomato juice, orange juice, milk and water? Nothing!"

And fruit is still the best dessert, he added.

Dr. Mayer said HEW Secretary Robert F. Finch's action should be viewed "in proper perspective." The HEW secretary emphasized that at this point there is no evidence that cyclamates have caused cancer in humans.

"At this point there is not one case of cancer related to man," Dr. Mayer pointed out. "But this action is a very good preventive measure. The report was received last Tuesday and by Saturday the action was taken.

Dr. Mayer, who calls dieting "the rhythm method of girth control," said "There's still saccharine . . . there's no ban on that and it does NOT leave a bitter aftertaste."

Dr. Cortez F. Enloe Jr., editor of Nutrition Today (the most widely read publication on nutrition in the world), said in a telephone interview, "The world is not going to come to an end and we will not all become fat like Winnie the Pooh."

The Dulaney amendment to the food additive law requires the HEW secretary by law to take any product off the market immediately if there is any evidence of its causing injury to animals or man, Dr. Enloe pointed out. (The evidence in the cyclamates case was reports of cancer in the bladder of rats treated with the chemicals in doses about 50 times normal.)

[From the Washington Post, Oct. 21, 1969]

CYCLAMATES—BAN'S EFFECT

(By Elizabeth Shelton)

"Harmful to what, rats?" the housewife wanted to know as she took a six-pack of diet cola from an almost untouched stack of sugar-free soft drinks and placed it in her shopping cart.

Then she explained, almost apologetically, that she and her husband plan to have no more children. Their youngest is already 5. "And it isn't any worse than smoking anyway, is it?"

Most shoppers in the chain supermarket, however, were wheeling determinedly past cyclamate-content food and drink in the upper Connecticut Avenue store. They had read in the newspapers and heard on radio and television that the sweetener developed as a substitute for sugar has been banned by secretary of Health, Education, and Welfare Robert Finch.

Shoppers felt that if laboratory tests had proved cyclamates (and the cyclohexylamine some bodies produce as a result of high intake of the synthetic sugar) cause chromosome breaks, bone marrow changes and cancerous tumors in rats, they were not going to take any chances with the health of their children and husbands.

Empty Tab bottles were turned in for real Coca-Cola. "I'll be drinking real cola, but I just won't be able to drink as many," a plump matron admitted. She also bought a rich cake with real sugar in it, explaining that she has a house full of guests.

One store manager had a busy morning refunding money. A lot of people poured their cyclamates down the kitchen sink over the week-end, but the frugal knew they could get a refund for a filled, as well as an empty bottle.

"I was glad to give them their money back," said Sol Blaufeld, manager of a Super Giant on Western Avenue. "Anything to get them into the store. Giant spends a lot of money just to get people into its stores."

Canned fruits on the diet foods shelves were moving more rapidly than the artificially sweetened soft drinks. "If her husband has a bad heart and has to keep his weight down she has to find sugar substitutes," a store manager said.

One doctor's wife said that she had stopped feeding any cyclamate products, including artificially sweetened vitamin pills, to her children "a long time ago." As soon as she suspected they might be harmful, she immediately quit, she said.

A male shopper called the whole controversy "a political matter." "It's all because of the sugar lobby, and you know that Finch's announcement was made over the weekend while the stock market was closed," he collaborated.

The stores have been given until Jan. 1, 1970 to clear their shelves of cyclamate diet beverages, and until February to remove other foods.

A wide array of weightwatchers' foods and beverages contains cyclamates. Among them are ice creams, baking goods mixes, powdered fruit flavored ades, the diet drinks that almost all name brand soft drinks manufacturers make as a second line, and similar store-brand canned and bottled low calorie beverages.

Yesterday, most of the big soft-drink companies were making plans to rush substitute diet drinks to the public as soon as possible.

Coca-Cola is abandoning the production of Fresca and Tab until its new formula is ready.

Pepsi-Cola is developing a substitute drink an official said will contain saccharine (not a cyclamate) and "a touch of real sugar." Royal Crown Cola, manufacturer of Diet-Rite Cola, is working on a modification of its formula.

General Foods' plans to withdraw all of its cyclamate foods with the exception of its D-Zerta line of dessert products which are used extensively by diabetics. Pillsbury Co. plans to replace cyclamate in its low calorie products.

Ironically, it was tests by the world's largest cyclamate maker, Abbott Laboratories of Chicago, that led to Secretary Finch's ban on the sale of cyclamate products. The company argues that no human system could be bombarded with the amounts of cyclamate dosed to laboratory rats.

But under the law, foods and drugs must be banned if they contain any additives which cause cancer in humans or animals. There has not been any evidence during the years since 1937 when cyclamate was synthesized by Dr. Michael Sveda of Greenwich, Conn., that it has canused cancer in humans.

[From the Wall Street Journal, Oct. 22, 1969]

CANADA TO PHASE OUT CYCLAMATES IN FOODS

(By a Wall Street Journal Staff Reporter)

OTTAWA.—Health Minister John Munro said the Canadian government would phase out the use of cyclamates over a period of months in a variety of food products.

The health minister said the artificial sweetener would be banned in dietetic soft drinks and mixes Nov. 30 this year, in dietetic jams, jellies, desserts and ice cream on April 1, 1970, in pediatric drugs next June 1, and in dietetic canned fruits next Sept. 1.

The health minister said, "As approximately 80% of the cyclamates now used in Canada are in dietetic soft drinks and mixes, these are to be phased out first. They are widely used by teenagers and children, and this is a major reason why they must be removed from the market as quickly as possible."

Mr. Munro added: "As dietetic jams, jellies, desserts and ice cream are used mainly in the diets of diabetics and persons undergoing medical treatment, I feel it is essential to allow sufficient time for their diets to be modified and the persons to adjust to new diets."

Mr. Munro told a press conference that "the danger to humans from cyclamates is undoubtedly very small. Nevertheless, as I have said, we are acting to phase out the use of cyclamates, since I feel it essential that we follow a course of action that affords the greatest protection to the health of the Canadian public."

The health minister stressed that "we have no scientific evidence at this point to indicate that cyclamates have caused cancer or any other harmful effects in humans."

WASHINGTON (UPI).—The Food and Drug Administration ordered an investigation into saccharin, an artificial sweetener, following its recent ban on cyclamates.

Joshua Zatman, assistant commissioner said, "There aren't the kind of findings that have been reported in cyclamates, but we think we ought to look into saccharin very thoroughly just to make sure the public is safe."

[From the Washington Evening Star, Oct. 23, 1969]

THE CYCLAMATE AFFAIR

Within a week of the shocking news that cyclamate, the artificial sweetener, produces cancer in rats, HEW took it off the market. It also went out of its way to damp down unfounded alarm by emphasizing that there is no proof at all that cyclamate produces cancer in human beings.

Clearly, the ideal time to discover the potentially harmful effect of a food product is before—not after—the product has been marketed. So the question arises: Why was that not done with cyclamate? And what, if anything, can be done to improve the way that the government tests food and drug products?

As to cyclamate, a bit of history is in order. This sweetener was first marketed in small quantities in 1951, primarily as an aid to diabetics. Thus it considerably predated the 1958 amendment to the Food and Drug Act requiring government approval of food additives. There were, of course, other additives on sale at the time that had not received government approval.

The government's response was to test these additives after the fact and then put the successful ones on something known as the GRAS (generally recognized as safe) list. Cyclamate passed its test.

Secretary of HEW Robert Finch has ordered a review of the products on this list, which seems definitely needed.

The secretary might also want to review the procedures whereby food and drug products are tested. For one thing, most of the actual testing takes place in industry laboratories and the data are then reviewed by his department. It is worth asking whether more of the testing should be done by the government itself.

How broadly should the Secretary of HEW interpret his authority to ban a food product that poses an "imminent hazard to health?" On the one hand, a timely action may well be in the interest of the general public. The government,

however, must also consider the financial loss this would inflict on the industry for what may later prove to be a false alarm.

In the case of cyclamate, Secretary Finch interpreted his authority narrowly. Back in April, a test showed that cyclamate produced genetic defects in the offspring of chickens. Rather than ban cyclamate at that time, however, HEW initiated an elaborate review and appeal procedure. Once there was evidence that cyclamate produced cancer in rats, it was no longer a matter of the secretary's direction. The ban was required by law.

The cyclamate experience suggests the need for a careful review of the ground rules for the exercise of the secretary's discretionary authority to ban the sale of food and drug products. He should by all means be encouraged, when in doubt, not to take chances where the public's health is concerned.

All this bears directly on the plans of the diet-product manufacturers to substitute saccharin by itself, or in combination with sugar, as a replacement for cyclamate. Saccharin is on the GRAS list. Most of the tests on it have been run by the industry itself.

The HEW department has ordered new tests on saccharin—some of them to be conducted in government laboratories. Whether to hold the reconstituted diet drinks off the market until the testing is complete is a close question. Either way, the public should be informed of the basis for HEW's decision.

[From the New York Times, Oct. 23, 1969]

F.D.A. To Restudy Four Substances—Saccharin, Salt, MSG and Starch To Be Examined

(By Harold M. Schmeck Jr.)

Washington, October 22.—The Food and Drug Administration is restudying saccharin, monosodium glutamate and two components of baby food in the aftermath of the decision to halt general use of the cyclamates, widely used artificial sweeteners.

The drug agency has asked its experts to go through the entire list of food additives that are generally regarded as safe and report, as soon as possible, whether further testing will be needed on any of them.

Saccharin, the only remaining nonnutritive sweetener on the list now that cyclamate has been removed from it; monosodium glutamate, a flavor-enhancer, and modified starch and common salt, which are used in baby foods are high-priority items on the second-look roster.

When the announcement was made last week that cyclamate would be withdrawn from general use Dr. Herbert L. Ley Jr., Commissioner of Food and Drugs, noted that very little valid information was available on saccharin, although it has been in wide use for about 50 years.

Today, Winton B. Rankin, deputy commissioner, said it seemed probable that some further testing would be needed to insure that saccharin merits its present clean bill of health. This will not be determined, however, until the F.D.A. experts have gone through all the scientific literature pertaining to the substance to see what testing has been done already and what gaps in knowledge may exist.

NEW DIET ADDITIONS

He said that monosodium glutamate and modified starch were more recent additions to the American diet and it was possible that all the necessary testing had already been done on them. Again, the drug agency staff will search the literature to find out whether or not this is true.

Modified starch is ordinary starch that has been altered chemically to modify such properties as its thickening or jelling characteristics. It is used in prepared foods for adults as well as in baby food, but the F.D.A. is particularly concerned over its safety in the latter use.

Mr. Rankin said some of a babys' organs were not entirely developed and could be affected differently from those of an adult. Furthermore, giving any food item to a baby raises the possibility that it will be used throughout his entire lifetime. Such potential long-term use raises safety issues distinct from those of shorter-term adult use.

Opponents of the use of salt in baby food have argued that babies cannot taste the salt and that it is put in the product to make the food taste better to the

mother. Some nutritionists believe that Americans use more salt than is good for their health and that starting to consume it in babyhood simply makes the situation worse.

In recent years there has been some controversy over the safety of monosodium glutamate. It is used widely in oriental foods and has been linked to the so-called Chinese restaurant syndrome—burning sensations, a tightness in the head, occasional headaches and chest pain experienced sometimes by some persons who eat in Chinese restaurants.

Altogether there are several hundred items on the F.D.A.'s lists of substances generally recognized as safe for their intended use. These range from aluminum calcium silicate, used as an anticaking agent in table salt, to caffeine and ordinary sodium bicarbonate.

NUMBER IS NOT KNOWN

The drug agency is uncertain how many of the items will have to undergo further testing. Mr. Rankin said he expects that the number will be small. Not until the newly started literature search has produced some results will it be known what kind of tests will be required or who will do them.

One standard procedure is to feed the substance being tested to at least two species of laboratory animals during the animals' normal lifespan and compare their health and growth with animals fed the same diets minus the key item.

What does seem clear, however, is that any new nonnutritive sweetener that becomes a candidate to replace the cyclamates will have to undergo thorough and extensive testing before it goes into use. Several artificial sweeteners have been under development in recent years. At least two such items have been developed from citrus fruit extracts, according to an article in Chemical and Engineering News.

One of these was developed from a bitter substance in grapefruit. Far more powerful, however, is the other one extracted from Seville oranges. It is said to be 2,400 times as sweet as ordinary table sugar.

The article, by Howard J. Sanders, a senior editor of the magazine, said more than a dozen artificial sweeteners had been the subject of active research. None could be used in food without long and expensive safety testing first.

[From the Washington Post, Oct. 24, 1969]

BABY FOOD ADDITIVE WARNING

(By Elizabeth Shelton)

Dr. Jean Mayer, the Frenchman at the White House who wants Americans to eat more nutritious food, said yesterday that if it were up to him he would order both salt and monosodium glutamate removed from baby food.

Speaking to a Women's National Press Club audience lunching on flank steak in the Gramercy Inn, Dr. Mayer received applause when he replied, "I would take the damn stuff out" to a question about MSG in baby food.

Dr. Mayer said scientific studies show babies would eat just as much food without salt. "They need no more salt than there is in mothers' milk on which generations for hundreds of years have thrived very happily."

Dr. Mayer, on leave from Harvard to direct the December White House Conference on Food, Nutrition and Health, said there is no proof that MSG has had effects on adults or babies.

That is, beyond the "Chinese restaurant syndrome"—sickness caused in adults by the MSG in oriental sauces and soy sauce, Dr. Mayer explained. But he said he had worked on studies of animals suffering brain lesions from doses of the chemical.

Later Thursday afternoon, new research was released relating to brain damage.

Dr. John Olney, of St. Louis, reported that he had produced brain lesions in mice using the same dosage of monosodium glutamate that is being put in baby foods today.

"I've treated a number of species of experimental animals in the period of infancy and I've found that every species I have studied is susceptible to brain damage from monosodium glutamate," Dr. Olney said.

Dr. Olney, who conducted his research under a National Institutes of Health grant, said baby food manufacturers would be using "bad judgment" if they continue to use MSG in the absence of further research on its hazards.

"So long as there is any doubt as to the safety at all, I think it the better part of prudence not to have it in baby foods and I think it will disappear within the next few months," he predicted.

After hearings recently by the Senate Select Committee on Nutrition and Human Needs, the Food and Drug Administration asked the National Academy of Sciences-National Research Council to undertake a new review of baby food additive studies.

Dr. Mayer told the group and their guests that he favors the collection of far more data on food additives which may not be carcinogenic but which cause suspicion and confusion in the minds of consumers.

While some additives may pass tests, there should be a continuous review of new foods and new methods of processing, he said.

Like many homemakers, he is concerned about the cumulative effects of the additives which are multiplying on the market.

Just last week Americans learned that some of the artificial sweetners they had been using for several years were determined unsafe and ordered removed from production.

[From the Washington Evening Star, Oct. 24, 1969]

DR. MAYER LAYS IT ON THE LINE

(By Marion Burros)

Dr. Jean Mayer doesn't think there should be any monosodium glutamate in baby food and said that if it were up to him he would "take the damn stuff out."

The man who single-handedly saved the food stamp program from extinction under Nixon's new welfare plan, probably has enough political clout to see that it is done.

Although he doesn't think there will be any new scandals breaking on food additives, like the removal of cyclamates from the market, he feels that additives should not be in foods "unless they benefit the consumer."

And in this regard, he would like to see some of the salt taken out of baby foods since it is more for the mother's taste than the baby's.

Dr. Mayer spoke before the Women's National Press Club about the White House Conference on Food and Nutrition and neatly fielded another question on the lack of funds for the Conference.

Only $250,000 of the necessary million has been funded but he said "we have all the pledges we need to carry out our work."

The conference, of which he is chairman, will consider the problems of hunger, food safety and nutritional value and the desire for more information on nutrition.

The 26 pre-conference panels are to submit their recommendations by Nov. 1.

They will be circulated among the participating community action groups by Nov. 20 so that the reports and reactions to them will be available to the conference when it begins on Dec. 2.

In talking about the conference and its hoped for recommendations on a "national nutritional policy" the French-born Mayer, on leave as professor of nutrition at Harvard, ranged over a wide variety of topics affecting the health of the country.

He said that the outlay for health costs in the past 10 years has quadrupled but there has been no increase in the life expectancy of the adult man.

Since nutrition plays an important role in health, he considers it shocking that only 8 out of the country's 90 medical schools teach any nutrition at all.

On the subject of government programs he said that many of them "are not doing what they are supposed to do. Two-thirds of the children below the poverty line do not have school lunches, and "food stamps are really a program for the middle poor."

[From Time Magazine, Oct. 24, 1969]

TOXICOLOGY—HEW BANS THE CYCLAMATES

First there was sugar, squeezed from sugar cane and white beets. Dentists blame it for damaging the teeth; it makes people gain weight, and some cardiologists now suspect that its excess use may be a factor in heart-artery diseases. Then, 90 years ago, chemists hit upon saccharin, which is 500 times as sweet as

sugar and does not add calories to the diet. But saccharin has the disadvantage of leaving a bitter aftertaste in many people's mouths, and it cannot be widely used in cooking because it breaks down under heat. When a doctoral chemistry student, Michael Sveda, accidentally discovered cyclamate sodium (Time, June 5, 1950), it looked as if the ideal sweetener for people who do not want to get fat had been found: it is 30 times as sweet as sugar, leaves little aftertaste and survives the heat of cooking. In the years since, cyclamates have become the basis of a $1 billion-a-year business.

Last week the Food and Drug Administration condemned cyclamates as possibly dangerous to health and effectively banned their widespread use in the U.S. Robert Finch, Secretary of Health, Education and Welfare, ordered that all foods and drinks containing the artificial sweetener be removed from grocers' shelves and soft-drink vending channels no later than Feb. 1. In the case of products containing the largest proportions of cyclamates, the deadline is Jan. 1. The effects of this abrupt order on food and drink manufacturing, processing, distribution and marketing will be enormous (*see* Business).

Metabolic Variation. As the reason for his ban, Finch cited new evidence that cyclamates cause cancer in animals. At the same time, he emphasized that there is as yet "no evidence that they have indeed caused cancer in humans." HEW, he said, was being prudent, and will now check other food additives to see whether they may be harmful to human health.

The trouble with cyclamates (besides the sodium compound, there is a calcium combination for patients on low-salt diets) is that they do not behave predictably in the human body—unlike sugar, which is completely and naturally metabolized. Cyclamates break down in the body, forming chemicals, notably cyclohexylamine (CHA). This, in large doses (upwards of 50 times the probable human dose of cyclamate), is known to cause bladder cancer in rats. Because of the emergence of CHA, cyclamates injected into incubating eggs cause grotesque deformities in many of the chicks and kill others in the shell.

Many human beings convert only 1% of their cyclamate intake to CHA, and so minute a quantity might well be harmless. But for unknown reasons other, equally "normal" people convert as much as 40% to CHA; if they are heavy users of cyclamates, the resulting high dose of CHA might cause cancer or other diseases. Like countless other chemicals, cyclamates also cause breaks in the chromosomes of both man and animals, but the genetic significance of these breaks is not yet known.

It is impossible to single out the high-risk, high-CHA converters, or to regulate the cyclamate intake of free-living human beings. So Finch saw no safe middle course and concluded that he had to impose a flat ban. Exceptions will be made for diabetics and those on reducing diets under doctor's care, for whom cyclamates will be available on prescription. For the rest, it will be back to sugar or saccharin.

[From the New York Times, Oct. 24, 1969]

Doses of Monosodium Glutamate Found to Affect Brains of Mice

(By Harold M. Schmeck Jr.)

Washington, October 23.—A scientist in St. Louis said today that he had fed infant mice monosodium glutamate in amounts greater than those in baby food and had produced brain damage in the portions of the mice's brains regulating appetite.

Monosodium glutamate is a food enhancer.

The area in the rodents' brains that was affected, according to the scientist, was the hypothalamus. Among other things, the hypothalamus has the function of controlling the desire for food and water.

Dr. John W. Olney, assistant professor of psychiatry at the Washington University School of Medicine, said this new evidence, added to research he has done previously, had convinced him that the widely used substance should be removed from baby food. The same view was expressed independently today by Dr. Jean Mayer, internationally known nutritionist.

However, two executives of companies that manufacture baby food entered demurrers.

The first, Imri J. Hutchings, general manager for research of H. J. Heinz Company, said he doubted that Dr. Olney's research was applicable to man.

Daniel F. Gerber, chief executive officer of Gerber Products Company, also

expressed doubt that monosodium glutamate had any potential harm for human beings.

Dr. Mayer is director of the first White House Conference on Food, Nutrition and Health. It will be held here in December.

Asked about monosodium glutamate at a luncheon today at the Women's National Press Club, he said that there had not been any evidence that the flavor enhancer, usually called MSG, had any dangerous effects on man. High concentrations of it do have effects on baby animals, he said, causing damage to the part of the brain called the hypothalamus. Among other functions this regulates food and water intake.

The scientist, a professor of nutrition at Harvard, said he would favor taking the substance out of baby food if there was the "slightest presumption of guilt," even though unproven. In answer to a question, he said bluntly: "I would take the damn stuff out of baby food."

During a telephone interview, Dr. Olney said he had tube-fed mice an amount of sodium glutamate about five times as great as that found in a 4½ ounce bottle of baby food and he found brain damage in seven of nine animals.

At higher dosages he got substantially higher percentages of brain damage.

CELLS ARE KILLED

Specifically, he said, cells were killed in the hypothalamus. If this kind or damage occurred in a human infant, he said, it might pass unnoticed, but later the individual might have obesity problems or impaired fertility.

Dr. Olney said he had been attracted to research in this area by the observation that infant animals injected with MSG often became obese later in life. Last spring he reported that injections of the substance under the skin of baby mice produced brain damage. Testimony on this point was presented to the Senate Select Committee on Nutrition and Human Needs.

A logical step was to see whether or not the same effect could be produced in a primate, because these animals are far closer to man, genetically, than are mice, Dr. Olney and a coworker, Lawrence G. Sharpe, published a report confirming that this can be done, in the current issue of Science, weekly journal of the American Association for the Advancement of Science.

Damage to nerve cells in the hypothalamus of an infant rhesus monkey were produced after an injection of a relatively heavy dose of MSG, the report said.

The details of the production of similar lesions by the feeding of infant animals has not yet been published although it has been submitted to a scientific journal. Dr. Olney said the research had already been reviewed by a pathologist of the Food and Drug Administration.

Today this was confirmed by the pathologist, Dr. Howard Richardson of the F.D.A. Bureau of Science. He said the evidence he was shown clearly showed brain damage.

Dr. Richardson said the fact that the effect was attributed to a single feeding of the substance was particularly interesting because it showed that "a single insult" to the infant animal body from the chemical could produce such a result.

Dr. Olney said the 10-day-old mice were tube fed because they had not yet been weaned. He said their development age is about that of a three-month-old human infant. The dose of MSG with which he produced nerve cell death in seven of nine of the baby animals was one-half gram per one kilogram of body weight. This is a small amount that he said is about five times the amount of monosodium glutamate to be expected in a 4½ ounce jar of some baby foods.

This afternoon Mr. Hutchings said he was familiar in general with Dr. Olney's research, but did not consider it at all applicable to man.

He said infants were not likely to get baby food that contained MSG before the age of five months because the substance is used primarily in vegetable and meat mixture. At that age, he said, the human brain is far more developed and thus, presumably is less likely to be harmed.

Furthermore, even at that age, he said, the amount of MSG a baby would eat would be extremely small in relation to the amounts the animals received.

Mr. Gerber also expressed doubt that the substance had any potential for harm to human beings.

"We want to find out the truth whether it is harmful or not," he said. "If we find that it is harmful we certainly will eliminate it. We don't feel, at the levels we are now using, that there is any indication that it is harmful."

Mr. Gerber said he thought industry in general would stop using the substance if there was any valid evidence that it is harmful.

[From Time Magazine, Oct. 24, 1969]

FOOD—CRISIS IN THE DIET MARKET

The ban on cyclamates, ordered by HEW Secretary Robert Finch last week, might hit millions of weight-watchers in the waistline, but it is a real body blow to the rich diet-food industry. In the 20 years since cyclamates were discovered, sales of products containing the nonnutritive sweeteners have risen to $1 billion annually. An estimated 21 million pounds of cyclamates will be consumed this year. The biggest manufacturer, Chicago's Abbott Laboratories, figures that cyclamates account for 4% of its sales, which were $351 million last year.

Worst hurt will be the processors of foods containing the sweetener. Most of the cyclamate supply now goes into diet drinks, which have gained at least a 15% share of the market for soft drinks. There is some question whether diet drinkers will switch back to sugar-sweetened drinks or just give it all up in favor of water. Cyclamates are also used in puddings, gelatins, salad dressings, jams and jellies, ice cream and practically all diet foods. The producers of "cured" bacon commonly use cyclamates, which are cheaper than sugar. Cyclamates even go into the making of children's flavored vitamins, pickles and dog food.

Diet drinks containing cyclamates must be removed from shelves by Jan. 1. The announcement took some producers unaware. Instead of trying to fight the ban, Coca-Cola officials say that they are experimenting with other "formulations" for the Tab and Fresca diet drinks, and will probably switch to some other low-calorie sweetener. Pepsi-Co. which was obviously not caught napping, immediately announced that it will begin marketing within a few weeks a cyclamate-free Diet Pepsi-Cola "with a touch of real sugar."

General Mills, General Foods and other major food processors that have extensive low-calorie lines will most likely change to some other sweetener. "The public will continue to look for other diet products rather than return to sugar products," says Marvin Eisenstadt, an official of Cumberland Packing Corp., producers of Sweet 'N Low, a sugar substitute made of saccharin and a cyclamate. It is unlikely, however, that dieters will switch to saccharin, since it often leaves a bitter taste. Obviously a big pot of sugar awaits the inventor who can formulate a new product that is safe, sweet and noncaloric.

[From the Washington Post, Oct. 25, 1969]

MANY "ACCEPTED" ADDITIVES MAY BE CYCLAMATE'S EQUAL

(By Joshua Lederberg)

HEW Secretary Robert H. Finch's order banning the use of cyclamate as an artificial sweetner puts a decisive period closure to a messy controversy of great potential importance to public health. My only criticism is that it was not done sooner, but this was difficult in the fact of ambiguities both in the legal authority of the Food and Drug Administration and in the scientific evidence that cyclamate is a hazard in man.

We may never know the answer to this question, for it is more likely that new compounds will be discovered as alternatives to cyclamate than that cyclamate could be exonerated by further studies (even if it is essentially innocent) once it had been indicted.

Finch's decision does not answer the scientific question, although the regulatory label of "safe" or "unsafe" is often confused with a factual reality that can never be so categorical. Nor does the cyclamate affair set a satisfying precedent for the way such issues should be dealt with in the future.

Our principal need, of course, is for the improvement of methods of scientific evaluation of safety. There is no particular rationale for banning an additive on the basis that it can be shown to induce tumors in some experimental animal at high doses when we know nothing of the way the additive works.

On the other hand, Dr. Marvin Legator of FDA's research laboratories had shown over a year ago that a derivative formed in the body from cyclamate, cyclohexylamine, caused chromosome breaks in rat germ cells when given in modest doses for short periods of time. This information was administratively ignored, perhaps because the language of the law is still innocent of any knowledge of genetic damage.

In fact, among the thousands of compounds "generally accepted as safe" or specifically licensed as food additives by the FDA, there are surely dozens which will prove to be at least as hazardous as cyclamate but have yet to reach the same kind of public attention.

Organic peroxides are proven mutagens—but are widely used for bleaching starch and maturing flour. Mustard oil is historically interesting as the first known chemical mutagen; it has, however, come to legislative attention as a cruel blistering agent for "soring" horses. Phenethyl alcohol is a synthetic perfume essence, but biochemists know it as a powerful inhibitor of DNA synthesis.

Many other additives are suspect simply on the grounds of their chemical reactivity, for they must then produce a wide and unpredictable variety of secondary products when used in foods. Many other compounds belong to classes that we do not yet recognize as having biological potency.

If the FDA indeed had to give adequate scientific assurance about the absolute safety of every additive, we might starve to death while the necessary research was being done, and then again when new insights into sources of peril emerged. Nevertheless, the food industry and the scientific community, as well as government, should be sharpening their focus in dealing with these vital problems.

Meanwhile, we must also think of more flexible legal and regulatory approaches to these problems. Abbott Laboratories should not be charged with insincerity for having asserted its confidence that cyclamates were safe, but the main risk was being borne by millions of consumers, not the corporation. On the other hand, a government agency might be in the position of having little to lose in responding to public arousal by banning a product before all the evidence was in.

The law could provide for unconditional liability for the eventual hazard of a product when the FDA has certified a bill of particulars, for example, about bladder cancer or mutation. And Abbott Laboratories would then have to back up its confidence by sharing the risk that it was mistaken with its customers.

It might also be required to post an insurance bond. This device would help to bring in the informed businessman's judgment of a third party: the insurance underwriter who must make wise decisions about the premium to charge.

In the long run, the cost of insurance is embedded in what the consumer has to pay. But this would indirectly pay for important research on hazards and for the development of safer alternatives, as well as encourage greater discretion by the purveyors of unproven products.

[From the Washington Post, Oct. 25, 1969]

Cyclamates Ban Sparks Crash Changeover at Royal Crown

(By Philip Greer)

Columbus, Ga., October 24.—Of all the bombshells that ripped through the food industry last Saturday when Secretary of Health, Education, and Welfare Robert H. Finch announced the ban on food products containing cyclamates, none exploded louder than at 1000 Tenth Ave. here—the home of Royal Crown Cola Co.

That's because cyclamate-sweetened products may be more important to Royal Crown than to any other food company. Royal Crown is the producer of the country's largest selling low-calorie soft drink, Diet Rite, with sales estimated at 100 million cases in 1968. Even more important, Diet Rite accounts for 23 per cent of Royal Crown's $80 million in sales.

"Before you ask, we were caught completely by surprise," says Royal Crown's outspoken president, William C. Durkee. "I received a phone call at 5:15 on Oct. 17 telling me that Secretary Finch was going to ban cyclamate."

Until that moment, Durkee says he had no idea that tests conducted by Food and Drug Research Laboratories, in Maspeth, N.Y., had revealed cyclamates caused cancer of the bladder in tests on rats.

At the same time Durkee was told about the ban, he was asked, along with officials of other food companies, to be at a meeting in Finch's office last Saturday afternoon.

After the meeting, at which Finch said he realized the problems created for the industry but explained that he had no choice under the law, Durkee returned to Columbus and Royal Crown immediately began producing a new Diet Rite, with a formula that includes natural sugar, saccharine and other artificial sweet-

eners from the Food and Drug Administration's GRAS list. GRAS stands for Generally Recognized As Safe.

The formula has been in development for about a year, but Durkee denies that it was due to any advance indication of problems with cyclamates. Rather, he says, it was developed in case publicity about cyclamates—which he blames on "the sugar interests"—generated a public furor.

"Cyclamates have been in general use for 20 years," he says. "There has never been any evidence of damage to human beings in 20 years, except for one case of photosensitivity in Japan."

The first step on returning to Columbus was to fire off a two-page telegram, the first of nine sent in 72 hours, to Royal Crown's 375 bottlers around the country. The telegrams reported on the meetings with Finch and laid out the steps in the switchover to the new Diet Rite.

The first step was to put the concentrate production on a two-shift schedule. Durkee won't say how much concentrate is turned out in one shift, but he says that the changeover depends more on getting new bottle caps and cartons than on having sufficient concentrate.

"There are 60 machines in the U.S. that can reface cartons with gummed-back labels," he says, "and we bought all of them over the weekend.

"Within 24 hours after I got back from Washington, I had approved new art-work for the cartons and new advertising. That same night, I made a tape for Mutual Broadcasting Co. which was sent to all our bottlers, explaining the situation. They all had it by Sunday night, ready for use Monday morning."

Monday morning, Royal Crown had 100 men stationed in supermarkets in various parts of the country. In some markets, Durke says, there was actually a run on the product. "Here in Columbus, the drugstores say they had a run on all kinds of artificial sweeteners because people said they were afraid they might not be able to buy them any more," he says.

Durkee says he has not received any sales figures from bottlers. In Columbus, he says, sales are running about 50 percent of normal, although the Diet Rite produced at the local plant is the new formula.

"My wife checked with three supermarket managers here on Monday," he says, "and they told her that sales were normal. But our trucks are coming back with about half the product," he says.

Durkee does not try to minimize the damage Royal Crown may suffer as a result of the publicity surrounding the ban. "Short term, it's going to have a substantial effect on our business, no doubt about that," he says. "Long term, it could be the same as the cranberries, which have never fully recovered."

Cranberries were banned for a time in 1959 because they contained small amounts of insecticide.

At the same time, he says, "Go down to southern Louisiana, where they didn't run headlines 'Diet Drinks Cause Cancer,' and it looks like nobody knows anything about it."

Durkee says he does not feel guilty about having used cyclamates in Diet Rite. No food additive has ever been subjected to as much testing, he claims. Nevertheless, he says he has wanted to add some sugar to the formula for the last four years, "but the government had some hangup about it." At the Saturday meeting, he says, Finch told the producers the government would permit mixing natural and artificial sweeteners.

As far as Royal Crown is concerned, Durkee says that he expects the company to recover from the blow. "The reason I'm not panicky," he says, "is that Royal Crown Cola has been showing considerable improvement, both in sales and in share of the market." In 1967, the firm collared 3.6 per cent of the total soft drink market, selling 125 million cases. In 1968, sales rose to 140 million cases, or 3.7 per cent of the market, according to Wall Street analyst John C. Maxwell Jr., and Soft Drink Industry, a trade publication. In all, artificially sweetened sodas account for about 15 per cent of all soft drink sales.

In addition, Durkee says, Royal Crown will soon introduce two new products. One is a carbonated version of Gatorade, a dextrose-sucrose combination developed by scientists at the University of Florida, originally for use by that school's football team. Noncarbonated Gatorade is made by Stokely-Van Camp, which holds the license on the product.

Gatorade has also used cylamates, but Durkee does not think the change to sugar will have any impact on sales. In fact, he says, "we expect Gatorade to be bigger next year than Diet Rite was at its peak."

Durkee declined to discuss the other new product, which will be introduced at a bottlers' convention. He said it had been planned for marketing in about six months, but it will not be brought out right away.

The ban on cyclamates is based on the so-called Delaney Amendment, passed in 1958 which prohibits the sale of any product found to cause cancer in humans or animals. Durkee is critical of the wording of the act.

"Under that law," he says "sunshine should be banned because you can get cancer from the sun. Certainly I'm not going to quarrel with a law that protects human beings, but why ban cyclamates and not cigarettes? Because there is a law about foods, but they've never been able to get one through on tobacco."

But Durkee says that the dosages of cyclamate given the rats that developed cancer "was equal to humans drinking 450 bottles of Diet Rite a day for the rest of their lives."

[From the Washington Post, Oct. 25, 1969]

BANNING CANCER-PRODUCING CHEMICALS—(EDITORIAL)

The country seems to have taken in stride the sudden abolition of cyclamates from its food supply. Commercial users of these artificial sweeteners as well as consumers promptly recognized that a potential menace to health had been identified. With remarkably little fuss and friction, cyclamates have been consigned to outer darkness even without any indication that they have caused cancer in man. The finding that they had produced cancer in rats, when taken in large doses over a long period, was enough.

The experience suggests a new sensitivity in commercial as well as official circles to potential hazards to health. If this attitude prevails, the elimination of cyclamates may be only the first of many steps to safeguard the public from chemicals that have previously escaped suspicion. Secretary Finch has ordered a review of other food additives heretofore deemed to be safe. And what about the vast number of substances known to be harmful to health which do not fall into the category of food additives? HEW's action in this case has opened a wide field of inquiry which may lead to new legislation as well as tighter administrative actions.

One immediate question is whether the Food and Drug Administration will act against DDT. This widely used insecticide has a long residual life and is known to produce cancer in mice and rats. Some scientists who have probed deeply into the hazards of DDT insist that the case for banning its use is much stronger than the case against the cyclamates.

The Environmental Defense Fund and California Rural Legal Assistance, representing five pregnant or nursing women, have petitioned the FDA to lower the tolerance limits on DDT residues in human food to zero. Their case is based on the provision in the Federal Food, Drug and Cosmetics Act which led to the undoing of the cyclamates. It says that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal." Since the cause of cancer is not yet known, Congress decided not to take chances with substances known to contribute to it.

Most of the present tolerance levels for DDT on raw argicultural commodities were established on the basis of hearings in 1950. The certain recognition of DDT as a carcinogenic agent is of more recent origin. Scientists now know, not only that DDT causes cancer in some animals, but also that it accumulates in body tissues after being ingested. In part the petition now before the FDA in regard to DDT rests on the finding that reservoirs of DDT accumulated over months or years will appear in a woman's milk after she has borne a child. So, it is said, a breast-fed baby may ingest three times the quantity of DDT considered safe by the World Health Organization and five to seven times as much as is tolerated in cow's milk sold on the market.

As in the case of the cyclamates, DDT is not known to have caused cancer in any human being. But a study at the University of Miami School of Medicine showed that human victims who died of cancer had twice as much DDT in their fat as did the victims of accidental death. If the FDA is ready to apply its sound rule against cancer-producing chemicals—that they are "guilty until proved innocent"—a ban on the use of DDT in its present form may well be in the making.

[From the Washington Post, Oct. 25, 1969]

TV Ads Are Quickly Purged of Cyclamates

New York, October 24.—The government ban of the artificial sweetener cyclamate last Saturday set off a flurry of activity along Madison Avenue that will be seen in advertising campaigns for months to come.

Some agencies turned out new television commercials and newspapers advertisements literally within hours.

"Cyclamates? Diet Pepsi can do better without them," newspaper readers were told Monday morning.

That night, millions watching "Mayberry R.F.D." on CBS were told that regular Kool-Aid was safe for children and that presweetened Kool-Aid "is being withdrawn from grocery shelves."

The commercial was repeated on NBC Tuesday night and on Wednesday Gray Advertising flew a crew to New Orleans to tape a second commercial with Danny Thomas. That commercial will be aired this weekend.

Kraft aired a live commercial over its "Music Hall" on NBC Wednesday night to report that its low-calorie salad dressings contained no cyclamates.

A commercial saying that Wink is "worry free" was taped today for use next week.

Normally, a television commercial takes at least six weeks to write and produce. Kraft usually plans its commercials three months in advance.

Dozens of other products containing cyclamates rushed out advertisements that the cyclamates had been removed. Sweet 'n Low, for instance, advertised today that "America's No. 1 sugar substitute now available without cyclamates."

Others without cyclamates, such as Wink and the Kraft dressings, wanted to reassure consumers that their products were safe.

The Kool-Aid commercial was made in less than a day, a record that probably will never be equaled—or attempted—again.

A group from Gray Advertising, led by the president, Ed Meyer, met with General Foods executives in White Plains, N.Y., at 9 a.m. Monday. By 9:30 they had all agreed to go on the air that night with a statement.

Jerry Baxter, account executive at J. Walter Thompson for Kraft low-calorie dressings heard news of the government ban on radio Saturday night in his home in Chicago. He called a Kraft executive in the morning and made arrangements to meet Monday.

The commercial was written and a copywriter was flown to New York to direct the production in NBC's studio 3K, which has a standing kitchen set for Kraft. The commercial was done live Wednesday night.

[From the Washington Evening Star, Oct. 25, 1969]

Firms Drop Baby Food Ingredient

(By the Associated Press)

Three companies say they will discontinue use of monosodium glutamate (MSG) in their baby foods although they believe the current public concern over whether is poses a threat to the health of infants is unwarranted.

Gerber Products Co., Beech Nut Inc. and H. J. Heinz Co. all announced yesterday they will stop using MSG at least temporarily.

Dan Gerber, chief executive of the nation's largest maker of baby food, insisted MSG "is a safe and wholesome ingredient in baby food" but his firm was stopping use of the additive "because a tremendous amount of unwarranted publicity has served to confuse the Consumer."

"Full Confidence" Cited

A spokesman for Beech Nut said the company will stop using MSG in all products "pending the outcome of the studies just initiated by the Food and Drug Administration."

The Heinz spokesman, voicing "full confidence that the industry use of MSG will be vindicated by more accurate and scientific findings than those now available," announced its decision to discontinue use of MSG "in deference to public concern."

Restrictions on use of MSG were urged yesterday by two senators.

Sen. George S. McGovern, D-S.D., said that until questions about the additive are resolved it "should be removed from baby food or the amounts in baby food drastically reduced."

Sen. Robert C. Byrd, D-W. Va., said the FDA should ban use of MSG in baby foods because experiments indicate the additive "may pose a threat to the health of millions of infants."

Byrd contended the additive has no nutritional value and apparently is added only "to titillate the taste buds of mothers."

Byrd, in a letter to FDA Commissioner Herbert L. Ley Jr., Byrd cited the rsearch of Dr. John Olney, of Washington University, St. Louis, suggesting MSG could cause brain damage to very young animals. There was no proof it could harm humans.

Just one week ago the government announced it would ban the artificial sweetener cyclamate because it had been found that large doses of the substance caused cancer in rats. Scientists said there was no proof, however, that it had caused any such damage to humans.

The cyclamate issue focused attention on more than 680 everyday food additives—including MSG—which are sold without any required tests for safety.

Attention was called to MSG during the summer when witnesses told a Senate committee it did not add to the nutritional value of baby food and was potentially dangerous.

And on Thursday, Dr. Jean Mayer, President Nixon's chief nutritional adviser, said MSG should be removed from baby food.

[From the New York Times, Oct. 25, 1969]

MAKERS OF BABY FOODS CURTAIL USE OF MONOSODIUM GLUTAMATE

(By Sandra Blakeslee)

The makers of Gerber, H. J. Heinz and Beechnut baby foods announced yesterday that they would no longer put monosodium glutamate, a popular food flavor enhancer, into their products pending further study of the chemical's safety.

The safety of monosodium glutamate was called to question Wednesday by Winton B. Raskin, deputy commissioner of the Food and Drug Administration. At that time Mr. Raskin announced the agency's intention to review at least four food additives, monosodium glutamate among them, that have been widely regarded as what are known as GRAS food additives—"Generally Recognized As Safe."

It may be that monosodium glutamate is not so safe after all, Mr. Raskin said. A St. Louis researcher has found that large doses of the substance fed to infant mice causes damage to that part of the rodents' brain that controls appetite.

In announcing their moratorium on the use of monosodium glutamate, the three largest producers of baby food in the United States were all critical of recent publicity about the substance. They said that the public had been unnecessarily alarmed and confused by the "unconfirmed body of evidence" against the chemical's use.

The Heinz Company, for example, said it planned to discontinue the use of monosodium glutamate in current packs "in full confidence that industry practice will be vindicated by scientific findings of a more valid order than those that have been used to promote the current controversy."

The study implicating monosodium glutamate and brain damage in mice was carried out by Dr. John W. Olney, an assistant professor of psychiatry at the Washington University School of Medicine.

A further criticism of the chemical was voiced yesterday by Senator George S. McGovern, who heads the Senate's Select Committee on Nutrition and Human Needs.

"MSG does not serve any nutritional purposes in baby food," the Senator said, "and there is no need to take any risk with a child's health until it has been proven safe."

It is generally recognized that monosodium glutamate is added to baby food to make it more palatable to the mother.

Senator McGovern also criticized the Food and Drug Administration for taking a "timid" approach to the question of the safety of food additives.

"Food additives are permitted for use without advance proof of safety and manufacturers are allowed to decide for themselves whether they have to prove products are safe before selling them," he said.

"What we really need," the Senator said, "is to change the name of the GRAS list to the PAS list instead—Proven as Safe."

680 INGREDIENTS ON LIST

There are currently 680 food ingredients, including monosodium glutamate, on the GRAS list. That is, they are considered safe enough by the F.D.A. to be used by food manufacturers in any desired amount. Other GRAS additives are salt, pepper, cinnamon, cloves and a wide range of spices and organic chemicals.

Another 2,000 food additives are liberally used in food production but must meet Government regulations and minimum standards after a long testing procedure.

Monosodium glutamate was put on the GRAS list nine years ago when the F.D.A. revised its system of reviewing food additives. Experts reviewing the list of GRAS additives at that time believed the chemical to be a harmless substance that had proved itself to be safe after thousands of years of use by cooks throughout the world.

No one knows when monosodium glutamate was first found to enliven the taste of foods—especially meat and vegetables—although the Chinese have cooked with it since antiquity.

FOUND IN SEAWEED

Then, in 1908, Dr. Kikunae Ikeda of Tokyo University recognized that a chemical he had isolated from a certain type of seaweed—monosodium glutamate—was the active agent that enhanced food flavors. The Japanese had been crushing the seaweed for centuries to obtain the flavor enhancer.

After Dr. Ikeda made his discovery, scientists began to look for ways to extract the substance from natural foods, generally found in those rich in carbohydrates, and purify it for later addition to foods.

A process of extraction was used for many years and then replaced by a fermentation process, which is how most of the monosodium glutamate is manufactured in the United States today.

American housewives and food manufacturers purchased approximately 43 million pounds of monosodium glutamate last year, which is only a small part of the total world consumption of 180 million pounds. The average American ate less than the two ounces of the chemical last year, which is one-fourth the amount consumed in a year by most Asians.

Monosodium glumate, which is a naturally occurring chemical substance that a chemist also calls a sodium salt of an amino acid—has baffled scientists trying to figure out precisely how it works to enhance food flavor. What they know is that when it is added to food, food tastes better.

According to many experts, it might be that the substance stimulates sections of the taste buds or that it stimulates saliva flow.

Although monosodium glutamate is tasteless in small amounts, it can have a slightly meaty flavor when eaten in larger doses. The flavor may result from impurities in processing but the scientists are not even sure of this. Perhaps the meaty flavor, some scientists have said, causes the substance to make food taste better.

Researchers know that monosodium glutamate works best to enhance the flavor of foods high in protein, and it is fairly useless in starchier foods. They guess that the chemical acts to replace glutamate, which is found in highest concentrations in high protein foods, when it is cooked or processed out of such foods.

[From the Chicago Sun-Times, Oct. 25, 1969]

THREE BABY-FOOD MAKERS HALT USE OF ADDITIVE—GERBER, BEECHNUT, HEINZ RESPOND TO DEMAND BY MCGOVERN ON MONOSODIUM GLUTAMATE

WASHINGTON, October 24.—Senator George S. McGovern (D., S.D.), chairman of the Senate Committee on Nutrition, today recommended an overhaul of government practices which permit sale of more than 680 every day food additives without requiring safety tests.

The special, government-exempt list of additives included cyclamates until last week, when this type of artificial sweetener was banned because of a high incidence of animal cancer found in laboratory experiments.

EXPECT VINDICATION

Gerber Products Company, the nation's largest maker of baby foods, said it is discontinuing the use of monosodium glutanate, "because a tremendous amount of unwarranted publicity has served to confuse the consumer."

Meanwhile, Beechnut, Inc., announced it had discontinued the use of monosodium glutamate in all products "pending the outcome of the studies just initiated by the Food and Drug Administration." A spokesman for the firm said only a minimal amount of the substance was included in a few of the company's baby foods.

The H. J. Heinz Company announced that "in deference to public concern" it would discontinue the use of MSG "in the limited number of its baby-food products" in which it was used. A company spokesman said the firm had "full confidence that the industry use of MSG will be vindicated by more accurate and scientific findings than those now available."

In making his recommendation, Senator McGovern termed the exempt list of additives "a never-never land of non-regulation."

"Food additives are permitted for use without advance proof of safety," he said in a prepared statement. "And manufacturers are allowed to decide for themselves whether products are safe before selling them."

ALL TYPES OF ADDITIVES

The long used additives on the list—ranging from the well-known monosodium glutamate to the little-known preservative butylated hydroxytoluene—enjoy congressional exemption from animal safety tests required for government approval of most new additives.

Representative Paul G. Rogers (D., Fla.), a ranking member of the House public health subcommittee, said today that a panel of the World Food and Drug Administration examination of the list is insufficient.

He called instead for an "immediate and systematic review in clinical testing of all chemicals" on the exempt list. And the Health Organization has reported "possible harmful effects" from two color additives now in the exempt list—benzyl violet and Ponceau SX or Red No. 4, used in maraschino cherries.

Benzyl violet is possibly linked with cancer, Mr. Rogers claimed.

SPICES NO DANGER

The safety of most additives on the list, some of them century-old cooking aids such as spices, never has been seriously challenged. But cyclamates were on the market 17 years before tests showed they increased the incidence of cancer in rats.

A high-ranking official of the Food and Drug Administration agreed with Senator McGovern's description of the exempt list.

"The list is indeed a land of non-regulation," the official said.

"It is bad first because it permits additives in foods without advance proof of safety, and second because it allows additivemakers to decide for themselves whether they must prove their products safe before they sell them."

Commissioner Herbert L. Ley, Jr. of the FDA followed up last week's cyclamate ban with a promise to examine the special additives list and conduct any laboratory tests that seem necessary.

The FDA will focus on MSG, the widely used taste-enhancer found in baby foods, among other places. MSG in high dosage has been found to cause brain damage in infant animals.

Earlier, Senator McGovern said that if the revelations about MSG are resolved, it "should be removed from baby food or the amounts in baby food drastically reduced."

Dr. Jean Mayer, President Nixon's chief nutrition adviser, had said yesterday that the "stuff should be removed" from baby food.

Dr. Ley, however, believes MSG still has a place in baby food: "Our present position is based on the lack of adequate data that would implicate MSG as being harmful to human infants when ingested in amounts currently in use."

Senator McGovern said the action against cyclamates "opened a Pandora's box in the food additive field."

PROVE ALL SAFE

"Now that the box is open it should not be closed until every food additive in it is proven safe beyond doubt for human consumption," he said.

"If the FDA needs more authority or resources to do that job, Congress should give either or both.

"In the last analysis, the FDA should apply the same test to food additives as to drugs. They should be proven safe before they are approved for public use."

The National Academy of Sciences estimates that 2,000 chemicals are employed as additives. They are generally intended to retard spoilage, add nutritives, enhance flavor and make foods look better.

[From the Chicago Sun-Times, Oct. 25, 1969]

McGOVERN SEEKS REVIEW OF 680 ADDITIVES

WASHINGTON.—Chairman George S. McGovern (D-S.D.) of the Senate Committee on Nutrition recommended Friday an overhaul of government practices that permit sale of more than 680 everyday food additives without requiring tests for safety.

The special, government exempt list of additives included cyclamates until last week when this type of artificial sweetener was banned for causing cancer in animals.

McGovern termed the exempt list "a never-never land of nonregulation."

"Food additives are permitted for use without advance proof of safety," he said in a statement. "And manufacturers are allowed to decide for themselves whether products are safe before selling them."

The long-used additives on the list—ranging from the well-known flavor enhancer monosodium glutamate (MSG) to the little-known preservative butylated hydroxytoluene—enjoy congressional exemption from animal safety tests required for government approval of most new additives.

Rep. Paul G. Rogers (D-Fla.), a ranking member of the House public health subcommittee, said Friday a mere Federal Drug Administration examination of the list is insufficient.

He called instead for an "immediate and systematic review in clinical testing of all chemicals" on the exempt list.

The safety of most additives on the list, some of then century-old cooking aids such as spices, never has been seriously challenged. But cyclamates were on the market for 17 years before tests showed they caused cancer in rats.

FDA Comr. Herbert L. Ley, Jr., followed up the cyclamate ban with a promise to examine the special additives list and conduct any laboratory tests that seem necessary.

One of the additives FDA will focus on is MSG, widely used in baby foods among other places. MSG in high dosage has been found to cause brain damage in infant animals.

McGovern said that until safety questions about MSG are resolved it "should be removed from baby food or the amounts in baby food drastically reduced."

Three companies said Friday they were removing MSG from their baby food products.

Gerber Products Co., the nation's largest maker of baby foods, said it was discontinuing MSG "because a tremendous amount of unwarranted publicity has served to confuse the consumer."

Beech Nut Inc. and H. J. Heinz Co. made similar announcements.

[From the Washington Post, Oct. 26, 1969]

MSG REPORT ALARMS ASIANS—WIDELY USED IN ORIENTAL COOKING

News that monosodium glutamate (MSG) is considered harmful in the United States and is being withdrawn from prepared baby foods is causing repercussions in Asia, where it figures prominently in Oriental cooking.

The basic ingredient of Ajinomoto, the all-purpose seasoning which no Asian housewife can do without, is MGS. Ajinomoto Co. president Kyoji Suzuki said yesterday in Tokyo that the average Japanese consumes two grams of MSG every day.

Suzuki added that he could not understand why "that amount of monosodium glutamate is bad for the human body." and an official in Japan's Welfare and Health Ministry declared that "there is no fear whatsoever as long as monosodium glutamate is used in a normal way."

But Suzuki said that he and other manufacturers of the flavor-enhancer would ask the ministry "to conduct a thorough study of the chemical agent."

Asian cuisine first ran into trouble in the United States when researchers concluded that MSG was responsible for the "Chinese restaurant syndrome," in which diners suffer nausea, faintness and chest pains shortly after enjoying Oriental cuisine. Other research indicated that MSG caused eye and brain damage in laboratory animals.

[From the Washington Post, Oct. 26, 1969]

SOME BUYERS IGNORING BAN ON CYCLAMATES

(By Don Battle)

NEW YORK.—"He said he was going to die someday anyhow, but he was going to lose weight first," related on Ohio supermarket salesman after a dieting customer stocked up with $13 worth of soda containing cyclamate.

The incident in a Cincinnati suburb, however, was not typical across the country. Supermarket cash registers have been getting a workout ringing up refunds for consumers returning foods and soda containing the artificial sweetner, found to produce cancer in rats.

The Department of Health, Education, and Welfare announced last weekend a ban of public sales of drinks containing cyclamate after Jan. 1 and on food and other products containing it after Feb. 1 under a 1958 law prohibiting the sale of foods that have been found to cause cancer in animals. Abbott Laboratories, the major producer of the artificial sweetener, first allerted the government to research findings that massive doses of cyclamate had caused cancer in rats.

"One lady brought back 30 bottles of cyclamate drink and asked what I was going to do with it," commented a Milwaukee store manager. "I said I'm going to put it back on my shelf and sell it. When you stop and think about it, if you've been drinking it for the last 20 years or so, what's another two bottles or six bottles going to hurt?"

But one Milwaukee waitress expressed a different viewpoint.

"I don't care if they haven't proved that it causes cancer in human beings," she said, "if it's not good enough for rats, it's not good enough for human beings."

A clerk in a Whittier, Calif. market said: "It seems that older people are the ones who are most concerned with this. They're the ones who come in and want to exchange what they bought last week for other drinks without cyclamate."

In a Grosse Pointe, Mich. market, manager Bob Eschrich said, "My diet-pop sales have stopped cold. Who's going to pay me for all those?"

A spokesman for Albany Public Market, operator of six stores in Albany, N.Y., said of foods with cyclamate: "They're still buying it, in small lots. You'd have to say that sales are pretty much off and the situation is pretty much up in the air. The customers are still confused."

A spokesman for the Este Dietetic Candy Co. in New Jersey said that right after the announcement there was a drop in sales, but now a hoarding trend appears to be developing. The spokesman attributed the move to speculation that requiring prescriptions to buy the candy would push up the price. Some customers also feel that they may not like the substitute product and want to stock up on the cyclamate candy, he said.

Persons requiring nonsugar diets for medical reasons, such as diabetes or obesity, still could, with a prescription, get products containing cyclamates. Some store operators attributed any runs on cyclamate foods to these persons stocking up now. Not all are doing this, however.

Mrs. Don Carey, an Oak Ridge, Tenn., woman whose husband is a diabetic, said she has stopped using cyclamate foods and has turned to saccharin, another noncaloric, artificial sweetener.

Most stores are waiting for suppliers to pick up stock containing cyclamate and either make refunds or substitute it with noncyclamate products.

Pepsi-Cola said Wednesday it expects to be out in the "next few days" with a new Diet Pepsi without cyclamate. In some areas, the consumer may be

able to get it already. The new product will use as sweeteners both natural sugar in small amounts and saccharin.

Cott said its reformulated soft drinks will be on store shelves in the next two or three weeks.

Royal Crown Cola, which said its Diet Rite Cola represented 25 per cent of its sales volume, announced Wednesday that bottlers should have its new Diet Rite Cola by the end of the week.

[From the New York Times, Oct. 26, 1969]

Food—Fresh Look at What Is and Is Not Safe To Eat

(By Harold M. Schmeek, Jr.)

Washington.—Several years ago, when regulations of the Food and Drug Administration were being tightened, some food industry officers complained that they might soon need special permission from the Government to put mustard on a frankfurter.

A multitude of new additives and other products of human use had been appearing on the market and a dilemma arose in 1958 when the F.D.A. was made responsible for the safety of food additives. There seemed, at one point, to be only two logical alternatives Either authorize all the items and combinations already in use under a grandfather clause, or treat everything as new and unauthorized until it could be proved safe. A grandfather clause—saying that anything already in general use should be permitted—was unacceptable to the F.D.A. for obvious reasons.

There were many things in common use that had never been safety tested at all. There was no assurance that they were all safe. But the obvious alternative was not very good either. If extended to its logical conclusion, it would mean that tests would have to be done on some ridiculously commonplace things—mustard when added to frankfurters, for example.

The outcome of the F.D.A. problem was a series of lists—called GRAS lists, for substances "generally recognized as safe" for their intended uses.

Winton B. Rankin, Deputy Commissioner of Food and Drugs, explained recently that the Government drew up one list; industry another and a large panel of experts culled through both and chose those items that were indeed to be rated safe. There have been flaws in this arrangement, however, and last week there were signs that the GRAS lists were beginning to wilt.

ABRUPT DECISION

It started with the abrupt decision, a little more than a week ago, to halt the general use of the artificial sweeteners called cyclamates. They had been on the food additive GRAS list, but Robert H. Finch, Secretary of Health, Education and Welfare, rescinded their sanctioned status after animal experiments were reported to show that heavy doses fed to rats daily throughout the animals' lifetimes did sometimes lead to bladder cancer.

Last week Dr. Herbert L. Ley., Jr., Commissioner of Food and Drugs ordered his experts to restudy everything on the GRAS lists—several hunderd items altogether—to see whether any of them needed further experiments to confirm their safety. The survey was to be done primarily by reviewing the published and unpublished information already on hand. In some cases there was little of this because the products had been in use long before anyone thought safety testing was worthwhile.

Saccharin appeared to be such a case. This artificial sugar substitute has been in widespread use for at least 50 years and it is generally regarded as safe for man. An F.D.A. spokesman said it will be given high priority in the current reevaluation. Three other items were also scheduled for priority attention. These are: The ubiquitous flavor enhancer called monosodium glutamate; modified starch, as used in baby food; and salt, also as used in baby food.

The safety of monosodium glutamate was under attack earlier this year. Senator George McGovern's Select Committee on Nutrition and Human Needs heard from a scientist in St. Louis who had produced brain damage in infant mice by injecting them with monosodium glutamate. Last week that scientist, Dr. John W. Olney, of Washington University Medical School, St. Louis, added two items to that original report.

He produced the same effect—death of brain cells of the hypothalamus—in an infant rhesus monkey showing that the effect could occur in a primate, a species far closer to man than is a mouse. Further, he said the same kind of damage was produced when, in this case, he fed infant mice monosodium glutamate, which is often present in baby food vegetable and meat mixtures. He said he thought the material ought to be taken out of baby food. On Friday, three baby food makers announced that they would no longer use the material pending further study.

Presumably, Dr. Ley's orders meant that the drug agency's experts were thinking anew about the safety of an incredibly diverse collection of food items, some of which are household words while others are hardly known except to experts. Included are anti-caking agents such as the aluminum calcium silicate used in table salt; sodium bicarbonate, and even nutmeg, licorice, sage, rosemary and thyme.

[From the Wall Street Journal, Oct. 27, 1969]

Monosodium Glutamate Removal Sparks Scientific Controversy on Food Testing

(By Jerry E. Bishop)

New York.—A scientific controversy suddenly broke out over the food-flavor-enhancing substance, monosodium glutamate, or MSG.

The three major producers of baby foods said over the weekend they will voluntarily stop using MSG in their products because of publicity about experiments by a St. Louis psychiatrist. In the experiments, mice injected with large doses of MSG were found to have brain damage.

However, in New York, the scientist who heads the same laboratories that did the research that led to the banning of the cyclamate artificial sweeteners defended MSG. Bernard L. Oser, biochemist and toxicologist who heads Food & Drug Research Laboratories in Maspeth, N.Y., said MSG is a substance the body produces naturally in the normal course of digesting almost any protein. The amounts added to food to replace that lost during processing is only a fraction of what the body produces naturally from foods, he said.

The St. Louis experiment, Mr. Oser charged, were "absurd" studies from which to draw conclusions about MSG's safety in foods. He accused the food processors, particularly the baby-food makers, of "panic" and causing a "great deal of unnecessary alarm" in eliminating MSG from foods.

The Food and Drug Administration has asked the National Academy of Sciences to take a look at MSG research.

USED FOR CENTURIES

MSG has been used as a commercial flavor-enhancer for decades and the Chinese are believed to have used it in the form of fermented soybeans for centuries. It was first identified as monosodium glutamate in 1908 in Japan. The Japanese produced and exported it to the U.S. for years under the brand name Ajinomoto.

An estimated 47 million pounds annually are used in the U.S., two-thirds of which is used in processed food. The largest producer is International Minerals & Chemicals Inc., Skokie, Ill. Other producers include Merck & Co., Commercial Solvents Corp. and Great Western Sugar. International Minerals sells a consumer brand of the substance under the name Accent.

Only a small fraction of production apparently goes into baby foods where it is used primarily in the meat-vegetable mixtures. Recently, International Minerals said that only 0.7% of its output is sold to baby-food makers.

The substance is derived from glutamic acid, one of the amino acids that are the building blocks of all proteins. Whenever a protein is digested it is broken down into its basic amino acids. Some of the glutamic acid is converted naturally into monosodium glutamate during digestion.

The substance is produced commercially by breaking down or hydrolizing proteins that are high in glutamic acid, notably soybeans, wheat or corn gluten, or protein wastes from sugarbeet processing.

The MSG controversy has been brewing for several months. The groundwork was laid last year by the "discovery" of the so-called Chinese Restaurant Syndrome. A physician of Chinese ancestry had asked readers of the New England Journal of Medicine if they, like he, had ever experienced a temporary flushing and headache following a meal in a Chinese restaurant. The medical journal received and published several replies from readers relating similar experiences.

RECEIVED WIDE PUBLICITY

The replies were picked up by news media and given wide publicity, which, in turn, helped trigger research on the syndrome. Some researchers traced the syndrome to excessive amounts of MSG in Chinese restaurant food. The flushing and headaches apparently are experienced by only a few people who eat MSG-laden food.

The current controversy centers over experiments by Dr. J. W. Olney, assistant professor of psychiatry at Washington University in St. Louis. In May, Dr. Olney published in the weekly journal, Science, a report that infant mice injected under the skin with large amounts of MSG developed brain damage. He raised questions then as to whether there was any risk to the fetus by a pregnant woman eating food containing MSG.

Dr. Olney's conclusion was challenged in a letter to Science, published early last month, by Mr. Oser, Frank R. Blood, a biochemist at Vanderbilt University and Philip L. White, secretary of the American Medical Association's Council on Foods and Nutrition. Mr. Oser, in addition to heading his own research concern, is a member of the National Academy of Science Committee on Food Protection.

The three claimed that Dr. Olney's "observations don't have any revelance to the question of the safety of MSG as a food-seasoning agent," largely because the MSG was injected under the skin of the mice.

The critical experiments, the three scientists said, would involve feeding MSG orally to the animals and this had been done using doses far in excess of what is normally used. They conceded such huge amounts fed orally might produce some effects that should be studied further "but in this respect, MSG is no different from common salt, sugar or vinegar."

Dr. Olney replied that his interest was in determining how much MSG had to be in the blood to cause brain damage and it didn't matter how the MSG got into the blood, by injection or orally. He said it was up to "anyone who advocates the use of MSG as a food additive" to prove whether his experiments had any relevance to humans.

Several days ago, Dr. Olney published a second report in which he found a newborn monkey developed brain damage after under-the-skin injections of MSG. The study received wide publicity at the weekend after Dr. Jean Mayer, a Harvard nutritionist, told newsmen during a press conference that he thought MSG should be removed from baby foods if there was any question at all about its safety.

Dr. Olney then told reporters he had conducted experiments but hadn't yet published them in which newborn mice had developed brain damage after being tube-fed MSG in amounts several times that found in a jar of baby food.

CONVINCED OF ITS SAFETY

The three baby-food makers, Gerber Products Co., H. J. Heinz Co. and Squibb-Beech Nut Inc., all said over the weekend that they were removing MSG from baby foods because of the publicity. The substance is used in only a few baby foods, notably the vegetable-meat mixtures. The companies said they were convinced of the safety of the product, however.

Mr. Oser, in an interview, charged that Dr. Olney's experiments of injecting the MSG involved a technique that was completely new and unproven as a method of testing food safety. The proven method, he said, is to administer the substance in the same way that it's taken normally—that is, oral feeding. "Women aren't injected with MSG under the skin and neither are infants," he said. "The route of administration is highly critical" in food testing as any substance can cause damage if given in a certain way, at a certain time and in certain amounts, he added.

The scientist said that officially MSG is in the same class as salt, vinegar and sugar in being recognized as safe, although all three substances can cause damage in animals if given in certain ways and amounts. The lethal effects of massive amounts of salt are well known, he added.

Mr. Oser argued that it's up to Dr. Olney to prove that his method of testing is relevant to MSG use in humans, rather than being up to others to disprove it.

As for the safety of MSG, Mr. Oser said that most people produce more MSG during normal digestion of proteins that they ever receive in processed foods.

Mr. Oser said he agreed that more research has to be done on Dr. Olney's findings and that oral feeding experiments on several species should be done with MSG.

The elimination of MSG from baby foods, he said, "suggests to the public that this is an imminent hazard—but it isn't."

Mr. Oser said his laboratory hasn't any contracts or monetary connections with MSG producers or with the baby food makers; that he was just angered by the "unwarranted" uproar over MSG.

The laboratory is a private concern that does research and consulting on food and drug safety for industry and government. Its experiments in which cyclamates caused bladder cancer in rats led to the banning of the sweeteners.

[From the Washington Evening Star, Oct. 27, 1969]

FOOD ADDITIVE MAKER REQUESTS NETWORK TIME

SKOKIE, ILL.—The nation's largest manufacturer of the food additive monosodium glutamate has asked for nationwide radio and television air time to defend the product.

The safety of the food additive has been questioned by federal officials including Winiston B. Raskin, deputy commissioner of the Food and Drug Administration, who took note of recent studies showing brain damage in infant mice which have been fed large doses of the additive.

The makers of Gerber, H. J. Heinz and Beechnut baby foods have announced they will no longer put it in their products pending further study.

In a telegram sent yesterday to the major radio and television networks Nelson C. White, president of International Minerals & Chemical Corp., said "no danger to the well-being of humans has ever been evident in its use as a food flavor enhancer." He said he based his request for air time on the fairness rulings of the Federal Communications Commission.

[From the Washington Post, Oct. 29, 1969]

EGEBERG RAPS FOOD ADDITIVE

BOSTON.—The nation's top medical officer says he is more concerned about the food additive monosodium glutamate than the recently banned cyclamate sweeteners.

"I would tell my daughter not to feed her infant child any baby food that has monosodium glutamate in it," said Dr. Roger O. Egeberg in an interview last night.

Dr. Egeberg, assistant secretary for health and scientific affairs in the Department of Health, Education, and Welfare, was in Boston to address a Harvard Medical School audience.

Dr. Egeberg said Dr. Jean Mayer of Harvard, President Nixon's nutrition adviser, had told him of seeing brain lesions in infant mice as a result of feeding monosodium glutamate to the mother. He said this evidence suggests pregnant women should be careful about foods containing the additive.

Dr. Egeberg suggested the public should not become too alarmed about foods containing cyclamates "as long as they ingest only small amounts."

"I'd even advise by daughter to stock up a bit on diet drinks—which will disappear from grocery shelves Jan. 1 by federal order—as long as she drank only a bottle or two a day."

He explained that the rat-cancer study which caused the government to ban cyclamates involved amounts equivalent to 300 bottles of cyclamate-sweetened soda pop daily.

[From the Washington Evening Star, Oct. 29, 1969]

MAYER SAYS BABY FOOD SHOULDN'T CONTAIN SALT

(By Marian Burros)

Dr. Jean Mayer, President Nixon's consultant on nutrition, says baby food companies should not use salt in baby foods.

Elaborating on comments he made last week before the Women's National Press Club when he suggested that neither salt or monosodium glutamate has a place in baby food. Dr. Mayer said yesterday, "It would be the statesmanlike thing for them to do before they are forced to take it (salt) out."

At the same time he suggested that companies start a campaign to explain to mothers that babies don't need salt in food. "What they (the food companies) are afraid of is if they do it and others don't, they will be at a disadvantage," Dr. Mayer said. "But I don't see any point in experimenting with our kids."

Dr. Lewis Dahl, chief of medical service at the Brookhaven National Laboratory, who has done studies on salt intake and hypertension, said in a telephone interview, that the high incidence of death from hypertensive diseases, 66,819 in 1966, is due to two things: "a child gets a salt appetite (from eating salted foods as an infant) which then must be satisfied the rest of his life".

"If there's a family history of hypertension, and he takes a lot of salt in his food, he may get it early in life," Dr. Dahl said.

HYPERTENSION SHOWS EARLIER

Hypertension is beginning to show up in the teens and the twenties now where it had once generally made its first appearance in the thirties and forties.

In the January 1969 edition of "Clinical Nutrition," Dr. Mayer wrote about "hypertension, salt intake and the infant."

He referred to a 1963 study done by Dahl among a large number of adults divided into three groups, according to low, average and high sodium intakes. "He found that over 10 percent of the group with high intakes had hypertension, compared with 7 percent of the average group and less than 1 percent in the low group."

NEW REPORT CITED

Dr. Mayer also mentioned Dahl's experimental work with rats. "In an experiment involving 30 diffierent varities of baby foods (all of which showed a sodium content greatly in excess of the unprocessed meats and vegetables from which they were made), Dahl . . . found that hypertension developed within four months in most rats (hereditarily) predisposed to hypertension that were fed these foods. Dahl also found that very young rats are more immediately sensitive to the effect of high-salt diets than are older animals."

Dr. Mayer does not see why infants should be exposed to intakes of sodium "that are proportionally higher than those of adults and enormously higher than those resulting from breast feeding." By contrast, there appears to be no risk whatsoever in low sodium intake, he said.

Dr. Dahl has completed a new study using rats, but since the report had not been published in a scientific journal he would not release the specific findings. He did say, however, that the new study, which was done over a period of eight months, twice as long as the original study, confirmed the findings "in spades."

When asked to comment on Mayer's statement on not using salt in baby food, Dahl said, "I couldn't agree more. This is what I have been suggesting for years."

Dr. Mayer suggested that mothers should be instructed "not to add any salt to eggs, cereals or other dishes they prepare for their infants."

He said a study had shown that "babies often eat more and certainly don't eat less if there's no salt in the food."

[From Time Business, Oct. 31, 1969]

FOOD—CYCLAMATES' SOUR AFTERTASTE

After the Government banned cyclamates, the diet-food industry last week began one of the fastest turnarounds in U.S. industrial history. Officers of firms in the $1 billion-a-year diet market hustled to cut their ties with cyclamates, to find an acceptable substitute, and to redirect marketing efforts to preserve demand for their heavily promoted brands. From now on, many of the diet drinks will be sweetened by a sugar-saccharin compound that may contain 30 calories in eight ounces, compared with only one or two calories in a cyclamate drink and 105 in a cola sweetened with straight sugar. The revised drinks will, of course, be labeled "new," and printing on the package will note prominently that they contain no cyclamates.

THE PRINTERS GOT UP AT MIDNIGHT

Terribly Intuitive. Coca-Cola officials, caught unprepared by the ban, worked round the clock, preparing advertising copy and arranging to start production of a saccharin-sweetened syrup for Fresca, which will contain only two calories in eight ounces. "This was a jumping joint," says Charles W. Adams, senior vice president. "We got a lot of printers up in the middle of the night." PepsiCo, which began marketing a new Diet Pepsi the day the ban was announced, attributed its switch to a burst of altruism. Big ads in newspapers noted solemnly: the "Pepsi-Cola Company cannot in good conscience offer its customers any products about which even the remotest doubt exists." The ad urged that "other soft-drink companies . . . follow Pepsi-Cola's lead in developing cyclamate-free beverages." Mary Wells Lawrence, the adwoman whose agency had just completed a new campaign for Royal Crown's Diet Rite when the ban was announced, claims that she had little trouble adjusting to a non-cyclamate new version being introduced this week. "Either we're terribly intuitive or somebody up there loves us, she said, "but the new campaign has nothing to do with dieting."

Most of the producers of diet canned fruits have just completed their autumn packing, and are likely to be stuck with huge unsold stocks. David E. Guerrant, president of Libby, McNeill & Libby, which has a low-calorie canned-fruit line, called the Government ban "unwarranted." He asked that the Feb. 1 deadline for withdrawing all items containing cyclamates be extended to Sept. 1. Meanwhile, the search for a palatable low-calorie formula goes on. Almost a dozen diet-food producers have approached Adolph's Food Products, which manufactures a sugar substitute composed mainly of glycine, an amino acid.

Actually, the concrete evidence of the cancer threat in cyclamates came out of a private study commissioned by Abbott Laboratories, the major manufacturer. To its credit, the company immediately brought the results to the Food and Drug Administration. The Delaney Amendment, signed in 1958, requires the FDA to brand as unsafe any additive that has been shown to induce cancer in humans or animals. Last week New York Congressman James J. Delaney, the bill's sponsor, warmly recalled the support he had received from Actress Gloria Swanson, now 70, who roused interest in the bill in a 1952 speech to congressional wives. "I was screaming at the wind until she came along," said Delaney.

Fresh Doubts. The furor over cyclamates in the U.S. prompted Britain, Sweden, Denmark, Germany and Finland to ban the sweetener last week. The furor also raised fresh doubts about other food additives that are now listed by the FDA as "Generally Recognized As Safe," or GRAS in bureaucratese. The agency is now taking another look at the list, especially at monosodium glutamate (MSG), which has been found to cause brain damage in infant mice. Last week major manufacturers of baby food said that they will stop adding MSG. As if the diet-conscious American had not enough to worry about, the FDA also announced that it was again assessing the safety of saccharin.

[From the Washington Post, Nov. 1, 1969]

CYCLAMATES AND THE PILL

(By Morton Mintz)

A few days after the government learned that the artificial sweeteners called cyclamates caused bladder cancer in rats, it ordered an immediate halt to production of soft drinks and foods containing the chemicals.

But the oral contraceptives cause a wide variety of tumors in five species of experimental animals, including rats—and yet remain on sale with the blessing of the Department of Health, Education and Welfare.

The question for today is, does this make any sense?

The short answer is that the situation makes little if any sense medically and scientifically, even if it makes legalistic sense under the anomalies of the food and drug laws.

In 1958, Congress enacted legislation, sponsored principally by Rep. James J. Delaney (D-N.Y.), requiring the government to stop production of any food treated with a chemical additive that causes cancer in laboratory animals.

The basic idea of the law, which was invoked last Saturday by Robert H. Finch, Secretary of HEW—when he told a press conference of his order on the cyclamates—is that no additive makes a contribution to a food product so important as to outweigh the possibility that it could cause cancer.

Now cyclamates are expected to be handled as drugs. The main result will be that they will be available not to everyone but to patients with diabetes and high blood pressure who buy them on the advice of a physician.

In acting against cyclamates, Finch invoked not only the law, but also the importance of following "a prudent course in all matters concerning public health." Is "a prudent course" being followed in the case of The Pill?

Dr. Herbert L. Ley Jr., commissioner of the Food and Drug Administration, told the news conference that the cyclamates, classified as drugs, will be "in an entirely comparable position" to The Pill.

The use of The Pill, he said, "is limited, the benefits are significant, and medical supervision is exercised." Let's take these points one at a time.

A few weeks ago, users of The Pill were estimated by the FDA's outside experts—The Advisory Committee on Obstetrics and Gynecology—to number 8.5 million in the United States and 10 million elsewhere. These figures excluded additional millions of women who have used The Pill but do so no longer. This is "limited" use?

Dr. Ley termed the benefits "significant." He didn't say for whom. He might, for example, get an argument from those women—or their survivors—who got a disabling or fatal blood clotting disease and who would not have taken The Pill had they been warned by their physicians or, for that matter, by the FDA, about these and numerous other hazards.

Many private patients and most clinic patients are not told about the hazards. In the preface to "The Doctors' Case Against The Pill," a new book by science writer Barbara Seaman, this cultivated ignorance is characterized as "a public scandal" by Dr. Hugh J. Davis, director of the Contraceptive Clinic of Johns Hopkins Hospital.

As to "medical supervision" of women on The Pill, that indeed has its uses. But it is irrelevant to the question whether The Pill does, or does not, cause cancer.

In a 200-page report last month, the FDA's Advisory Committee said there is much data suggesting indirectly that steroid hormones such as those used in The Pill, particularly estrogen, "may be carcinogenic"—cancer causing—in humans. The report went on to say:

Surely this conclusion is as troubling for a healthy woman on The Pill who could reliably use another form of contraception as the discovery of cancer in one organ of rats given artificial sweeteners for a healthy woman who could drink a beverage sweetened with sugar instead of one sweetened with a cyclamate.

And certainly the Advisory Committee was deeply troubled, because its very first recommendation to the FDA said that whether oral contraceptives induce cancer in women "is the major unsolved question . . . Funds to investigate this relation are urgently needed."

Most of the Advisory Committee's report is a catalogue of cause-effect relationships with The Pill that have been established, such as blood clotting, hair loss, skin blotching and liver disease, or those that have not been established or disproved but are suspected as possibilities. In this category are not only cancer but also the effects on the offspring of users and on every organ system of the body.

Yet at a press conference in which the report was released, Dr. Ley was able to announce it "favorable." That, of course, was a legal judgment.

When Finch met with reporters about the cyclamates, the subject of The Pill was raised, to the amazement of almost everyone, by Dr. Roger O. Egeberg. The Assistant Secretary of HEW for Health and Scientific Affairs, he was affectionately introduced by Finch as "the nation's top health officer, the world's most reasonable man," and the speaker who would "put things in perspective."

Dr. Egeberg's perspective proved to be one that would make many a scientist shudder. For one thing, he said that the synthetic sweeteners "have probably saved and prolonged a tremendous number of lives the last few years by helping people keep their weight down . . ."

There is no medical evidence that the cyclamates have saved lives. It turned out that there isn't even significant medical evidence that they help people keep their weight down. Dr. Egeberg finally conceded that his claim was based on nothing more than personal experience in losing 30 or 40 pounds after giving up cigarettes. In short, his claim was a testimonial.

Bringing his perspective to The Pill, Dr. Egeberg said that it has "drawbacks . . . But if you think of the number of young girls who are killed each year or were killed through aseptic abortion, you have something to balance there, too."

In a new book based on a workshop on The Pill sponsored by The National Institutes of Health, three professors of medicine—Drs. Hilton A. Salhanick of

Harvard, David M. Kipins of Washington University and Raymond L. Vande Wiele of Columbia—said that the oral contraceptives are "not natural substances . . . their effects cannot be equated with phases of the menstrual cycle, pregnancy or pseudopregnancy . . . We believe that semantic oversimplification which equates the pharmacological state induced by contraceptive steroids with biological states such as pregnancy should be abandoned."

More seriously misleading have been the pamphlets on The Pill prepared by the various makers and put by doctors in their waiting rooms—the point of sale. These booklets have touted The Pill in ways that at best understated the risks and at worst engaged in downright falsehood. One pamphlet, for example, claimed that the brand it was pushing had been "proven safe." No brand has been "proven safe."

As if all of this weren't serious enough, now we have Dr. Egeberg talking about "balance" and Commissioner Ley rating the Advisory Committee report "favorable."

What may be most useful is to require the manufacturer to include in every package received by the user a fair, factual summary of the risks—in plain English. Of course, the FDA and organized medicine will oppose such an idea. Their principal reason is that doctor knows best. But doctor was handing out The Pill like candy when he didn't know beans about its safety.

The opposition should not prevail. The risks are too great, not only to the users, but possibly, eminent scientists warn, to the offspring of users. Again, there hasn't been the testing to determine if there is, or is not, a genetic risk.

On Monday night, in Milwaukee, Sen. Gaylord Nelson (D-Wis.), Chairman of the Senate Monopoly Subcommittee, said he is considering holding hearings. "Women using The Pill are not being told of the possible side effects," he said.

Concerned as he is with "balance," Dr. Egeberg ought to be the first to cheer Nelson on.

[From the New Republic, Nov. 1, 1969]

CYCLAMATES AND CIGARETTES

The cyclamates business was peculiar to a society that can afford products without function. Advertising implied that diet drinks satisfy appetite, thus reduce weight, but no one proved it. Cyclamates may, however, as HEW Secretary Finch concluded when he ordered cyclamate products off the market, cause cancer; at least they do in lab rats when injected in doses approximating 50 times normal human consumption. It seemed tenuous grounds for an action of such apparent sweeping economic and psychic consequenes. Cylamates have been on the market for 19 years.

Whether Secretary Finch was doing a favor for the sugar lobby or the saccharine faction, or slapping the hand of the Food and Drug Commissioner who serves under him and had been rather equivocal about the hazards of artificial sweeteners, or what, we don't know. The stated reason was a provision in the amended Food, Drug and Cosmetic Act which prohibits use of food additives that cause cancer in animals. The action also, of course, made FDA vulnerable to the suspicion that other of the proliferating food additives on its "Generally Recognized as Safe" list might also be suspect. The FDA is looking into that.

The affected cyclamates industry has shown its resilience. Companies that make cyclamates have other things to do; they won't go out of business. The inventor (who also worked on mustard gas and DDT) signed over rights to his find to duPont years ago. By discontinuing the use of cyclamates, the food industry now has something else to promote, "cyclamate-free" products—principally dynamic combinations of saccharine and sugar—which will keep the frivolous business going. Diet Pepsi, readers learned from two full-page *New York Times* ads last week, will in future taste more like Pepsi than before.

The cyclamates decision is most notable for what it reveals about the arbitrariness of bureaucracy. Cigarettes, in contrast to cyclamates, are *known* carcinogens, in man *as well as* animals. Yet the Agriculture Department, as a matter of policy, subsidizes the advertising of US tobacco abroad. Congress can't enact a suitable packaging and advertising warning. The networks had to be ordered to broadcast antismoking messages. No one in Congress or HEW has the guts to suggest cigarettes be banned.

[From Newsweek, Nov. 3, 1969]

THE SWEETENERS TAKE THEIR LUMPS

Up to last week, if the average American had been asked what a cyclamate was he might have guessed it was one of a pair of tandem bike riders. Then suddenly, overnight, the name of the artificial sweetener, a salt of cyclamic acid used in most low-calorie soft drinks and a variety of dietetic foods, had burst into nationwide unpopularity. Full-page newspaper ads screamed disavowal:

"Cyclamates? Diet Pepsi Can Do Better Without Them."

"Goodbye cyclamates! Hello Yoo-Hoo" (chocolate drink).

"Trident Sugarless Gum Does Not Contain Cyclamates."

In supermarkets across the country, housewives were passing up their once favorite diet drinks and foods, or returning for refunds those they had already bought. "We're going crazy giving money back," said a Pittsburgh supermarket manager. The big soft-drink companies were readying cyclamate-free substitutes to be rushed to store shelves as soon as possible. On the New York Stock Exchange, as the week opened, frantic selling of shares in a dozen affected companies sent their prices tumbling, while speculative buying in sugar stocks produced sharp gains.

OVERSEAS

Not only in the U.S. was the anti-cyclamate outcry swelling. The Canadian Government announced early in the week that cyclamates would be banned in soft drinks after Nov. 30 and phased out of diet food products in the next ten months. Two days later, the British Government announced that food and drinks containing cyclamates could no longer be sold after Jan. 1. Similar action was taken by Sweden and was expected in other Scandinavian countries.

All this commotion, at home and abroad, in local stores and in company board rooms, had been created by Secretary of Health, Education and Welfare Robert Finch's abrupt announcement the previous weekend that he had ordered cyclamates "removed from the list of substances generally recognized as safe for use in foods." Production of foods and beverages containing cyclamates—which currently account for about $1 billion a year and are used by an estimated 70 to 75 percent of the U.S. population—must be discontinued at once, Finch said, and products now on the market must be gradually recalled—beverages by next Jan. 1, foods by Feb. 1.

Finch's action came as a blow, even if not entirely unexpected, to a substantial segment of the food and drink industry. But it was taken on legal grounds that left no room for controversy. Laboratory experiments on rats, he pointed out, had disclosed malignant bladder tumors in those fed with heavy doses of cyclamates through their life spans. The fact that the rats had been given some 50 times as much cyclamates as any human being was likely to absorb was, legally speaking, beside the point. The so-called Delaney Amendment[1] to the Food, Drug and Cosmetic Act requires removal from the market of any food additive shown to cause cancer when fed to humans or animals.

In the circumstances, the affected industries had little choice but to swallow the government's bitter pill without a fuss. "It's been beautiful," said an official of the Food and Drug Administration. We haven't had as much as a whimper from either the soft-drink or food industries. It's been the best cooperation I've ever seen." As president Fred Dickson of Atlanta-based Coca-Cola, U.S.A., put it: "When you have a product with a degree of doubt cast on it, you want to withdraw it and find an alternate." At the same time, Dickson noted that an adult would have to drink 550 Frescas a day to get as much cyclamate as the rats had received. "You'd drown," he said wryly, "before you'd get cancer." Many other industry leaders privately felt the same way, but all they could do for now was take their unsweetened lumps.

SUFFERER

Probably the hardest hit of any individual company was Chicago's Abbott Laboratories, the world's biggest producer of cyclamates with better than 50 per cent of the U.S. market. (The other two major producers are Chas. Pfizer & Co. of

[1] Looking back on his fight to get his amendment passed in 1958 twelve-term Democratic Rep. James J. Delaney of New York recalled last week that he had been given a major assist by actress Gloria Swanson, a dietary faddist, when she addressed a group of Congressional wives in support of his bill.

New York and Miles Laboratories of Elkhart, Ind.) A spokesman for Abbott—which promptly halted cyclamate production—estimated that the firm would lose about $16 million in sales, or about 4 per cent of its total sales of chemical products as forecast for 1969. The earnings loss, he said, would be less than 3 per cent. Ironically, it was Abbott itself that had sponsored the experiments on rats that led to Finch's decision. It was noteworthy, too, that Abbott submitted its report to HEW a few days after one of its executives, Joseph C. Lowey, had warned a food-and-beverage seminar that the American sugar industry "has subsidized a large number of studies for the sole purpose of finding things wrong with cyclamate." Evidently, Abbott's discovery of cyclamate's tenuous link to cancer in rats had brought such quick and drastic action against cyclamates, the government had not taken more stringent action against cigarettes, which HEW itself had blamed for lung cancer in humans. Finch's answer was simply that the law gave him no jurisdiction over cigarettes, but at least one FDA official took a more skeptical view. "I understand the law," he said, "but not the logic. I think the government could do a lot more about cigarettes if it really wanted to."

"The fact remained that more people appeared to have been roused by the possible perils of cyclamates than by those of cigarettes. Indeed, not since the great and short-lived cranberry scare of 1959 had such a food fuss been stirred up, even if no real danger to humans had been proved. As a waitress quoted by The Milwaukee Journal put it: "If it's not good enough for rats, it's not good enough for humans."

[From the National Observer, Nov. 3, 1969]

How United States Keeps Tabs on Food Additives

The safety of processed foods and beverages has been called to question by recent Federal moves against commonly used food additives. The Government banned use of cyclamates after cancer was discovered in mice that had been fed large doses of the artificial sweetener. Then the Government ordered further testing of several other food additives, including the flavor-enhancer monosodium glutamate (MSG). Some laboratory animals injected with large doses of this chemical developed brain damage.

Both cyclamate and MSG were on the Food and Drug Administration's (FDA) list of approved ingredients, which it describes as "generally recognized as safe"—the so-called GRAS list. The list includes some 680 other substances that are widely used as additives in canned and frozen vegetables, fruits, meats, soups, and drinks. Government sanction of these ingredients, which include common spices as well as chemical agents, is usually based on an additive's common use in food before enactment of Federal testing standards 11 years ago.

When Congress in 1958 passed the Food Additive Amendment to the Federal Food, Drug, and Cosmetic Act of 1938, it extended Government premarket clearance of new drugs to new food additives. What's more, it prohibited the use of any food additive if when fed to humans or animals, even in exaggerated quantities, the substance induced cancer.

The 1958 amendment defines a food additive as any substance that becomes a part of food or affects its characteristics. The law, however, recognizes the probable safety of many additives already on the market because of their long history of use with no recognized ill effects. Thus the substances on the GRAS list, cyclamate and MSG among them, were not automatically submitted to Government-controlled testing. But they are constantly reviewed by the FDA and private laboratories, and often new scientific knowledge requires changes in the regulations governing the use of a particular additive or its removal, as happened with cyclamate.

The same re-evaluation is made of the hundreds of other food additives not on the GRAS list but which are widely used in foods and beverages. These are subject to close regulation by the FDA and the Department of Agriculture. Since 1958 every food additive must pass premarket testing for usefulness, effectiveness, and safety. Then the FDA establishes the dosage safe for use in a particular food or drink; meat additives are exempt from FDA standards only to the extent that they are regulated by the Agriculture Department. In seeking approval of an additive, the food processor or meat packer is supposed to show that the additive is safe for its intended use.

Federal regulations always try to provide a safety margin. For example, one of the most common additives used in cured meat products, sodium nitrate is

derived from a major ingredient of gunpowder. As little as 0.6 gram of this substance, if ingested at one time, has been fatal to humans. Thus, Federal food additive regulations restrict sodium nitrate content to about 0.09 gram per pound of meat product, or 220 parts per million.

Once the formula for an additive is approved as safe, the manufacturer is free to process and market the product with its contents accurately labeled. The FDA does not inspect every package, can, or bottle. Rather, the food inspectors spot check the factory, shipments, and retail counters to determine whether the contents comply with the approved standards. If not, the FDA can halt production and recall the product.

[From the National Observer, Nov. 3, 1969]

THE CASE OF MSG—ADDING TASTE—AND MAYBE TROUBLE—TO FOOD

(By James G. Driscoll)

Dissolve monosodium glutamate in hot water, and the water tastes like won ton soup. Sprinkle monosodium glutamate (MSG) over ordinary meats and vegetables, and they may taste like gourmet foods. But feed MSG to a baby mouse, and the animal's brain may be damaged severely.

The flavor-enhancing properties of MSG have been known for decades, and it is used widely in foods by housewives, restaurant cooks, and food processors. Only in the past few months, however, has the substance been found to cause brain damage in mice, the result of experiments by Dr. J. W. Olney, an assistant professor of psychiatry at Washington University in St. Louis.

His work has set off sharp debate among scientists, compelled baby-food manufacturers to remove MSG from their products and caused the Government to ask the National Academy of Sciences to study the suitability of MSG as a component of baby foods. The consumer has been left in a gray area, unsure whether MSG is safe to use, although current concern is focused largely on its use in infant foods.

Monosodium glutamate is the sodium salt of glutamatic acid, one of the amino acids that are the basic constituents of proteins. Adults in the United States normally ingest 15 to 20 grams of glutamic acid daily without adding MSG to their regular protein diet of meats, vegetables, and grains. The highest natural levels of glutamic acid are found in onions, sugar beets, wheat gluten, and mushrooms.

WHY ONION SOUP IS POPULAR

"The reason onion soup as an appetizer has gained such an acceptance and popularity is because the high glutamate level increases the mouth's feel and sensitivity to flavor and the enjoyment of food," says R. Steven Mason, a vice president of International Minerals & Chemical Corp.

One important scientific question now debated is whether MSG in its "free" form—separated from glutamic acid and sprinkled directly on food—is absorbed so quickly into the blood that it may cause brain damage, especially in infants whose bodies have not matured enough to metabolize it quickly. Mr. Mason's company, the largest American producer of monosodium glutamate, contends that its 27 years of research has shown no untoward results from human or animal consumption of MSG. Dr. Olney, however, suggests caution in using MSG, especially for infants and pregnant women.

Under a grant from the National Institute of Mental Health, Dr. Olney, 38, has been investigating possible hidden causes of brain damage in infants. He knew that MSG had been shown 12 years ago to damage the retinas of infant mice, and he decided to follow up those studies. He injected MSG under the skin of Swiss albino mice from 2 to 9 days old. "In a few hours, there was quite conspicuous brain damage," he says. "There was irreversible death of brain cells."

Dr. Olney repeated his experiment several times over a year, then submitted his report to Science magazine. It was published on May 9, 1969, setting off a spirited controversy.

Some scientists attacked Dr. Olney for injecting MSG instead of feeding it to the mice, and for using high dosages of the substance. In a letter to Science, three scientists asserted that Dr. Olney's "observations do not have any relevance to the question of MSG as a food-seasoning agent."

AN OPPOSING VIEW

The three, Frank R. Blood of Vanderbilt University, Philip L. White of the American Medical Association, and Bernard L. Oser of the privately operated Food and Drug Research Laboratories, added that MSG "has been the subject of extensive studies (other than Dr. Olney's) at oral doses far in excess of normal usage. This is not to say that excessive amounts might not produce disturbing responses worthy perhaps of further study, but in this respect, MSG is no different from common salt, sugar, or vinegar."

Dr. Oser said the studies referred to in the letter were done by other laboratories, principally on animals. There was no evidence of any brain damage in the animals, he said.

Dr. Olney has since fed MSG orally to infant mice through a tiny plastic tube and has found that they too suffered brain damage, whether their stomachs were empty or contained milk. The doses, he said, were "not far removed" from being equivalent to the amount of MSG contained in some baby foods. His report on these later experiments has not yet been published.

Baby-food manufacturers have been assailed by some critics, including consumer advocate Ralph Nader, for allegedly putting MSG in baby foods so it would taste good to the mother when she tasted to see if it was all right for the baby.

R. Burt Gookin, president of the H. J. Heinz Co., talked of the reason for using MSG in baby foods in testimony before the Senate Committee on Nutrition and Human Needs in July. "Mothers were suspicious of food that didn't taste good," Mr. Gookin contended. "They didn't know whether it was meant to taste that way or whether there was something wrong with it. . . . Babies were influenced by the mother's attitude toward the food during feeding."

THE PRACTICE BEGAN 20 YEARS AGO

About 20 years ago the manufacturers of baby food began putting MSG in their meat and vegetable products. Of Heinz's 130 varieties of baby food, 33 contain MSG. Of the 76 varieties made by Gerber Products Co., 17 have MSG. The third major manufacturer, Squibb-Beech Nut Inc., has a similar proportion of baby foods that contain the substance. The three companies have announced they will no longer put MSG in their baby-food products, but defended the substance as "generally safe and wholesome." MSG is one of 680 food additives listed by the Food and Drug Administration as Generally Regarded As Safe. The companies do not plan to call back MSG products already in stores.

Monosodium glutamate also has been blamed for the "Chinese restaurant syndrome," a feeling of chest pains, pressure under the eyes, and a burning sensation at the back of the neck that afflicts some persons a few minutes after they have eaten in a Chinese restaurant.

Existence of the syndrome was confirmed in tests conducted by Dr. Herbert Schaumberg and Dr. Robert Byck of the Albert Einstein College of Medicine in New York City. In testimony before the Senate Committee, Dr. Schaumberg said that because glutamic acid is naturally present in some foods, its derivative, MSG, has been largely unregulated. "One might assume from its [MSG's] practically ubiquitous presence in prepared foods that it has been thoroughly tested and found harmless," Dr. Schaumberg testified. "This is not so."

Pointing out that MSG "is not a nutritional necessity," Drs. Schaumberg and Byck suggested that it be eliminated from baby food, removed from the Government's list of safe food additives, and that safe levels be established for the intake of MSG during pregnancy. They acknowledged that MSG has been important in enhancing the flavor of prepared foods, and that "it may be very important in developing palatable but inexpensive foods for the world's population." In their research, they found that the least expensive Chinese restaurants used the most MSG. In one, they found six, 100-pound drums of MSG in the kitchen.

"The most enlightening experience I had with MSG," says Dr. Byck, "was that when dissolved in water it had the ineffable taste of won ton soup."

Orientals have flavored their foods for centuries with seaweed and soybean products that are rich in glutanic acid. In 1908, MSG was first isolated as a separate salt in Japan, and the world's largest manufacturer today is the Japanese concern, Ajinomoto Co. The average Japanese consumes about 22 ounces of MSG a year, while in the United States, the average is 4 ounces. International Minerals

& Chemical of Skokie, Ill., produces 30,000,000 pounds of MSG a year, with two-thirds going to food processors, and the rest split between housewives and institutions such as restaurants, hotels, and schools.

"A GIRL'S BEST FRIEND"

MSG is used in many canned, packaged, and frozen foods: soups, meats, pickles, vegetables. It also can be bought directly off the supermarket shelf as a flavor intensifier under numerous brand names. The best known of these is Ac'cent, marketed by International Minerals & Chemical. The company had ambitious plans for Ac'cent this year, built around an advertising theme of "Ac'cent Is a Girl's Best Friend." That friendship, to the extent it existed, has been stretched to the breaking point by the recent research and its attendant publicity.

The Government has taken no official action on MSG, but the nations top medical official did indicate that he is quite concerned about it. Dr. Roger O. Egeberg, assistant Secretary for health and scientific affairs in the Department of Health, Education, and Welfare, said last week that he "would tell my daughter not to feed her infant child any baby food that has monosodium glutamate in it."

[From the Washington Post, Nov. 6, 1969]

FINCH FAVORS SOFTENING OF FOOD ADDITIVE LAW

Secretary of Health, Education and Welfare Robert H. Finch said last night he wants a softening of the law that forced a ban on the artificial sweetener cyclamate in foods and drinks.

The Delaney provision of the 1958 Food and Drug Amendments calls for market removal of any food additive shown to cause cancer in animals or man—no matter at what level dosage.

Finch said in an interview on the National Educational Television network that the government should be given flexibility to set maximum or tolerance levels for cancer-causing additives. He pointed to cyclamates, which produced bladder cancer in rats at intake levels of 50 times higher than recommended for man.

"The important thing is the public ought to know there's a danger there," Finch said. "But who's to say that using Fresca or some other diet drink, Diet Cola, isn't better for you than the problems of overweight or diabetes?"

In the meantime, two suits were filed against Finch and HEW over the cyclamate ban.

In Cincinnati the Nehi Beverage Co. filed a suit in the U.S. Sixth Circuit Court of Appeals asking for a temporary order to stop the government from banning the sugar substitute from diet drinks. The company said it wanted to prove that cyclamate was not harmful.

In San Francisco, seven persons, claiming they were acting for diabetics and the obese, asked a three-judge federal court to halt the Finch order.

[From the Washington Post, Nov. 8, 1969]

PENTAGON TO USE UP STOCK OF CYCLAMATES

The Defense Department, caught with a three-month supply of cyclamates, said yesterday that it would use up its stocks of the recently banned artificial sweetener through "normal requisition and issue procedures" unless it finds "reduced troop acceptability."

Most commissaries and post exchanges have cyclamate products among their stocks, the Pentagon said, but only the Marine Corps and Navy have products for troop issue that contain the sweetener.

These are 14 varieties of artificially sweetened beverage bases, the Pentagon said, which "may be used as supplements to field, operational or combat rations until Department of Defense stocks are exhausted."

The Defense Department said it "fully supports" the Department of Health, Education and Welfare, but it ordered the military services to take no "special measures with respect to the disposition of existing stocks of food and beverages containing cyclamate" until the department could survey the situation.

"In view of the limited Department of Defense stock of items containing cyclamates and the lack of evidence of harmful effects on humans at the levels used in the military personnel feeding program," the Pentagon said yesterday, "normal requisition and issue procedures will be followed until stocks on hand have been depleted.

"If these items cannot be used within a reasonable period of time due to a possible reduced troop acceptability as a result of the publicity given this subject, this office should be notified for further disposition instructions."

[From the Washington Post, Nov. 8, 1969]

AMA URGES CHANGING FOOD-BAN PROCEDURE

CHICAGO, Nov. 7, (UPI)—The American Medical Association (AMA) reiterated today its demand that Congress repeal or revise a clause to the 1958 food additives amendment that brought about the recent banning of the artificial sweetener cyclamate.

The demand, first made by the AMA's council on foods and nutrition in 1961, cited the mandatory withdrawal of cyclamates from the market despite "great inconvenience and potential harm to persons with diabetes."

"The public should understand that the Food and Drug Administration had no opportunity to weigh arguments for and against withdrawing cyclamate once it had been established that test animals had developed carcinoma (cancer) of the bladder," a council statement said.

Inconvenience and potential harm to persons with diabetes could not be considered," the statement added.

[From the Washington Post, Nov. 8, 1969]

MSG REVELATIONS MAKE ONE WONDER ABOUT OTHER FOODS

(By Joshua Lederberg)

Monosodium glutamate (MSG) is about the last substance that any student of biochemistry would have expected to see under attack as a food additive. It is the sodium salt of glutamic acid, among the commonest of the amino acids, making up, for example, over a fifth of the composition of milk protein.

However, it is not an essential part of the human diet, but only because it is synthesized in large amounts within the body. Besides its role in the structure of proteins, glutamic acid is an important intermediate in metabolism, involved in basic reactions by which nitrogenous compounds are cycled.

More recently, glutamic acid has been found to have a special role in the energy supply to the brain, where it is unusually abundant. Speculations based on this finding led to fruitless trials some years ago in which extra glutamic acid was fed to children of low or borderline intelligence without effect.

For several decades, MSG has served as a flavor enhancer for hamburger and the like. It then crept into baby foods, apparently more for the benefit of the mother than the infant. The first reports that MSG might need some second thoughts came out as the near-joke of the "Chinese Restaurant Syndrome," a subjectively unpleasant reaction experienced by some people to rather large doses, like five grams of MSG in won-ton soup.

Why other people (like the writer) do not react to moderate doses is unknown. That the action was unnoticed for so long should make us wonder how many similar responses to common dietary substances remain to be discovered.

Last May, Dr. John W. Olney of the Department of Psychiatry, of Washington University Medical School, St. Louis, reported that new-born mice suffered specific brain damage from injection with a very large dose of MSG, equivalent to 35 grams in the adult. Subsequently, rats, rabbits and one monkey were reported to show similar responses, mainly in the hypothalamus—a part of the brain concerned with the regulation of hormones, temperature and body weight.

Dr. Olney quite properly suggested that his findings invited a reconsideration of the use of MSG, particularly in baby foods. However, so long as only modest amounts of MSG are used, small in relation to the volume of glutamic acid normally furnished by the rest of the diet, it is hard to see any basis for concern.

On the other hand, MSG is entirely dispensable in infant diets—and together with salt and sucrose, it may be suspected of setting up invidious tastes that at best do the young child no great good.

The fuss about MSG as a food additive may be obscuring the deeper interest of Dr. Olney's finding. It is startling that a natural amino acid, even if only at high levels, can cause serious disease in a specific part of the brain—and it will be very surprising if this does not have important implications both for further research and in understanding some kinds of brain damage that may be related to "normal" glutamic acid metabolism without our knowing it. The toxicity of MSG reminds one of the effect of another amino acid, phenylalanine, that can only be observed in the rare genetic disease PKU, which can often be treated by careful dietary control.

We know very little about the blood levels of glutamic acid that may obtain in the fetus or in some infants under various conditions. We also have to look into the chance that other brain structures may be sensitive to MSG overdosage at other stages of development.

MSG toxicity may also be related to an imbalance of its concentration compared to that of other amino acids, or to its conversion to GABA (gama-aminobutyric acid), an important transmitted substance in the brain. Until we have answers to these questions, we should neither shrug off the possibility that Dr. Olney his discovered another important diet-related disease nor be content with driving MSG out of baby foods as our only response to the challenges he has raised.

[From the New York Times, Nov. 9, 1969]

Food Safety a Worry in Era of Additives

(By Sandra Blakeslee)

When a housewife strolls into a supermarket today she is confronted with a cornucopia of things she can shake 'n' bake, brown 'n' serve, whip 'n' chill or heat 'n' eat.

But now more and more shoppers are beginning to eye the labels on products with suspicion, trying to find out whether the foods they shake, brown, heat and whip are really safe to eat

The Food and Drug Administration recently banned cyclamates, the artificial sweetener used in many diet products, after evidence of cancer was found in a few laboratory rats fed massive doses of the chemical.

And now it is examining monosodium glutamate, a popular food flavor enhancer sold under the brand name "Accent," and many other chemicals long considered safe for use in foods.

The Federal agency's action has stirred up a sweeping controversy involving the American consumer, chemical and food manufacturers, medical experts and others over whether additives are safe and adequately tested.

A White House conference on food and nutrition will address itself to the problem, as well as hunger and malnutrition in America, early next month.

The controversy is of increasing importance to American consumers because their use of additives has been rising sharply in recent years—to perhaps three of the 1,400 pounds of substances the average American eats in a year.

This reflects a rising public demand for processed foods (such as frozen, canned or freeze-dried products) for special dietary and low-calorie foods, for snack foods, and particularly for so-called convenience foods (products such as TV dinners that can be prepared with a minimum of effort). All contain additives.

What exactly are food additives? What do they do? Why are they there? Are they safe? How are they tested? And is their use warranted in all cases, especially in baby foods?

Many of the food products stocked on the shelves of American supermarkets today are there only because of the additives they contain. One commonly cited example is General Mills' "Rice Provence," a flavorful pre-packaged rice concoction that has among its numerous ingredients monogylcerides and diglycerides, monosodium glutamate, butylated hydroxyanisole, butlyated hydroxytoluene, proply gallatem propylene glycol and citric acid.

Such easy-to-prepare foods require larger amount of additives, food manufacturers point out, because they are prepared under more severe conditions of temperature pressure and agitation that rob many foods of their natural chemicals and nutrients.

Thus food additives put back into food what modern processing takes out. The same holds true, experts say, for frozen foods, freeze-dried foods, canned foods and most other processed foods.

Other reasons for the increasing use of additives in foods include an increasingly urban population that wants its foods to last longer and stay fresh on shelves before use; a change in eating habits that reflects a more mobile American who likes to snack and run; a growing diet consciousness among often overfed Americans, and a growing taste for more exotic, seasoned dishes.

REGULATED BY LAW

Thus food additives can be of two sorts, those aded intentionally and those that sneak into food accidentally.

Accidental or unintentional food additives include pesticides and minute particles from food packaging that manage to "migrate," as the experts say, into the food itself.

The Food and Drug Administration says that it has its eye on pesticides, such as D.D.T., and conducts periodic "market basket tests" to determine levels of pesticides in a typical basket of groceries with enough food in it to feed a growing teen-ager.

Substances that migrate into foods from packages (cellophanes or glues from box tops, for example) are regulated by a lengthy group of laws that set limits on how much of an unintentional additive may be tolerated.

Limits are set, for example, on how much of the plastic substance surrounding vegetables that "cook in their own specially sealed flavor pouches" may get into the vegetables.

As many food experts have pointed out, more has been done to limit and control the migration of unintentional additives into food than has been done to control or limit the use of intentional additives.

But precisely what is a food additive? According to the Food and Protection Committee of the Food and Nutrition Board, it is defined as "a substance or mixture of substances, other than a basic foodstuff, which is present in food as a result of any aspect of production, storage or processing."

International additives are chemicals that are put purposely into food to carry out a host of functions.

The public is often frightened by the word "chemical," experts say, not realizing that all food is chemical in nature. "There are myriads of substances present in foods, both natural and added," said Dr. Bernard L. Oser, a biochemist and toxicologist who heads the Food and Drug Research Laboratories in Maspeth, N.Y. "There are more than 100 chemical substances in orange juice alone, and not all of them can inherently be bad."

THREE TYPES OF ADDITIVES

Critics of food additives agree with Dr. Oser's viewpoint, but hasten to emphasize that while chemicals added to food on purpose should not be judged as inherently bad, neither should one assume that they are inherently good.

Food additives are derived in three ways. A few, such as the spice cinnamon, occur abundantly and are called "naturally occurring additives."

Another group is called "natural identicals" because they occur in limited amounts in the natural world but are synthesized in the laboratory to increase their use in food products. Natural vanilla bean and vanilla extract that is produced in a laboratory, both of which look identical to an organic chemist are an example of natural identicals.

A third category consists of entirely synthetic compounds, developed especially by food scientists to carry out specific functions in food production. Saccharine and cyclamate, both sugar substitutes, are examples of pure synthetics.

Some 2,500 to 3,000 food additives are currently in use, including flavoring and colors. Some of the most commonly used additives are: 30 preservatives to keep foods fresh; 28 anti-oxidants to retard the oxidative breakdown of fats and oils in foods, so as to keep shortenings, potato chips, chicken pot pies and other foods from turning rancid; 44 sequestrants (to separate trace elements from foods that might otherwise interfere with food processing); 31 stabilizers to keep food at a uniform, smooth texture), and 85 surfactants (or wetting agents that allow two surfaces to come together by lowering their tension at surfaces of contact).

Such substances make food look better, feel better, taste better, hold together better, age better, mix better, spread better, pour better, and so on.

An example of how additives are used (or misused, as some critics would say), in baby foods is found in certain modified starches.

When pure starch is added to baby food, the infant digests it almost immediately, upon contact with its saliva. Some of the baby's saliva, however, gets back into the jar, which, when the mother opens it the next day, seems "clogged" and of poor consistency because some of the saliva has reacted with the starch.

Manufacturers of baby food, therefore, began to use modified starch, which does not react so readily with the baby's saliva.

Critics of this practice say that while it may not harm infants, according to the evidence known today, it may not be totally innocuous in the long run. Because it is not absolutely necessary for the good of the baby, they say, the practice should be stopped.

The use of monosodium glutamate (MSG) in baby foods, mainly to please the tastebuds of mothers, has also been under attack. The major producers of infant food, in fact recently announced their plans to stop putting the chemical in their product until more is known about it.

Here are a few examples of what food additves actually do:

Flavorings: More than 1,100 are used. They restore the zest taken from food as a result of rigorous processing. Thus frozen strawberry-cream pie has strawberry flavor added to it because the real strawberrys in the pie are not nearly flavorful enough on their own.

Emulsifiers: These compounds also called dispersing agents, serve to allow the particles or globules of one liquid to mix well with another liquid. Thus store-bought salad oil, mayonnaise, or peanut butter do not separate in their bottles. Emulsifying agents are used in nondairy creamers to speed dispersion of the product in coffee.

STABILIZERS AND THICKENERS

These impart a uniform texture to foods. Commercial ice cream has that creamy texture because stabilizers work to absorb or bind part of the water in ice cream, thus preventing it from freezing into grainy crystals. Thickeners are added to icings, cheese spreads, syrups and other "gooey" products to keep them nice and gooey.

Preservatives: These work to keep food fresh longer. Where smoke and salt were used by our ancestors, modern scientists have at their disposal calcium propionate and sodium propionate (to inhibit molds), ethyl fomate (to control yeasts), sodium diacetate (to control rope, a slimy condition caused by rope bacteria), antibiotics (to preserve chilled uncooked poultry and seafoods), and sodium sulfate (to prevent brown splotches from forming on fruits, potatoes and similar produce).

These varieties of food additives are present in food because, as one authority put it, "We don't live down on the farm anymore."

As more and more Americans have moved into the cities it has become harder to deliver fresh produce to everyone's doorstep, food experts say. Additives became necessary, therefore, to keep food fresh and safe as it often travels hundreds or thousands of miles, and then sits on a supermarket shelf for days or weeks before it is used in the home.

Another reason for food additives is that Americans have more leisure, and with it a desire to put some leisure into kitchen duties as well. Thus convenience foods—something, say, that can be prepared in 10 minutes by a hung-over bachelor—were developed by manufacturers to meet the demand of housewives wishing to undo the age-old image of themselves as "slaves in the kitchen."

Some 10,000 different food items are available today on the shelves of a large supermarket (there were 1,500 items 20 years ago) and many of them are explicit time-savers; waffles for the toaster, instant mashed potatoes, instant oatmeal, even instant breakfast, pies that cook their own crust and vegetables that come in their very own "clinging butter sauce and other delicate seasonings."

Since processing often destroys many properties of foods, additives put back in what the processing takes out. One expert referred to the example of peaches, which, he said, after having gone through a uniform processing technique, come out tasting like "vulcanized rubber." Without additives, he said, many canned fruits would be unpalatable.

Food processing techniques also deprive foods of many nutrients. Wheat, for instance, has 23 nutrients crushed, ground and squeezed out of it during processing.

TASTES ARE CHANGING

One food industry critic, James Turner, a lawyer with consumer advocate Ralph Nader, complained, however, that only four of these nutrients are generally put back into flour. Mr. Turner is currently preparing a report on the food-protection activities of the Food and Drug Administration, based on the findings of a group of 20 lawyers and medical students known as Nader's Raiders. The report is expected to be ready by the first of the year, he said.

Yet another reason for the proliferating use of additives in food is the diet consciousness of Americans. Artificial sweeteners and low-calorie foods are big business. This is reflected by the fact that the use of artificial sweeteners in domestic foods rose from 0.25-million pounds in 1955 to some 21 million pounds in 1969, an increase of 8400 per cent.

Finally, tastes are changing, many experts say. One executive of the Arthur D. Little Corporation said that his children refused to drink fresh organe juice because it tasted "peculiar" to them. They have grown up on frozen orange juice, he said, and they are convinced the frozen product is how orange juice should taste.

How valid are the industry's arguments that food additives are necessary to keep food fresh. One critic, Dr. Barry Commoner, a biologist from Washington University in St. Louis, says that the industry should do a lot more to speed up the delivery of foods, and thus lessen the need for so many additives.

"In Paris," Dr. Commoner said, "you can get fresh fish from the Mediterranean with no trouble. But in Pittsburgh, just try to get fresh fish from the Atlantic Seaboard."

The majority of critics, however, place less emphasis on what food additives do to food or are supposed to do to food and focus on the procedures used to test food additives for safety. The question they ask is: How, and how well, are food additives tested?

[From the New York Times, Nov. 10, 1969]

CHALLENGE TO FOOD TESTS

(By Sandra Blakeslee)

What could possibly be harmful about a maraschino cherry?

Probably nothing, according to the Food and Drug Administration. Plenty, according to the World Health Organization.

The W.H.O. bases its position on a 1965 study that found a red food dye in the cherries "harmful and not for use in foods."

The F.D.A. followed suit by banning the food dye from all foods except maraschino cherries, which is exempted because its food experts felt that the small amount of color additive consumed while nibbling the cherries would probably not hurt anyone.

This sharp divergence of policy over the safety of a seemingly harmless everyday food products, while not itself a current subject of debate, exemplifies a fundamental issue that underlies the growing controversy in this country over the safety of food and the heavy use of additives in processed food.

The questions are: How, and how well, is American food being tested for safety? Are the additive laws adequate? Is the F.D.A. doing its job? Where is the food industry headed? And what does it all mean for the consumer?

Caught up in the controversey are food and chemical manufacturers, scientists, doctors, lobbyists, Federal officials, legislators, lay critics, and, of course, the great mass of ordinary people who every day take additives into their bodies in the faith that their health is secure.

The position of the food industry's outspoken defenders was summed up in a statement by the American Medical Association: "There is no reason to believe that the present use of chemicals in foods is endangering the health of the people."

Less vocal in defense of the industry are perhaps the largest number of scientists. Their cautious view was expressed in Lancet, the British medical journal: "The question of the ultimate effects of food additives on man is unanswered. Human experiments are possible only on a very small scale, and, in any case, they do not mimic the life-long, very low doses to which man is exposed."

Finally there are the critics of the industry, who hammer on one major point: If we don't know the effects of food additives on human beings, then should we go blithely on with their use? As James Turner, a lawyer who has worked with Ralph Nader, the consumer advocate, puts it: "The question is in the testing of food products who will be the test animals—rats or human beings?"

LAW GOVERNING ADDITIVES

Before 1958 the Food and Drug Administration, responsible for the purity of foods under the 1938 Food, Drug and Cosmetic Act, could take no action against a possibly harmful food additive until one substance was already in use in foods involved in interstate commerce.

In the early 1950's, however, a series of Congressional hearings, the outgrowth of nationwide concern over unmonitored food practices, ended in the Food Additive Amendment of 1958.

The amendment declared for the first time that no additive could be used in foods unless the F.D.A., after a careful review of test data, agreed that it was safe at the levels of use intended for it.

A major exception was made, however. Because the Government felt that it could not abruptly stop the use of all additives all at once, it issued a first list of substances that its own experts thought could be classified as "generally recognized as safe."

This early list, known as the White List and later shortened to its acronym, GRAS, and called the "Grass List," is one of the major objects of attack by food policy critics.

The original white list proposed that approximately 190 chemical compounds be declared safe for use at commonly accepted levels set by manufacturers—without toxicity tests—provided qualified experts generally recognized them to be safe on the basis either of known research or of experience in their common use in foods.

CIRCULATED AMONG EXPERTS

The list was circulated among about 900 pharmacologists, toxicologists and other experts from the industry, the universities and independent research laboratories, according to Lessel L. Ramsey of the F.D.A.'s Bureau of Science.

Of the first 190, he said, about 180 were approved as GRAS substances. Examples are pepper, cinnamon, baking powder, citric acid and monosodium glutamate. Cyclamates, an artificial sweetener recently banned by the Federal Government, were also on the list.

But Mr. Turner, the industry critic, says that research by a group of young lawyers and medical students known as "Nader's Raiders" shows that of the 900 experts first petitioned for comments only 350 responded. Of these, Mr. Turner says 200 agreed that all the substances were safe.

Mr. Ramsey of the F.D.A. described the agency's policy thus: When a candidate for the GRAS list is submitted for agency consideration, a proposal to "pass" the substance is published in the Federal Register. Criticism from experts is invited, but not solicited. If no criticism is voiced, or if it is and is judged as inadequate, the substance is added to the list.

Supporters of the GRAS list, such as Dr. Bernard Oser of Food and Drug Research Laboratories, an independent organization in Maspeth, N.Y., says that the law cannot require proof beyond any possible doubt that no harm will result from a substance under any conceivable circumstances. The F.D.A. does the best it can, Dr. Oser says.

The agency withdrew cyclamates from the market as soon as new evidence linking them with bladder cancer in rats was presented. But the critics were not satisfied.

For some time it has been known from controlled experiments, they say, that cyclamates do not help a whit as weight reducing agents.

Also they say, cyclamates have been suspected to be harmful since 1960, yet they are still being used in children's vitamins and in old people's cereals.

British scientists complained of the "precipitous" manner in which cyclamates were banned. The way the new evidence was handled, the British scientific journal Nature writer, "transformed the question from largely a scientific issue into a political bandwagon."

When new food additives especially purely synthetic compounds, are not considered candidates for the GRAS list, Mr. Ramsey says, they are required to undergo stringent testing procedures.

Because the procedures often require up to five years of testing on animals and perhaps $250,000 in research funds, he says relatively few new additives are approved by the agency in this manner, perhaps no more than a dozen a year.

The larger chemical manufacturers, who usually bear the burden of such research, say they tend to work on only three or four new additives a year, preferring to find new uses for old additives (such as adapting an emulsifier in ice cream for use in potatoes) whenever possible.

Officials at Pfizer Chemical Corporation say that testing begins within an overall evaluation of the additive by industry scientists who determine what tests are needed to prove the additive safe.

A full cycle of tests on animals, the officials say, includes acute, chronic and life-long toxicity tests on one or more species of laboratory animals.

From the tests, scientists gain an idea of most toxic level as well as its most innocuous level consistent with effectiveness.

Then, when a safe level of use has been determined, scientists say they usually follow this rule of thumb—they divide the level at which the substance is thought to be safe in animals by 100. "This is a big safety margin," Pfizer officials said, "and we do it to protect the consumer."

Once all of the scientific evidence on an additive is collected, it is presented to the F.D.A., whereupon agency scientists evaluate the information to determine whether the additive is safe at its intended levels of use.

TOLERANCE LEVELS SET

In approving many substances for use in foods, the F.D.A. often sets tolerances on how much of the material may be added.

The subject of tolerance is particularly touchy to many food scientists because of what they consider a senseless clause in the Food Additive Amendment of 1958. The clause, named after Representative James J. Delaney, Democrat of New York, states that no chemical may be added to foods if in any amount it produces cancer when ingested by man or animals.

Most food experts are quick to point out that no substance is entirely harmless; there are merely harmless ways of using substances. Salt, sugar and almost any compound, when consumed in too large quantities, will cause toxic effects, even death.

The Delaney clause, according to its critics, is an emotional response to a scientific matter that should be left up to scientists, not legislators.

It is likely that many more additives will be connected with untoward biological effects as time goes on, scientists say, as analytical tools and concepts of research continue to improve. It is likely, too, they say, that foods and eating habits will change.

John Angeline, a food marketing expert with the A. D. Little Corporation in Cambridge, Mass., predicts that there will be more snack foods, better-tasting canned goods and synthetic foods—meat analogues extracted from vegetable proteins, such as the soya bean, and doctored to taste like real meat.

All these developments will mean more and more food additives, Mr. Angeline says.

Of mounting concern to health experts around the world, therefore, is this question: As we consume more additives, what will be the long-term destructive potential of everything we eat?

Most scientists say they do not have the foggiest idea.

At least one critic of the food industry, Jerome I. Rodale, who has written a book called "Our Poisoned Earth and Sky," is calling for immediate answers to these questions:

"How can the body cope with the sheer volume of chemical substances which trickle into it from a hundred different food sources each day? How much of a strain is it on the body's organs to process and rid itself of so many useless and harmful substances? Do all of them leave the body? How do these chemicals react on one another while they are in the body?"

Another question health experts are raising is this: What are the synergistic effects of all these chemicals? That is, how do drugs, pesticides, food additives, car fumes and polluted water affect the body altogether? Perhaps, they say, the total effect is greater than the sum of its parts.

Mr. Turner points with concern to the fact that the life expectancy rate in the United States ranks only 32d in the world. The infant mortality rate in this country, he says, fell from 15th place in 1950 to 18th place last year.

Finally, he says, American mothers suffer a particularly high rate of unnaturally terminated pregnancies, such as natural abortions and stillbirths, compared with mothers in many other countries.

Could the chemical environment we live in have something to do with these figures, Mr. Turner asks?

That too many chemicals may be hazardous to health, most experts say, is a possibility that no one can deny.

Some even feel that it may be time to take seriously what many members of the younger generation, especially the hippies, have been saying for quite some time: You Are What You Eat.

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