1975

M. G. Stemmermann's Correspondence and Materials on Monosodium Glutamate

Huntington Doctor's Work Adds To 'Story' On MSG

By JACQUELINE SWANN
Herald-Dispatch Staff Writer

Monosodium glutamate.

It is called for in dozens of recipes. It is found in its natural form as glutamic acid in large amounts in tomatoes and peas. Numerous packaged, canned and prepared foods on the super market shelves contain it. It is widely used in restaurant cooking.

And, it causes the "shivers."

Nothing more than a flavor enhancer, monosodium glutamate, or MSG, is the sodium salt of glutamic acid, but research has credited it with causing such symptoms as a tingling of the skin, a feeling of pressure in the chest. and headaches. These symptoms were dubbed the "Chinese Restaurant Syndrome," because MSG is used so lavishly in Chinese cooking, especially soups. and thus, as a first course, it is rapidly absorbed into the bloodstream and reaches the nerve endings posthaste.

Dr. M. G. ,Margaret) Stemmermann of Huntington believes it might be equally well dubbed the "Sausage Syndrome... "Sausage is the chief offender," Dr. Stemmermann said.

In an article by nutritionist and syndicated columnist, Dr. Jean Mayer, carried recently on the Family Scene page, reference was made to the case work of two doctors, Liane Reif-Lehrer, a bio-chemist with the Harvard School of Medicine, and Stemmermann, an internist, with sub-specialization in neurology, now "retired," and on a retainer by the Owen Clinic Institute at 1319 6th Ave.

"I II,\\ EN'T done any research in MSG," Dr. Stemmermann said. "Most of my work is in the neuro-psychiatric field. Most patients I see are sticky ones: they have been to doctors and are still having uncontrolled seizures.

"I have this little girl patient. She had been to everyone. I was one of the lucky ones: I saw a seizure, which was not a seizure. It was a shiver. I had her mother make a list of all foods the girl ate and when the seizures came. I always do that on any youngster, and on some adults, who have uncontrollable seizures. Children can't talk for themselves, so I have the mother list everything the child eats and drinks, to find any correlation between the attacks and foods.

.. I found out the clusters of attacks came in the afternoon or early evening, after lunch or dinner. If a doctor can see an attack, he has a pretty good idea. The child had been in two hospitals, one of them on two occasions. No doctor saw her attack: in the hospital, she was fed ordinary baby foods, and so no attacks occurred."

From her examination and the record kept by the girl's mother. Dr. Stemmermann was able to determine that the child was not undergoing epileptic seizures, but "shivers," caused by her intolerance to monosodium glutamate.

The determination was made when the little girl was 13 months old, now, a year later, the seizures do not occur when the diet is controlled.

HOWEVER, Dr. Stemmermann was faced with another possibility.

She had read articles by Reif-Lehrer regarding the latter's research in eye diseases, with special refcrence to experiments with chicks embryo eyes kept in a culture and fed differ,- ent chemicals. Reif-Lehrer noted that relatively small amounts of MSI caused holes in the retinas of the specimens.

"Having read her articles.·· Dr Stemmermann said, "I thought of that youngster and wondered if the child would be blind tomorrow. So last May, I got in touch with Dr Reif-Lehrer . . . my only contact with her has bem via Uncle Sam and Ma Bell."

So far, Dr. Stemmermann·s little patient has had no visual problems

Together, Dr. Stemmermann and Dr. Reif-Lehrer wrote the article on their cases of MSG intolerance in children which was published in the New England Journal of Medicine in December 1975, and which was mentioned by Mayer.

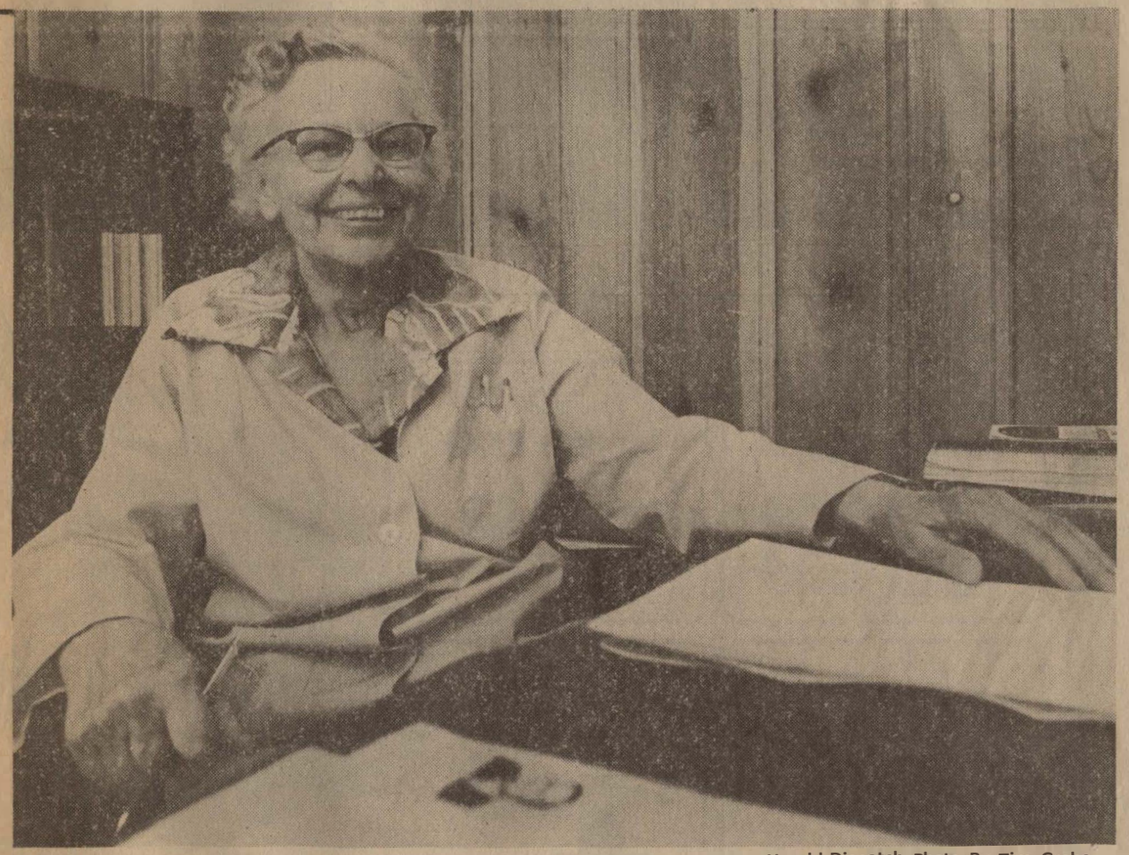
.. I hasten to add." Dr. Stemmermann said, "that MSG is innocuous. It Just makes some people feel funny. But the damage in a child is unknown. A child"s brain under three years doesn't have all its insulation, the insulation is not completed till age 3 or 5. What does do no damage whatever to an adult may be something else again to a child.

"Now. everytime I do an EEG (electroencephalograph on a child, I make sure the parent gives the youngster something with MSG in it. That way. I can tell whether it has an effect on the EEG. I tell the parent to give them sausage for breakfast . . . All sausage contains it, at least, all I have found in the super markets.

"II''S FOUI'\ID in flavor enhancers such as Lawry·s and Accent, soy sauce: Campbell's chicken soup has it; and most hot dogs but not all. but all baloney has it: cheese does not. Chef Boyardee pizza mix has it but Franco American does not. Go look in the super markets, it's always on the labels. There·s no reason for putting MSG in anything that has tomatoes in it: they are natrually high in glutamic acid . . . some people get the shivers when eating tomatoes.··

So far as is known, Stemmermann pointed out, the use of monosodium glutamate is not "a life and death matter. unless in young children it has bad effects. The symptoms in adults arising from MSG are benign, no damage, it just makes them uncomfortable. Dr. Reif-Lehrer thinks the incidence of susceptabihty is 25 per cent: I don't think it's more than 10 per cent.

"Nowadays, when so many different chemicals are added lo our foods for some reason other. it behooves us as physicians to find out what our patients put in their mouths, along with where they work and what thev are exposed lo,.. Dr. Stemmermann said.



Herald-Dispatch Photo By Tim Grobe

Dr. M. G. Stemmermann has been in the field of research most of her professional life, and only in the past 10 years has done active medical practice. At 66, she says she is retired, but still is doing work in the neuro-psychiatric field, which has led to her interest in the effects of MSG in young patients.

MSG for children scored

By Ed Orloff

FOOD: By now, you've probably heard of the Chinese Restaurant Syndrome: a tingling that starts at the back of the neck, headache, a burning sensation, facial pressure, generalized weakness, and palpitations. The cause appears to be the monosodium glutamate **(MSG)** that Chinese chefs add to food. MSG also is the basis of a store-bought product which many cooks use in the kitchen. All of which brings us to Dr. Marguerite Stemmermann, of Huntington, W. Va., whose young patient was having spasms from time to time. After many checkups, the doctor reported in the magazine Emergency Medicine, she got lucky. The patient came in with a "seizure" right after a meal that had included liberal doses of MSG. Once it was removed from **her** diet, she was fine. The doctor suggests that there are probably many more children whose symptoms (which could also include migraine and hyperactivity) stem from MSG in the diet. Incidentally, MSG turns **up** in a lot of commercially made sausage, hot dogs, and soups.

TB: How infectious ls tuberculosis once drug treatment **is** started? Dr. R.L. Riley of Baltimore says it's no hazard after one or two weeks of therapy, even though the TB organisms persist in the sputum for quite a while. The most infectious period **is** just before the disease is diagnosed and the symptoms - particularly severe coughing - cause the patient to seek help.

SURGERY: Women who undergo extensiv pelvic surgery still can have sexual relations once they recover, even if they lose both their vagina and clitoris. Dr. J.A. Lamont of Ontario's McMaster l!niversity

MEDICINE TODAY

says the vital factors in sexual rehabilitation are a partner who can accept the reality of the surgery, encourage open communication, and maintain an interest in continued sexual activity. Lamont and his associates have developed a program which aims at overcoming the common psychological problems **of** such patients and th ir spouses.

ALLERGY: Cinnamic aldehyde, in case you were wondering, is widely used by manufacturers of toothpaste, mouthwashes, perfumes, and some foods to provide flavor. It may also be a cause of unusual inflammation of the soft tissues of the mouth. Drs. T.E. Drake and H.I. Maibach of the University of California, writing in Archives of Dermatology, ten of a businessman who developed an eruption on his lips and fingers. It was treated, but recurred after a trip, The doctors traced the problem to a tube of toothpaste he kept in his travel bag. Test results showed he was reacting to ingredients containing the cinnamic aldehyde.

AGE: Considering the state of the world, you may not really want to live on into old age. But if youdo, Dr. Richard L. Reece of Minneapolis offers this advice in Medical Economics: Stay lean, quit smoking, sleep well; **drink** lightly, ignore your enemies. and don't retire. A federal survey of Jongevity notes that 10 states offer the best opportunities for lasting: Hawaii, Minnesota, Utah, North Dakota, Nebraska, Kansas, Iowa, Connecticut, Wisconsin, and Oregon.. The next move is yours.

SPORTS: 1l you're into tennis, it might be a good idea to wear the sort of eye protector used by handball players, or sunglasses made of shatterproof plastic. You also ought to learn how to hold your racK• et so that your face is protected as you rush up to the net. That's the advice from eye specialists who studied 10 patients injured while playing or watching **tennis:** all suffered severe eye contusion. Example: One rushed the net to return **a** shot. The ball, traveling at high speed, hit **his** left eye, scratching his cornea (the transparent **part** that admits light) and causing an inflammatory reaction that led to bleeding within the eyeball. **A** tom retina eventually was diagnosed, and surgery was needed.

ASTHMA: H you're a pregnant woman with a severe case of asthma, the disease may worsen after the fifth month, University of Miami researhers have found. In women with mild asthma, 12 per cent of the group studied actually improved. And 40 per cent in the group with moderate asthma were better. What it adds up to is that **severe** asthmatics require increased medication.

TREATMENT: Does one type of doctor do a better job in handling a problem like sore throat in children? The publication Infectious Dis• eases cites a recent survey of pediatricians and general practitioners designed to test the adequacy of their performance. Conclusion: More of the child specialists (88 per cent) provided proper care, according to generally accepted standards, than the generalists (44 per ent).

Restrictions On MSG In Foods Seen Likely

By OR. JEAN MAYER

You have probably heard of Chinese Restaurant Syndrome. Perhaps you have even experienced the symptoms yourself - a tingling of the skin, a feeling of pressure in the chest and headaches, ranging from mild to se• vere - all of which appear about half an hour aiter beginning a Chinese meal.

A few years ago, the "culprit" was identified as monosodium glutamate, or MSG, a flavor enhancer that is used lavishly in Chinese oooking, especially in first-course soups. With nothing in the stomach to slow down digestion, the MSG is rapidly absorbed into the bloodstream, reaching the nerve endings all at once. Although the resulting symptoms are unpleasant, they are temporary, with no lasting effect on adults.

Biochemically, the problem begins with glutamate, the salt form of glutamic acid, an amino acid that occurs naturally in every protein and m particularly large amounts in certain vegetable protein§. MSG is the so-ldium salt of glutamic acid. As a part of proteins. glutamate is tolerated by ever!Tone. But when it is consumed by itse in concen&ated amounts, as in Chinese restaurants, one ou of every four peo le reacts0 suffering varying gegrees o dlscomf rt.

IT ALSO APPEARS that some youngsters are unable to tolerate high levels of glutamate, such as those found in MSG, and suffer particularly severe reactions. Two doctors, Liane Reif-Lehrer and M.G. Stemmerman. - described three such cases m a recent issue of the New England Journal of Medicine.

One child began to suffer epileptic-like attacks when he was 6 months old, after he first began being fed adult-type foods. In a test, it was found that a commercial spaghetti sauce containing MSG brought on an attack. And when those foods that contained MSG were removed from his diet, the attacks stopped. Similar results were reported in another child, who developed "shivers" after eating foods containing MSG.

The third patient, a 14-year-old boy, developed intense headaches and vomiting after eating tomato products to which MSG had been added. The doctors concluded that he could tolerate small amounts of MSG, but since ter matoes are aleady naturally high in glutamate, the combination pushed the boy beyond his tolerance threshold.

With the exception of baby foods, however, monosodium glutamat is becoming increasingly common m o r foods. And that is the problem. It is added to canned and frozen foods, spaghetti sauce, prepared meat dishes. dried soups and a variety of other commercially processed foods. Plus. many housewives add it to home-cooked vegetable and meat dishes. (It is also sold by itself as a ••flavor enhancer" under a variety of names. l

If the work of Dr. Reif-Lehrer and Dr. Stemmerman is confirmed, it is likely that severe limitation in the use of MSG in food served to children will be recommended by pediatricians and by the Food and Drug Administration.

be acquitted. Even though he is found innocent, however, the resultant trial could have severely adverse effects on the "good" physician's reputation, in addition to the personal travail that it may have caused.

Illustrating the obstacles involved in seeking recompense for a wrongful suit, Mr. Rheingold cited the case of a Louisiana surgeon who was cleared of a charge that he had negligently left a [illegible] of a pa-

After suing the law firm and other attorneys responsible for bringing him to trial, the physician was awarded $33,000 based on defamation of character. The physician's chief defense was that the lawyers could not show probable cause for the belief that in fact a sponge had been left in the abdomen and also that the defendants had acted maliciously.

The attorneys in turn **appealed the case on the basis that the physician could not prove malice, and the original award was set aside.** In **addition, said** Mr. **Rheingold, the appellate court then "twisted the scalpel" by asking the physician to pay all court costs.**

Noting that the burden of proof was on the surgeon, the court concluded that there was not even evidence that the trial lawyers knew that their client's claim about a sponge was untrue and that they were entitled to take at face value what the client had told them.

Although legal remedies for righting a wrongful suit are nearly non-existent, Mr. Rheingold suggested that the plaintiff for attorney's fees and other costs involved in the trial, he said.

Questions About Safety Of Artificial Sweetener Revive Debate on MSG

Continued from page 3

mental Biology, together with a number of other **GRAS** substances.

Another investigator, Liane Reif-Lehrer, Ph.D., Assistant Professor of Biochemical Opthalmology at the Harvard Medical School, base reported degeneration in chick embryo retinas exposed to MSG in culture. Previous findings had been systemic, and the dosage needed to produce damage had not been precisely determined. Dr. Reif told MEDICAL TRIBUNE that as little as 0.3 **mM. MSG** in the bathing fluid caused damage within a few hours. MSG in normal human blood plasma may reach comparable levels.

Dr. Rt:if emphasized that she has no evidence that damage occurs in normal adults, thanks to blood retinal barriers that are built up during infancy. But she said damage in fetuses, babies, and adults with ocular and other diseases, or on medication, could not be ruled out so long as complete data on MSG was lacking.

While Dr. Reif did not advise against adults' using MSG, she said that there is "definite cause for more research on a substance that may not be entirely innocuous," and she agreed with Dr. Olney that the introduction of Aspartane "may complicate the problem, if indeed it turns out there is a problem."

the implications of the Edelin case in such circumstances?"

The increasing use of amniocentesis as a means of detecting genetic abnormalities in the fetus also challenges the genetic counselor with many potential legal issues, said Dr. Omenn, who is Associate Professor of Medicine in the Division of Medical Genetics at the University of Washington.

"One may predict that the first case in which a physician is sued for negligence for not providing genetic counseling or for not recommending amniocentesis will finally bring awareness of the value of genetic medicine to the fore . . . When health insurers do enter the field, some enterprising company may offer to pay for amniocentesis and abortion, if indicated, but ***not*** for subsequent medical care of the offspring, should abortion of a fetus affected with some specified and testable condition be refused."

Greater Problems Ahead

If abortion and amniocentesis raise difficult legal questions at the present time, the difficulties attached to artificial fertilization and other techniques of the future loom even larger, said Dr. Omenn.

For example, the birth of "test tube babies" which results from the ***in vitro*** fertilization of an ovum, followed by cell culture and implantation of the ovum in the uterus of a "mother" with blocked fallopian tubes, could inspire major problems not only for the parents and physician but also for the child's privacy.

"A healthy child should have few special problems of identity, status, and image. However, these children may face intense scientific curiosity about their physical, mental, sexual, and emotional development," Dr. Omenn said.

He also anticipates that successful ***in vitro*** fertilization of the ovum could lead to a situation in which an egg from one woman fertilized by sperm from her husband would be transferred to another woman to carry and deliver the child and return it to its genetic parents. The woman would "rent her womb" in effect.

"It is unlikely that this scenario would be chosen commonly; it is likely that the cost of 'renting' the use of another woman's womb for nine months would be substantial. Conflicts are to be expected; the bearer might decide to have an abortion or to keep the child. The husband and wife might change their minds and try to force the pregnant woman to undergo an abortion; or they might reject a deformed or defective baby."

Heart Valve Disease Study

Medical Tribune Report

BETHESDA, Mo. - The National Heart and Lung Institute is asking physicians for their cooperation in referring patients for study of valvular disease and treatment by aortic and/or mitral valve replacement.

Physicians wishing to refer patients should get in touch with Dr. Stephen E. Epstein, NIH Clinical Center, Room 7B-15, Bethesda, Md. 20014.

This is [illegible]
that [illegible]
correspondence

Ma7 16, 1975

Liane ReitLehNr, Ph.D.
Assistant P:rofessor of Biochemical Opthalmology
Harvard Medical School
Boaton, Mass

Deal' Dr. Reitl

I was v*e7"1* much intereated in 7our recent i-eport to MEDICAL TRIBUNE. I am enclosing a b:riet resume of a 7oungater whose condition I have called "Intantile Chineese Reatau:rant S111drame". Thia is the onl7 child I haTe •een with thid condition but I am sure there must be others. Possibly with your muoh larger population at Harval'd than I have there must be othei-a. I would look toi- this condition in children who begin adult foods at an earlier age than the average child.

It you or your associated have had similar expe:rienoes I would certainly like to hear abut them•

Sinoerely yours,

M. G. Stemmermann, M.D.

Enclosure

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
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Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

May 23, 1975

Dr. M. G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemmermann:

I really want to thank you so much for taking the trouble to write to me.

I am very interested in the data you sent me. Have you had any contact with this child since February 1974. Do you know anything about the childs mental development. Is she in nursery school, also, do you know if there has been any indication at all of any visual problems?

I would be most interested in keeping track of this child in the years to come. Also, if it were possible, I would like very much to get a urine sample. If and when Aspartame does get out on the market, General Foods will, in all probability, shortly thereafter come out with some products containing this artificial sweetener, I think it is important that this child's family be advised that she not be fed any food containing this material.

We are very much involved in continuing our studies on MSG knd I am scheduled to do a verbal survey of school children of various ages in a Boston suburb sometime next month. The rest of our data on adult populations is in the process of being programmed for computer analysis. I will be happy to keep you informed of our findings. Meanwhile I would likewise appreciate your keeping me informed about this particular patient as well as any others you may know that may relate to this problem.

There is perhaps some reason to believe that diphenylhydantoin (dilantin)may increase adverse effects of MSG. The evidence for this is sparse and we hope to get more data on it. Do you have any comments about this point?

Again, thank you, I remain,

Sincerely,

/s/
Liane Reif-Lehrer, Ph.D.
Asst. Professor

LRL:a

June 13, 1975

Liane Reif-Lehrer, Ph.D.
20 Staintord Street
Boston, Massaobusetta 02114

Dear Dr. Reif-Lehrer:

Many thanks tor 7our prompt repl7 to my letter regarding vhat I have labelled "Intantile Ch6nese Restaurant SJndl'ome". I regr t that I eannot give you any up to date information, as the tamily Or rrr,patient have moved to Columbus, Ohio. It I locate thea, I know the mother, Mrs. Tina Dail•J• would be on17 to happy to cooperate With follow up evaluation.

The last I aav this 7oungater waa Februal"J, 1974 when ahe was 2 9/12 fears. Thie waa approximately 27 months atter onset ot Shiver" attacks, 23 months atter withdrawal Or MSG and ceasation Or a.ttaoks, exoept tor "trial" purpoaes. In $arl7, 1974, she was doing w11 with no evidence or visual impail"SDent.

I have no int'omation regarding the interaction *ot* diphenylhydantoin and MSG. However, this ma7 be the answer to one of urr puzzling problemat Why do oocassional patients who have been on the drug for years develop toxicity and elevated blood levels? Aleo why do ocoassional patients have elevated blood levels with what would seem minimal dosage, but yet inadequate seizure control. (These patients are changed rom Dilantin to solin e or TegNtol).

If I tind an:, new babies I will keep you informed.

Sincerely yours.

M. G. Stemmermann, M.D.

LIANE REIF-LEHRER PhD
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Harvard Medical School
and
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July 11, 1975

Dr. M. G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemmermann:

It was a pleasure talking to you on the telephone this morning.

Enclosed are 2 items which may be of interest and which will indicate why I initially became interested in the whole MSG matter.

Thank you very much for giving me permission to cite your case history in my paper. I will send you a copy when it comes out.

I really appreciate your information about your latest case and look forward to getting the data on him. I have also written to your brother. Again, I really appreciate all the help you have given me. Thank you.

Sil◆◆ ;;) ' /)

LRL:a

Dr. Liane Re er
Asst. Professor

July 15, 1975

Liane Reif-Lehrer, Ph.D.
20 Stainford Stl'eet
Boston, M£asachusetts 02114

Dear Dr. Reif-Lehrer:

Many thanks tor the reprint--7our micrographs are indedd spatacular. There are mayy questions I would like to discuss with you but doubtless your continuing research will answer them, ror example, speciea dirterence with nocturnal or diurnal animals.

I am enteaing what little information I have to date on my latest, possible "LSO" bab7. I w111 be aading the urine spaoimens, collectedin bags with thJm(>1 added. Should I have additional ophthalmologic studies now and if so. what?

I would doubt that you could obtain muoh valid information from children regaroing subjective aymptoms. In the crucial infantile group, undet tw years betore myelinization is complete, lack *ot* apeech is the obvicus obstacle. Pre•school and primary graders usually don't understand what we are talking about. Therefore, we oan only judge b7 behavior.

I appreoiate your kmnd remarks about my astutenesa, but I had one adveutage over othe doctors who had treated my patient. I actually saw what the mother described as "seizurl.ng". I have been in ths "aeituring" business for JO+ years and had thought I had seen every type. This was different, w1th olarity of the sensorium the outstanding d1rrerence.

Sincerely yours,

M. G. Stemmennann, M.D.

Enclosure

KUAKINI HOSPITAL AND HOME

Liane Reif-LehrerJ Ph.D.
Aaaiatant Profeaaor
Department of Opbthal1110logy
Harvard Medical School &
Department of Connective Tiasue Research -
Boaton Bi01118dical Reeearch Inatitute
20 Staniford Street
Boaton, Maaaachuaetta 02114

Dear Dr. Reif-Lehrer:

Unfortunately I can give you no eetimate of the frequency of the "Chinue Restaurant Syudrome" aong Hawaii Japanese. I can aay that 1D011osodium glutamate 1a a universal condiment and 1a eaten every day by anyone eating Japaneae food•, excepting only those patients who have been placed on aodium restriction. A typical Japanese breakfast includes miao soup (clam broth atock, soy-bean paste, and heavily laden with 11011osodium glutamate). Such breakfasts are no longer the custom of H•aii, but remain ao in Japan it•elf. Miao aoup 1a a favorite food in pregnancy, eapecially in rural Japan. The noon and evening meals of Hawaii Japanese are pretty coamopolitan, including both Weatern, Japanese and Chinese items. It 1a difficult to imagine a 24 hour period with no expoaure to monoaodium glutamate. I have one Japanese proctologiat friend who auffers from the problem and who believes that it 1a 1110e common than moat of us are aware, uaually manifeating itself u tranaient diarrhea, akin tingling and other strange aenaory ruponaes in addition to the uaual headache. The Hawaii Japanese are very conservative and wouldn't think of using marijuana. Neither epilepsy nor opbthabmlogy fall• into my areas of competence• I have heard that 15% of the cuea of blindneaa in Japan are due to Bechet'a diaeue, but beyond this my information cupboard 1a bare.

I would auggeat that you communicate with a univeraity ophthalmology departaent in Japan to get an impreasion u to the frequency of retinal damage in adoleacenta in rural Japan. If high 110noaodium glutamate expoaure during pregnancy were reaponaible for permanent damage, I can think of no more vulnerable population than thia. A good target institution would be Akita Univeraity, Akita City, Japan. 'Ibia hu a very good neurology inatitute and aervea a prefecture which 1a the model for traditional diet and Japanese rural life atyle. You might also try Tokyo Univeraity which 1a the equivalent of Harvard. Unfortunately I do not know the namea of the department chief• of the e univeraitiea.

Sincerely,

G.N. STEMMERMANN, M.D.
Director of Laboratories

GNS:mck
cc: M.G. Stemmermann, M.D.

July 1,5, 1975

Liane Reif-L&hrer, Ph.D.
20 Stainford Streat
Boston, Massachusetts 02114

Dear Dr. Reit-Lebrer:

Many thanks for the reprint--your m1crographs are indedd spectacular. There are ma117 questions I would like to discuss with 70u but doubtless 7our continuing research will answer them, for example, spectes difre:N,nce with nocturnal or diurnal animals.

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Sincel"ely yours,

M. G. Stemmermann, M.D.

Enclosure

July 28, 197$

Liane Heit-Lehrer, Ph.D.
20 Stainford StNet
Boston, Massachuaetta 02114

Deax- Dr. Rait•Lehrer:

Under separate covex- you should have received a with and without mSG urine apeoimen trom Ull possible MSG baby, John Rhodes. Mra. Rb.odes has been most help l ancl since ehe vaa a math major and her bSaband • ineex-ing they are ver-, much intel'Oated in the scientitic implication• of 7our at•dies.

In 70ur last le•ter 7ou ask maey questions that I felt couJ.d be answered better by Y.ira. Rhodes. I therefox-e gave her that letter and 7ou should be receiving a reply shortly.

Please be assured of my continued interest and search tox- other ch11dNn possibly affected.

Sincerely yours,

M. O. Ste:mmennann, M.D.

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
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Boston Biomedical Research Institute

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July 31, 1975

Dr. M. G. Stemmermann
OWen Clinic Institute, Inc.
1319 Sixth Ave.
Hungtington, West Va. 25701

Dear Dr. Stemmerman:

Thank you for the urine samples which I received earlier in the week. Unfortunately everything leaked out of the box and we could only manage to retrieve a few lambda: from one of the samples. Meanwhile we are doing some testing with adult urine specimens. If it is not too difficult to get repeat specimens on this child, I would appreciate having them. Perhaps you could send them in a small viaf closed with a screw cap and sealed with parafin.

I realize that you must be busy, but, I am most curious to hear about this second "MSG baby".

If you know the answers to any of the questions to my last letter I would be most appreciative to hear from you on these matters.

As you probably know, I wrote to your brother and he has kindly responded very promptly. Every little bit of information I can get on this matter is very helpful and I appreciate your putting me in contact with him.

Thank you again for your help.

Sincerely, D ()

LRL:a **D .1 e ehrer**

P.S. This letter was typed 1/2 hr. before I received yours of July 28, for which I thank you. I will be waiting for a letter from Mrs. Rhodes.

is easier for you, perhaps, Dr. Stemmermann could send them for you.

I have recently written up my early thoughts on glutamate. If my papers are accepted, they would hopefully be published before the end of the year. I have put you on our mailing list to receive copies. Meanwhile, we are dong a variety of experiments with your sons" urine and if and when we get any interesting information, I will be sure to keep you posted.

I really appreciate your cooperation in this matter.

Sincerely,

L,ci,..e 02(- Lel:u.c

LRL:a
cc: Dr. Sternmermann

Dr. Liane Reif-Lehrer
Asst. Professor

LIANI!, IWIF-LEIJI?ER PhD
Depart,n1e11l of Opl1tbal111ology
llarvard Medical School
and
Departmenl of Co1111ective Tissue Research
Boston Bio1!leclical lfosearch lnslif 1te

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone:• 617 742-6580 x326

August 12, 1975

Mrs. J.E. Rhodes, Jr.
1443 Spring Valley Dr.
Huntington, W. Va. 25704

Dear Mrs. Rhodes:

Thank you very much for your letter of August 6th. The second set of urine samples have arrived intact and we have begun to work on them, but, it will take a while to get some results as it is necessary i:o run numerous control expe: imen:...s.

As Dr. Stemmermann may haye told you, I have become extremely interested in the possibility that MSG, which is probably not harmfql to most people, might possibl2 be ill advised for some people who for one reason or another have altered states of metabolism. Since my primary area of researcn has been retinal biochemistry, I am quite new to this field but have become thoroughly fascinated with it in the last year. Your son may possibly provide the missin<J clue in my thoughts on this subjecL, so, I hope you clo not mind my asking you a few additional questions:

Has Dr. Stemmermann observed the "shivers" your son gets after eating glutamate? Does he get these "shivers" every time he eats something with glutamate? Do you have any idea of the glutamate content of the foods that set off the "shivers". You mention that your son has been on chMSG-free diet for 2 months with no more ▪ shivers". Did he experience any "shivers" after eating the bacon mentioned on the urine samples? Do you know how long after the breakfast the "after" urine was obtained. Also, how much bacon did he eat? Do you know the brand?

You mention that at age 21 you had nigl1t blindness. Were you treated? What was the diagnosis, what was the treatment? Do you still have this condition?

Did your father ever get ''shiver" attacks as an adult? Do you know of any diseases in your, or your husbands family, of any kind; for example, diabetes

What is your childs' height and weight. Is anybody in your family overweight? (including parents, grandparents, brothers & sisters). Is there anyone at all in your family, or in your husbands family who is retarded. \vould it be possible £or you to send us a sample of your urine taken in the morning before eating and then 3 samples taken by you 20 minutes, 1 hour, and 3 hours after eating some glutamate-containing food. The sample should be frozen until mailing and should be sent airmail special delivery. We would be happy to pay the charge. If it

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and
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August 14, 1975

Dr. M. G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Hungtington, West Va. 25701

Dear Dr. Stemmermann:

Thank you very much for the repeat urine samples from John Rhodes which arrived intact.

We have some preliminary interesting patterns on thi (Tt_C) layer plates, but I really have to do many more controls before I can make any interpretation.

We are collecting before and after meal urine samples from people around the lab to try to standardize our TLC procedure.

My impression from the first run (which could of course be incorrect) is that there are strong s ots in the fter eating urine (but not in the"before eating 'urine) which seemed to run with the same Rf value as our glutamate standard.

I have gotten a letter from Mrs. Rhodes and have written to ask her some more questions, and asked her if she could provide urine samples. She tells me that both she and her father had shiver attacks as children.

Is there any possibility of tracking down the earlier MSG child.

I got a call today from a friend of yours named Ellen Grass. Perhaps we will get to meet sometime.

Thanks again for your continued interest in this matter.

Sincerely yours,

liane R-L

LRL:a

Dr. Liane Reif-Lehrer

August
August 24, 1975

Liane Reif-Lehrer, Ph.D.
20 Staniford Street
Boston, Mass. 02114

Dear Dr. Reif-Lehrer:

I have read your papers with great interest and jotted down the enclosed comments as I went along.

Your experience with a disappearing glutmate spot is not unique, especially when dealing with urine several weeks old, untrozen, or untrozen and refrozen several times. A urinary amino acid must be present in very large amounts to withstand such treatment.

Dr. Shih's findings a glycine "spot" in Mrs. Hager's urine is indeed intriguing. If the report were not from Shih's laboratory, I'd wonder if glycine had not been mistaken for glutamate, since the Rf is similar. However, now I will have to determine if Mrs. Hager is a non-Ketotic or benign familial heteroglycinuria. This requires an amino acid analyzer--a lot more difficult to find than the blood sample needed.

Sincerely yours,

M. G. Sturmann, M.D.

Enclosure

August 21, 197[illegible]

Lian Reif-Hehrer PhD
20 Staniford Street
Boston, Mass. 02114

Dear Dr. Reif-Hehrer,

You will be receiving two urine specimens, before and three hours after an MSG meal on a six year old, Glen Hage[illegible]. History of "shivers" was elicited only after questioning, probably because increase in hyperactivity and "meanness" were [illegible] more spectacular. This was brought to my attention during his first two neurological work-ups, ten days apart. On one his behaviour was not unusual for a six year old; on the second he was impossible and I learned he had had sausage for breakfast. No "shivers" at either time. His mother says they occur approximately one hour after a meal and last one hour. I will be sending you a complete report, after I see the boy again this week.

I do wish I could track down Denise Dailey for us both. The family left West Virginia one step ahead of the sheriff, with innumerable debts. Even the mother's best friend doesn't know where they are -- or does't choose to tell.

I will keep in touch and will send urines on other suspects from time to time -- until you tell me to cease and desist.

Sincerely yours,

M. G. Stemmermann, M.D.

MGS/na

Shuddering in children: portent of tremors to come?

For first time, familial relationship is traced

Attacks of shuddering seen in some young children are an early manifestation of essential tremor, says Dr. Michel Vanasse, resident in neurology at McGill University and the Montreal Neurological Hospital and Institute. In support of this contention, he offers his study of five pediatric patients whom he and his coworkers—Drs. Paul Bédard and Frederick Andermann—investigated in some detail.

Characteristically, the posture of these children when undergoing a shuddering episode consists of flexion of the head, elbows, trunk, and knees, as well as adduction of the elbows and knees. Sometimes head-turning, extension of the arms, elevation of one arm, and sympathetic changes are involved. The attacks tend to be brief, and their frequency variable; occasionally they may occur more than 100 times a day.

In describing these episodes, parents use expressions such as "it's as if water was poured down his back" and "as if he had gone out into the cold." Dr. Vanasse has his own graphic description: "The attacks are similar to what one might do when needing to void but unable to do so for lack of suitable facilities."

Of the five patients studied, three began to have attacks of stiffening when they were five to six months old, but these were not clearly recognizable as shuddering attacks until the children started to walk. Two patients didn't have any attacks—or at least were not observed to have any—until three and 3½ years of age, respectively. Precipitation of these episodes was usually associated with excitement, but they could also be brought on by fear, anger, frustration, embarrassment, or the need to move the bowels or void. In all cases, neurologic examination revealed no abnormality.

Dr. Vanasse notes that the incidence of associated ties in his small series was high. Two children clearly demonstrated sniffing, nodding, and throat-clearing ties. Two others had a less specific history of ties. "The reason for this association remains unexplained," he says.

All five children had tremor with the characteristics of essential or familial tremor. In two of them it was mild, but in the other three it was "rather marked." Usually the parents weren't aware of the presence of tremor until it was pointed out by them.

The course of the shuddering attacks is a benign one. Some patients go through a quite severe stage, as did one little boy who began having attacks of shuddering when he was 3½. He often had many attacks a day, but each would usually last only two or three seconds. At other times, however, they would be almost continuous over a period of hours. Mostly, he stopped eating or walking when a shuddering attack occurred, and sometimes fell if he was skating. But he gradually improved, and by the time he was five he had these episodes only rarely.

In four of the five cases in this series, a family history was available, and in all four the Montreal investigators found a parent with essential tremor. In three cases, the affected parents had older relatives with more severe tremor.

The father of the five-year-old, for example, has a mild essential tremor, and there are several other affected family members, including the father's brother, who is a successful banker. The uncle's tremor is reported to be so pronounced that when he's at a cocktail party and is offered a drink his wife has to lift the glass off the tray for him.

Commenting on the Canadian study, Dr. Sidney Carter, Dwight D. Eisenhower United Cerebral Palsy Professor of Neurology at Columbia University College of Physicians and Surgeons, declares that while he and many other neurologists as well as pediatricians have seen shuddering episodes in infants and children, neither he nor any of his colleagues with whom he had discussed the subject have noted a relationship between these episodes and essential tremor. Nor has he been able to find any cases in the literature.

Dr. Carter also was unable to find any clear-cut references, although he recalled back to the 19th century. He suspects that cases of shuddering attacks and an older essential tremor haven't been noted before simply because the relationship has not been looked for. "The tremor can be quite subtle," he told MWN, "and could easily go unnoticed."

One new development tends to support the "seek-and-ye-shall-find" concept just within the past few weeks, Dr. Vanasse's co-author, Dr. Andermann, has seen a sixth patient in this category at Montreal Children's Hospital. And again Dr. Andermann has been able to trace a family history of tremor. ■

Dr. Vanasse

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and
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August 29, 1975

Dr. M. G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Thank you for your letter of August 21. We received the urine specimens of Glen Hager and have just run them on TLC plates. Once again there seem to be appreciably larger glutamate spots in the after meal sample. Right now things are slowed because I am, at least officially, supposed to be on va*ion, and one of my assistants is also out. We really must get some control urine from children (as opposed to adults) before and after eating glutamate. Does either (ID Hager or the Rhodes child have a sibling who could provide such specimens.

We have also run the Rhodes childs urine on a amino acid analyzer. I have not yet seen the results, but the laboratory that did the work for me said there is some problem of dilution and that the data are confusing.

I am sorry we cannot track down Denise Dailey, but sometime next month I will be going around to try to see if I could find some additional cases here in the Boston area. I have just started checking into which people I could go to see to get such information.

Please do keep in touch and send urines on other suspects. I will not tell you to "cease and desist" since I really find this topic most fascinating.

Perhaps this is slightly premature, but I have been wondering whether you might be interested in co-authoring a research paper with me for something like Archives of Medicine or perhaps even the NEJ e&. describing these 3 cases------ and perhaps even asking other people to notify us of similar children. I would be happy to write the paper and send it to you for approval when the time is ripe. I suspect that this might be in the very late Fall since I am currently up to my ears in other projects. Please let me know your thoughts on this matter.

Sincerely,

Liane Reif

LRL:a

Dr. Liane Reif-Lehrer

P.S. We have had no response from Mrs. Rhodes in answer to my last letter. There is really no hurry but perhaps if you had a minute you could check to see if she got my letter. Thank you.

LIANE REIF-LEHRER *PhD*
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Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

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Sept. 11, 1975

Dr. Michel Vanasse
McGill University and
Montreal Neurological Hospital and Institute
Montreal, Canada

Dear Dr. Vanasse:

I have recently become interested in the effects of glutamate ingestion on humans. Through the kind courtesy of Dr. M.G. Stemmermann of Owen Clinic Institute, Huntington, West Va., and some investigation on my own, we now have accumulated three children with shuddering and one child with migraine-like syndrome (seizure equivalent). In these four children, symptoms were abolished by removal of added glutamate (MSG) from the diet. The cases described in connection with your work in the August 25th Medical World News of this year sound very similar to our cases. I have spoken to Dr. Stemmermann and we both wonder whether at least some of the cases that you see might not be also correctable by removal of excess glutamate from the diet.

I have two papers in press and one in manuscript with Dr. Stemmermann on this subject and will be happy to send them to you as soon as they are published. Meanwhile Dr. Stemmermann and I felt it important to call to your attention our thoughts on this matter in case this information might be helpful to you.

In reply to another comment in the MWN article about finding references to shuddering attacks in the earlier literature, I suspect th.at some of these symptoms may not have existed prior to th current increasing use of MSG as a food additive and condiment used in cooking. Glutamate as a condiment was not commercially available until after 1910. Since then, its manufacture and use has increased to the point where world production is 262,000 metric tons per year (1973). Average estimated per capita consumption in 1973 was 0.3 gm per day. Published measurements in the literature indicate that it is not unlikely for someone to consume more than 4 gram (not mg) at a single meal in some eating establishments. As you undoubtedly know, glutamate has been well established as a neuroexcitatory amino acid; moreover, an appreciable number of adults (25% according to our recent study) have at least some adverse reaction to ingestion of the quantities of this material used in many oriental restaurants. Our study indicates that the prevalence and symptoms are similar in a random grouping of young children.

I **would** very much appreciate your letting me know if any of your children respond to the restriction of their diet to foods which do not contain added glutamate.

Dr. Stemmermann and I feel that it is important to make pediatricians aware of the possibility that seizure attacks, in at least some children, may be caused by added glutamate.

Apropo of Dr. Andermann being able to trace a family history of tremors, we are currently in the midst of a study involving 5000 twins to try to determine whether the more general phenomenon of adult adverse reactions to glutamate ingestion is hereditary.

I look forward to hearing from you about this matter. Please do not hesitate to call me at the above number if you wish to discuss this further.

LRL:a
cc: Dr. Andermann
Dr. Sidney Carter
Dr. M.G. Stemmermann

Liane Reif-Lehrer, Ph.D.
Asst. Prof. of Biochemical Ophth.
Dept. of Ophthalmology
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September 11, 1975

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Hungtington, West Va. 25701

Dear Dr. Stemmermann:

Enclosed are copies of the letter we talked about. I decided that I would feel better if you saw them before they went out. If you approve, please sign them and return, and I will take care of sending them out. If there is anything that you would like to change, please feel free to do so. We will retype them and I won't feel so bad about signing your name once I know you have seen them.

I am also halfway finished writing up something for the New England Journal.

Dr. Jean Mayer of the Harvard School of Public Health has kindly offered to send a covering letter with that one as he is apparently quite friendly with the editor and he also feels that this is an important matter.

Trust I will hear from you shortly. Again, please feel free to make any changes you like.

Sincerely,

Dr. Liane Reif-Lehrer

LRL:a
enc.

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Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

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20 Staniford Street
Boston, Massachusetts ***02114***

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Sept. 11, 1975

Howard Cohn,
Editor
Medical World News
McGraw·-Hill
1221 Avenue of the Americas
New York, N. Y. 10020

Dear Mr. Cohn:

We hope you will publish the enclosed letter to the editor at your earliest convenience. We feel there is good reason to believe that at least a small number of children who have shudders and who are subjected to lengthened, expensive ahd time consuming neurological tests, may simply be exhibiting intolerance to the high levels of monosodium glutamte found in commercially prepared foods to which it is added as a "flavor enhancer". Two manuscripts on this subject have been submitted for publication and a third is in preparation; however, we feel that it is important for the medical community, and pediatricians in particular, to be aware of this possibility. This could save much worry and expense on the part of those who may fall into this catagory.

Thank you.

Sincerely yours,

Liane Reif-Lehrer, Ph.D.
Asst. Prof. of Biochemical Ophth.
Dept. of Ophthalmology
Harvard Medical School and
Staff Scientist, Dept. of
Connective Tissue Research
Boston Biomedical Research Inst.

and

M.G. Stemmermann, M.D.
Neurologist
Neurology Dept.
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

To the Editor;

MEDICAL WORLD NEWS

We were most interested in an article concerning shuddering in children which appeared in Medical World News August 25.

We have been interested in the general effects of glutamate ingestion on humans both with regard to the so-called "Chinese Restaurant Syndrome" and more particularly with respect to its possible effects on some children. We have case histories on 3 children who presented with "shudders" -which appear to be correlated with eating foods containing added monosodium glutamate (MSG). The best documented of these is a child who is normal in all other respects. This child was begun on adult foods at 6 months and seiz res began at this time. Seizures continued despite treatment with anti-epileptic drugs, but stopped when all foods containing added MSG were eliminated from the diet. Between the ages of 13 and 29 months seizures were observed on only 3 occasiqns; in each case after ingestion of foods with added MSG. The last of these incidents involved a deliberate trial with commercial spaghettisauce containing MSG. In the 6 months subsequent to the trial feeding, the child was kept on the diet, free of added MSG and no further attacks were observed.

A second child is 16 months old, retarded, and is reported to have 2 or 3 episodes of "shivers" shortly after eating foods containing added MSG. No shivers have been observed *in* the 2 months since the child was put on a diet free of added MSG.

The third child *is* 7 years old and has minimal brain dysfunction with mild signs of neurological impairment on one side. This child is also reported to have "shivers" after eating foods with added MSG.

A fourth child has recently come to our attention who may have a related problem. This 14 year old boy began to have episodes of very intense headaches and severe vomiting t age 10. This child has an abnormal EEG but is normal and healthy in every other way. The pediatrician described the childs condition as "migraine-like syndrome or seizure equivalent". In this case, which is less well documented than the others, the child appears to respond to MSG only in the presence of tomato products (he has no reaction to tomato products which do not have added MSG). The reaction begins about 20 minutes after eating, which is typical of reaction to MSG.

We wonder whether at least ome of the cases described by Dr. Vannasse and Andermann may be of a similar nature. It would seem very important to us that children presenting with shuddering, or headaches, especially if they have normal EEGs, should be tested on a diet restricted with respect to added glutamate.

We are continuing to pursue our studies of this phenomenon and would appreciate hearing from any physicians who may have information to contribute.

Liane Reif-Lehrer, Ph.D.
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Dept. of Ophthalmology
Harvard Medical School and
Staff Scientist, Dept. of
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Boston Biomedical Research Institute
20 Staniford St., Boston, Ma.02114

and

M.G. Stemmermann, M.D.
Neurologist
Neurology Dept.
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Septembsr 15, 1975

Liane Reif-Lehrer, Ph.D.
20·Stalnfo:rd Street
Boston, Massachusetts 02114

Dear Dr. Reif-LaJlrer:

Please rind the following enclosures: 1. Letter from Mrs. Dailey ror human interest (sorry the copy is so poor). 2. List *ot* changes £or your letter to World Hews. I have received recent data on the Dailey childT 3. $Igned letter to World News.

Good Luck!

Sincerely yours,

M. O. Stemroermann, M.D.

CHANGES SUGGESTED

Paragraph 2. Change "seizures" to "shudder attacks." Otherwise, it might be assumed we are rererring to bona ride epileptic seizures.

Paragraph 2. Le.st sentence "6 months" change to three yes.rs (sept., 1972-Sept., 1975). Add this sentence: "The child has received no anti-epileptic drugs tor 3½ years."

My orficial title is Medical Director, **Owen** Clinic Institute--not that it matters.

LIANE REIF-LEIIRER PhD
Department of Ophthalmology
Harvard .Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

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Dr. Jean Mayer
Harvard School of Public Health
677 Huntington Avenue
Boston, Ma. 02115

Sept. 17, 1975

Dear Dr. Mayer,

Enclosed is a copy of the manuscript which I have submitted to Dr. Ingelfinger for publication in the New England Jourrial of Medicine. If you find the manuscript suitable, I would like to take you up on your kind offer to write a letter of support to Dr. Ingelfinger pointing out the importance of getting this information to pediatricians as soon as possible. I have sent him the enclosed article from MWN. Both Dr. Stemrnerman and I think that at least some of those children may be "MSG cases". Moreover, Dr. Stemmerman says that the family of one of those children was subjected to great financial stress due to all the neurological testing, before the child came to her and was finally successfully treated by elimination of excess MSG from the diet. Obviously one would like to avoid this kind of thing and it would be easy enough to do a brief diet restriction test on children with shudders (especially if they have normal EEG's and the type of "seizures" or "'shudders" in which the child remains alert.) before subjecting them to more elaborate testing. This is why, although the data are preliminary, we feel it is important to publish on these cases. Also we hope in this way to get information on other cases around the country - to supplement what I hope to find when I start searching in the Boston area.

Thanks very much for your help.

Sincerely Yours,

L1

LRL:fg

Dr. Liane Reif-Lehrer

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
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Dr. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Sept. 17, 1975

Dear Dr. Stemmerman,

Enclosed is a copy of the manuscript which I have submitted to New England Journal of Medicine. Dr. Jean Mayer of the Harvard School of Public Health, is very interested in this problem as well, and since he is friends with Dr. Ingelfinger, the editor of New England Journal of Medicine, he very kindly offered to write a letter of support. If you have any changes or additions you would like to suggest, please do so and I will make the changes.

I know about Vivian Shih primarily from reading about Hartnups disease. In addition, Dr. Erbe, whom I went to see about advice concerning the twins study (which is now off the ground), also suggested I go talk to her - to date, I've called several times but have not been successful in reaching her. She is supposed to be calling me back this week.

Neither of my 2 control children (my own kids, who have no adverse reactions to MSG) show the intensified glutamate spots on TLC in the "after" (c.f., to "before") urine as we have seen in the case of both Rhodes and Hagelr. The latter samples have also now been run on an amino aicd analyzer and those results are confusing. They will do the controls before long I hope. Perhaps Dr. Shih can enlighten me on this if we make contact.

9/17 Dr. Shih has just called and said she will do some an ses on the urines - I'm bringing her the samples this afternoon - will let you know what happens.

What are the chances of getting before and after meal **urinfs** on l(hodes and Hage.r with ~~a-HI.cal~~ **with** a control meal known to contain no added glutamate to use as controls for what we see with the glutamate meals.?

Sincerely,

Liane Reif-Lehrer

Dr. Liane Reif-Lehrer

LRL:fg

September 18, 1975

Dr. Franz Ingelfinger
Editor
New England Journal of Medicine
10 Shattuck St.
Boston, Mass. 02115

Dear Dr. Ingelfinger:

Enclosed is a short manuscript concerning unpleasant effects which added Monosodium Glutamate in the diet seems to have on a few children. Although we are planning to do much further work on this topic and especially to look for many more cases, the enclosed article which appeared recently in Medical World News made us decide that it would be appropriate to submit a short communication at this time. Dr. Stemmermann in particular was concerned about the fact that in the best documented of the cases that we have (Case 1), a severe financial strain was put on the childs family because of the complete neurological work-up that was done on the child before Dr. Stemmermann saw the child and came up with the idea of the diet restriction, which solved the problem. Both Dr. Stemmerrnann and I think that it is quite likely that at least some of the cases from Dr. Vanasse practice discussed in the MWN article may possibly fall into this category, and we feel strongly that pediatricians should be made aware of this possibility. We have written a short letter to the editor of Medical World News, and, we hope that you will find this matter of sufficient interest and importance to publish the enclosed manuscript either as a short communication or a le'.::terto the editor.

Dr. Jean Mayer is quite interested in these results and has encouraged us to submit this manuscript. He has also kindly offered to write you a letter in our behalf which I trust you will receive shortly.

I hope that you will find the manuscript acceptable for publication in the New England Journal of Medicine. Thank you.

Sincerely,

L ,/ui (. vz, Q,)

LRL:a
enc.

Liane Reif-Lehrer, Ph.D.
Asst. Professor

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Sept. 22, 1975

Dr. M.G. Sternmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Sternmermann:

The letter to NEJ has been corrected and mailed out. We have not yet received the Vanesse letter but I will mail that out as soon as I get it.

Thank you for the case history on the Hager child. Actually you sent me a copy before but I was pleased to see your note on 9-16 about the normal EEG.

I was most interested to read the letter from Mrs. Dailey. Thank you for allowing me to send it out to Science, etc.

Look forward to getting the urine samples and further information on the Dailey family history.

Sincerely,

l,a Reif

LRL:a

The New England Journal of Medicine

10 SHATTUCK STREET, BOSTON, MASSACHUSETTS 02115-TELEPHONE 617 /734-9800

OFFICIAL PUBLICATION OF THE MASSACHUSETTS MEDICAL SOCIETY

OFFICE OF THE EDITOR

September 22, 1975

Liane Reif-Lehrer, Ph.D.
Assistant Professor
Department of Ophthalmology
Harvard Medical School and
Department of Connective Tissue
Research
20 Staniford Street
Boston, MA 02114

SEP 23 1975

Dear Dr. Reif-Lehrer,

Thank you for sending to the Journal, "Monosodium Glutamate Intolerance in Children. II This cormnunication !!light indeed be appropriate to the editor, but Letters to the Editor, if you will note from the enclosed copy of instructions, are limited to 1 1/2 pages, typed double-space.

I believe you can tell your message within this length, particularly if you lessen the length of the Case Reports, and also eliminate some of the references. Ideally, a letter should have no more than ten references.

May I also suggest that you change the references to include the first reports of the syndrome, at least under the name "Chinese Restaurant Syndrome." These reports appear as Letters to the Editor in the New England Journal of Medicine and should certainly be cited. They should also encourage you to submit this material as a Letter to the Editor, for it shows how influential even a Letter to the Editor may be.

Sincerely you[, ,//

Franz J. IngeilJ Y.

FJI/dsb
Enclosure

[illegible] Dr. Liane Reif-Lehrer, Harvard Medical School & [illegible] August 1975

A. Name ____________ Date of birth _______ Place of birth ________

Address ____

B. Name & address of your twin ______________________________

C. Mother's name: ____________________ Father's name: ____________________

J. Are you fraternal ______ or identical ____ twins?

2. Is your twin male ____ or female ______?

3. Age range: below 19___; 19-25___; 25-30___; 31-40___; 41-50___; 51-60___; over 60___.

4. Your sex: male______ female______

5. Do you eat in Chinese Restaurants (either at the restaurant or take-out to eat at home)?

never____; sometimes ____; often (once a week or more) ______.

6. [illegible] home, [illegible] ye[illegible]___ [illegible]___

7. Do you use any of the items below [illegible] cooking [illegible]
a) soy sauce..cooking___; [illegible]___; don't use___.
b) "Accent", MSG [illegible] ....cooking___; [illegible]___; don't use___.
c) Lawry's seasoned salt..........................cooking___; [illegible]___; don't use___.
d) commercially prepared foods [illegible]: yes______; no______; don't [illegible] commercially prepared foods______; use commercially prepared foods [illegible] if they contain MSG______.

8. If you eat Chinese Restaurant food (either in restaurant or "take-out") do you have [illegible] soup at the start of the meal? never___; sometimes___; always___; don't eat Chinese Restaurant food___.

9. If you eat Chinese Restaurant food (either in restaurant or "take-out"), do you have an alcoholic beverage with the meal? never___; sometimes___; always___; don't eat Chinese Restaurant food___. If you checked "sometimes" or "always" [illegible] or less___ [illegible] three drinks or more___?

10. If you do not eat Chinese Restaurant food, is it because you: don't like it___; get Chinese Restaurant Syndrome___; makes you sick (describe)__; food allergy (describe)___; religious reasons___; financial reasons___; other (please explain)__.

11. Do you know what Chinese Restaurant Syndrome is? yes___; no___; have heard of it but don't know what it is___.

12. [illegible] it [illegible] don't [illegible] it [illegible] get it [illegible]

13. [illegible] below [illegible] eat Chinese [illegible] restaurant or "take-out" (check "yes" or "no" [illegible] "quite uncomfortable").

				quite
	[illegible]	[illegible]	not bothered	uncomfortable
1. headache ([illegible])				
2. tight [illegible] around [illegible]				
3. [illegible] around [illegible]				
4. [illegible]				
5. [illegible]				
6. [illegible] back and back of [illegible]				
7. [illegible]				
8. [illegible]				
9. [illegible]				
10. sleepy, [illegible]				
11. [illegible] dizzy				
12. increased [illegible]				
13. [illegible]				
14. [illegible]				
15. [illegible]				
16. stomach cramps				
17. any ocular (eye) symptoms (please describe)				
18. [illegible]				
19. chills				
20. other (please describe)				

PLEASE CONTINUE ON REVERSE SIDE.
YOU MAY USE ADDITIONAL SHEETS FOR DESCRIPTIONS, IF NECESSARY.
PLEASE CUT OUT LABEL AT RIGHT AND USE AS ADDRESS LABEL TO RETURN QUESTIONNAIRE.

Dr. Liane Reif-Lehrer
Dept. of Ophthalmology
Harvard Medical School
and
Boston Biomedical Research [illegible]
20 Staniford St.
Boston, Mass. 02114

ANSHER nm QUES'IONS BELO\~/ ONLY IF YOU CHECKED "YES" 1011 AT LEAST ONE SYMPTOM IN QUES'flON 13.

l4o If you get symptrnns, do you get them: always e;et symptJms jn Chinese restaurants___; only in some restaurants __; ouly cometimes, even in the same restaurant ; get symptoms even from the s1naller arnounts of MSG used in packaged foods__. (Check asinany as apply)

150 How long after you begin eating do the symptoms first appear?_____

16 o llow long do the G;)%ptoms last?_____

	yes	no	I clon't know
lT. D:id you get these sym1itoms as a chHd?_____			
18. Were the symptoms 1-10rst when you were a chUd?_____			
19, Hei·e the syrnpto,us less severe 1411En you were a cl1ild?_____			
200 Here the symptoms alJout the sa111e when you 1-1ere / chi.ld?_____			
21. DoLG (did) your *wot*her get. syrnptoms?_____			
22. Docs (di.d) your fathlr get symptoms"?_____			
23. DoeG your t,,in get any syrnpto:ns?_____			
2J+. Do any other of y(iur hrotherc. an'1/or slsters [;et any sy1nptou1G?_____			
2;,. Do (did) any 01' ydLLr c;ranclpurents r•,et any syrnpto:us?_____			
26. TJo ,ll1y of ;rour cl liu..reu r:ct 1ny Gymptoms?_____			

2·7. Hm· maJ1y brotherr; and/or sisterr.; do you l1ave beside·. your "t11in?_____
(Gjvc sexe5 and ages)

28. Ilow 11Jany chilclr·e1, do yoll have?_____
(Give sexes and agc-s)

29. If your answer to quost:ious 24, 25, or 26 was "yo"", :indicate which relatives 13et the syl!!ptorr.s by giving the.Le sex cnd age_____

USE SEPARJ\'i.E S!IBETS OF PMER, IF NECESSARY.

1HAN'K YOU VERY MUCH FOH YOUR TU1E AND EFFORT. YOUR ANSWERS WILL BE USED TO DETERMINE, AMONG OTIIEn 'I'HINGS, WEEITHER OR NOr ADVERSE REACTIONS TO EA'.I'ING MSG ARE HEREDI'rARY.

-MSG- QUESTIONI AIRE . - DR. LIANE. RE-IF--LEHRER HARVARD MEDICAL SCHOOL 1975

NAME (optional) _____ **AGE** _____ **SEX** JI F

	Yes	No	I don't know
I Do you consume monosodium glutamate (MSG J\CCENT) in any form:			
1. Chinese food			
2. Japanese food			
3. Soy Sauce			
4. in commercially prepared foods			
5. as an additive when you cook			
6. other (please describe)			
II If you eat Chine e food: a. is it 1. at home?			
2. in restaurants?			
b. How often (ci;cle best answer): 1-:-a few times a -);ear- 2. once a month 3. twice a month 4. once a week 5. more than once a week			
c. Do you usually have soup first?			
d. If yes, is it usually clear soup (e.g.wonton soup?)			
e. Do you usually have an alcoholic beverage before the-- - meal? If yes, how many?			
III If you don't eat Chinese food, is it because ·(circle best answer): 1.you don't like it 2. you get Chi·nese Restaurant Syndrome 3. it makes you sick in other ways 4. religious reasons 5. other (please explain)			
IV Do you know what "Chinese Restaurant Syndrome" is?			
V Do you think you get "Chinese Restaurant Syndrome"?			
VI If yes, do you get it (circle best answer): 1. everytime you eat in a Chinese Restaurant 2. only sometimes 3. only in some restaurants			
VII a. If you get Chinese Restaurant Syndrome, how long after you begin eating do the symptoms begin: (circle best answer) 1. during the meal 2. 1/2 hour after the meal 3. several hours after the·meal 4. that night 5. next day			
b. How long do the symptoms last? (circle best answer) 1. 1/2 hour 2. 3 to **4** hours 3. one day 4. other (specify)			
VIII Do you get any symptoms or discomforts at all after you eat Chinese food? If yes, circle symptoms you get: [For each symptom you circle, check ·(in columns at right) whether you are (1) aware of it but not bothered **(2)** quite uncomfortable]			

	(1)	(2)
1. headache		
2. burning sensation in upper torso		
3. tight feeling around face		
4. tight feeling around chest		
5. any ocular (eye) symptoms (describe)		
6. sneezing		
7. diarrhea		
8. **dizzinesS**		
9. nausea		
10. vomiting		
11. stomach cramps		
12. chills		
13. other (please describe)		

	Yes	No	?
IX Does anyone else in your family get Chinese Restaurant Syndrome? If yes, please circle:- 1-:-Sililing-2;-Parent -3.Child- 4. Grandparent 5. Spouse			
X If you get Chinese Restaurant Syndrome: **a.** did you eat chinese food as a child?			
b. If yes, did you get it as a child?			
c. If yes, was it 1. worse 2. the same or 3. not as bad when you were a child compared to now. (please circle)			

Xl Please add any comments or pertinent information that you might have. (Ose reverse side)

September 22, 1975

Liane Heit-Lehrer, Ph.D.
20 Staniford Street
Boston, Massachusetts 02114

Dear Dr. Reif.tehrer:

Your paper is excellent. I would not think ot caanging or inserting a word. It 1s autticiently succi-t that busy pediatricians should be able to get the point in five minutes or las. I •aa also inteNated in the bibliography, tor some reterenoea had escaped me, #3, tor example.

I am enclosing a study pJtOgram that I had planned tor last year •Id couldn't get ott the ground. Thia deals with 30+ retarded children in residence in a treatment center tor whom I am the consultant. Being a captive population, it is much easier to control diet than with out patients. Unfortunately, the retardation intJtOduoea anM,her variable--signiticant in that some children are lmown to have metabolic disorders and others may be undetected.

I can get control urines on Hager but probably not Rhodes. The latter is just too ditticult (outside a hospital) and tor every successful collection tb.ai,e are two spills.

Many thanks.

Sincerely yours,

M. G. Stemmermann, M.D.

P.S. How about one ot the Pediatric Journals(? Diseases ot children) it the Nev England Journal isn't interested.

Just got a telephone call from the Dailey'•• You will be receiving urines (4 control+ MSG).

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Str_eet
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September 23, 1975

Dr. Franz J. tngelfinger
Editor
The New England Journal of Medicine
10 Shattuck St.
Boston, Mass. 02115

Dear Dr. lngelf inger:

Enclosed please find our manuscript entitled "Monosodium Glutamate Intolerance in Children" revised according to your suggestion in your letter of the 22nd and our phone conversation this morning.

I called Medical World News right after I spoke to you and the letter I sent to them has not even arrived there yet. The secretary promised to return it to me without even opening the envelope, as soon as it arrives. I hope this now clears the way for publishing the enclosed revised letter in the New England Journal of Medicine.

I'm sorry about the misunderstanding. Perhaps the enclosed letter will explain my desire to disseminate this information.

Sincerely yours,

Liane Reif-Lehrer.

LRL:a

Dr. Liane Reif-Lehrer
Asst. Professor

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and
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September 23, 1975

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Stemmermann:

I'm sure you have already thought of this; however, my overactive conscience together with my lack of experience with patients makes me want to say it anyway: If Mrs. Dailey is goint to test Denise with a glutamate feeding, does she need to be cautioned to perhaps have a physician standing by. I have never seen anyone seizure - or even shudder, but I have been told it is quite alarming. Also, could Mrs. Dailey keep track of how much of what she giv Denise (Brand name, etc) and the time of eating and of collection of urine specimen.

We are most anxious to get the samples. Thanks for arranging it all.

Sincerely,

Liane Reif

LRL:a

P.S. Just got the enclosed letter from NEJ. They will only publish if we do not also send a letter to Medical World News - so I have asked MWN to return that. Enclosed is a copy of the revised letter for NEJ.

September 29, 1975

Liane Rei •Lehrer, Ph.D.
20 Staniford 3tNet
Boston, Mass. 02114

Dear D:r. Rait-Lelll'&r:

Enclosed ia all the data I have oneDeniae Dailey. Mra. Dailey will be writing to 7ou. She is a good observer and will e happy to anawer any questions you may have.

Please dot to worry about MSG SEIZURE-induoed. This child has never had a "seizure", only shuddrs. Even the six I observed within 15-20 mia.utes were innocuous. At no time was she ever "limp", cyanotic, e.pneio o:r show an,: other gruesome signs Jte• quiring susitation. Long te:r:naffects on hypothalamus(? retina) ara possible but at themoment this question is unanswerable. Inoidentally, M:s. Daiby has continued yearly (swnmor.) trials. She thinks, perhapa, attacks were fewer this past summe:r, but ag:rees they may be dose related.

I am planning a trip to N.Y.C. the first week in De ember forme•tings *ot* tho Association for Research Or Nervous and Mental Disorders. God willing and the cricks don•t rise.

Sincerely yours,

M. 0. SteJ!llll9mann, MD •

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
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20 Staniford Street
Boston, Massachusetts 02114

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September 29, 1975

Dr. M.G. Stemmermann
Own Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Thank you for your letter of the 22nd with all the enclosures. I am very interested in your proposed study program. From your outline I have a few suggestions to make which you may have already thought of.

1. What do you plan to use for the measured dose of MSG.
2. It is important that the soup be clear broth and should be eaten first in the meal for the most interesting test.
3. Very important that diets of phase 1 and phase 2 be identical day for day down to the last detail. This is especially important because of Dr. Feingolds possible findings of a relationship between food colors and hyperactivity. It is also important because of the increasing literature on the effects of indoleamine and tyramine content in food with respect to migraines and possibly with respect to behaviour. Foods that are particularly suspect in this area would be milk products, especially certain chesses, fish, and chocolate.
4. Also very important to keep track of whether any of the children are taking any other drugs.
5. If possible, urine should be collected before and after the meal keeping track of the times of the urine collection, time meal was begun and time meal was ended.
6. Cola beverages have a high content of caffeine and would be best avoided completely. Could ginger ale, juice, or something else be substituted?
7. Is there a realistic way in this situation to make diets the first week completely identical to those of the second week with the exception of the MSG content.

I am up to my ears in paper work. Have just sent off a grant today and I am in the process of writing another one. Worst bog-down is all the Human Studies Permission committees that I have to get even for using urine samples collected by you or anybody else. Received the Hager urines today and will run them as soon as possible.

Hope to see Vivian Shih this week again to see results that she got on Hager urine.

Look forward to getting the samples from Dailey. I am so glad you found her.

Sincerely,

Liane Reif

LRL:a

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and
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October 2, 1975

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Thank you for all the data on Denise Dailey. I would like to just clarify your comment about the fact that Mrs. Dailey has continued yearly trials (summer). Do I gather correctly that Denise has had no seizures except after eating MSG and that she has had seizures each summer after being given the trial MSG. I am also somewhat confused about some of Mrs. Daileys notes according to which the child in some cases seems to have seizures after a breakfast documented as egg.J"biscuits,-with no indication of any MSG containing food until dinner. For example, the notation for the Friday on which the child was reported to have 26 seizures.

Since you will be in New York in December and since we have corresponded so much, I wonder whether you might consider coming up to Boston. It would be fun to get together and really talk about this whole business as well as just meeting each other. I wish I could offer to meet you in New York, but between work and my small children, who I don't like to leave, it is very difficult for me to get away.

I look forward to hearing from Mrs. Dailey. Thank you for all the documents.

Sincerely,

Jr pr/)

LRL:a

LIANE REIF-LEHRER PhD
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10/10/75

Well, I hope this is it —

Best regards,

Liane Reif

The New England Journal of Medicine

10 SHATTUCK STREET. BCSTON, MASSACHUSETTS 02115-TELEPHONE 617 /734-9800

·ocr: o ls7s

CWP'ICI,.L P'UBLIC,.TION ŒW THE MA55,.CHUSETTS MEDICAL SOCIETY

OFFICE OF THE EOITOR

October 9, 1975

Liane Reif-Lehrer, Ph.D.
20 Staniford Street
Boston, MA 02114

Dear Dr. Reif-Lehrer:

Thank you for your Letter to the Editor which, as I told you, the Journal will publish.

However there are a number of problems. You should try to write such letters very carefully if they are to be come part of the scientific literature.

A major error is to include in your cases a patient who has not even been tested yet ("the older child is currently being tested"). You simply cannot do that sort of thing. You have three cases that you can report on.

When you cite **a** certain syndrome, you should give the specific first reference, namely the letter written by **Kwok** in the New England Journal of Medicine 278:796, 1968. I am enclosing an Information Sheet for Authors so that **you** may prepare your references in Journal style. It is customary to check on a journal's style when preparing references.

Another Journal rule is that we do not cite references that the reader cannot find. We therefore will not be able to use your references **4** or **5** unless you can give us a specific journal in which the articles will appear.

I have also taken the liberty of eliminating a few unnecessary words to indicate that things can be said concisely and yet effectively.

I am sorry, but the New England Journal of Medicine does not publish so-callea"°promissory notes"-,-such as are exemplified by your last paragraph.

Self-praise (next to last line in the next to last paragraph) also does not sit too well.

Sincerely your\ /J

Fran0.s. Ingelf ger, M.D.

FJI/cs
Enclosures

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Departm.ent of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:
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October 10, 1975

Franz J. Ingelfinger, M.D., Editor
The New England Journal of Medicine
10 Shattuck Street
Boston, Massachusetts 02115

Dear Doctor Ingelfinger:

Thank you for your letter of October 9 informing me that the Mew England Journal will publish my letter to the editor.

I have revised the letter in accordance with your recommendations. However, both Dr. Stemmermann and I would very much like to include the last sentence if that is acceptable. If not, you may eliminate it without further consulting me.

Although you have mentioned enclosing the New .England Journal "Inform tion Sheet for Authors" in your last two letters, it was not actually enclosed in either letter. Since I do not have access to the New England Journal at our Institute, I took the liberty of preparing the references in accordance with that used in several reprints I have from your Journal. However, I would very much appreciate having a copy of your information sheet for my files if you would be so kind as to send one.

Thank you for your efforts on my behalf.

Sincerely yo ()

L -W

Liane Reif-Lehrer, Ph.D.

LRL/kn
Enclosure

MONOSODIUM GLUTAMATE INTOLERANCE IN CHILDREN

To the Editor: It is established that some adults react adversely to MSG and get "Chinese Restaurant Syndrome" (1-5). We have found that children seem to describe similar symptoms with almost the same degree of prevalence. We would like to describe 3 children who presented with symptoms which led them to be subjected to a variety of neurological tests and who subsequently were relieved of symptoms when exogenous MSG was removed from their diet.

Case 1. A normal child who was begun on adult foods at 6 months began to have "shudder attacks" at about the same time. Attacks continued despite treatment with anti-epileptic drugs, but stopped when all foods containing added MSG were eliminated from the diet. In the 3 years the child has been kept on this diet, no attacks have been observed except during several deliberate trial feedings. No anti-epileptic drugs have been used during this time.

Case 2. A 16 month old retarded child presented with episodes of "shivers" which always seemed to occur shortly after eating foods containing added MSG. No "shivers" have been observed in the 2 months since the child was put on a diet free of added MSG.

Case 3. An otherwise healthy, 14 year old boy with episodes of intense headaches and severe vomiting since age 10 was diagnosed as "migraine-like syndrome or seizure equivalent" (slight EEG abnormality not uncommon in children). Symptoms were traced to MSG, but only in the presence of tomato products.

Shuddering in children has been reported but not clearly explained (6). Some of these cases could be examples of MSG intolerance. The chief difference between epileptic "seizures" and MSG "shivers" is the absence of any sign of loss of consciousness in the latter case. It is interesting in this regard (a) that brain damage to young animals after MSG treatment has been reported in some species and that this damage is apparently confined to the hypothalamus (7,8), (b) that glutamate is a neuroexcitatory amino acid (9), and (c) that MSG has been reported to cause convulsive disorders in animals (10).

The cases reported here may be a severe childhood form of "Chinese Restaurant Syndrome". It is our conjecture that this condition may represent some lesion in either the transport or metabolism of glutamate which is challenged by the concentrations of this flavor enhancer used both in packaged foods and in the restaurant industry.

Although our data are preliminary, we think it important to call these cases of possible MSG intolerance to the attention of physicians. The family of one of the children was caused severe financial burdens from the extensive neurological testing before dietary restriction completely alleviated the symptoms.

We would appreciate hearing from any physicians who may have information to contribute.

Liane Reif-Lehrer, Ph.D. Dept. of Ophthalmology
Harvard Medical School and Dept. of Connective Tissue Res.
Boston Biomedical Research Institute, 20 Staniford St.,
Boston, Mass. 02114

and

M.G. Stemmermann, M.D., Medical Director, Owen Clinic,
Huntington, West Va. 25701

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October 18, 1975

Dr. M. G. Sternmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Sternmermann:

I have just come back from Vivian Shih's lab. They have run all the urines and found no interesting differences in any of the samples, and all samples look normal. The only possible exception seems to be that Mrs. Hager had an unusualljlarge glycine spot but it was increased both in the before and after urine and is therefore not of interest to the matter in question, so I guess that urine is not the answer.

We hope to start some serum work on adults with CRS within the next few months. When and if I figure out what to look for, and, when I have gotten my truckload of Human Studies Permission slip I may try to get some before and after serum on the 14 year old in Lo"" nc.c..tic\ if he volunteers. At some point after that, it will probably be necessary to feed one of the children a known amount of MSG in broth, observe reactions, and if possible, get serum samples before and after, but, I suspect that would not be until January at the earliest. Is this at all feasible.

I am still pondering what the increased glutamate spots that we saw on the TLC for Hager and Rhodes could have been, which we recently repeated (and did not see them again!)

I have just tried to get in touch with Dr. **Lembrose**, but he is out of the country until mid-November. His second "in command" is supposed to be calling me back. I am also trying to contact Dr. Pollen at Mass. General. Will let you know if and when I get anything of interest.

Enclosed are the revised forms of the 2 other papers that I have sent out. I wonder if you would have the time to read them and make critical comments. Thank you.

Si17-cerely,

Liane Reif-Lehrer

LRL:a
enc.

Dr. Liane Reif-Lehrer

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
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Boston Biomedical Research Institute

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October 21, 1975

Dr. M.G. Stemrnermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemrnermann:

As I have had no response to the letters that I sent Vanasse and Andermann some time ago, I decided to call Montreal today. Vanasse, who is a resident, is not there this year but is scheduled to return in January. I spoke to Dr. Fred Andermann who seemed very interested in the children and is apparently most interested in discussing them with you. He asked if he could call you, and of course replied that he could. Moreover, he is apparently also going to the New York meeting in December, and I suggested that perhaps you could meet each 9ther at that time. He has apparently forwarded a copy of etter to Dr. Leon Wolfe who is Professor of Neurochemistry at McGill. He seems very interested in examining the children and seeing how they compare to his patients which he refers to as "essential tremor". He now has 6 children, all of who have a family history of tremors. He wanted additional information which I promised to write to him and I am enclosing a copy of the letter. He said he would be very interested in trying the dietary regimen on his 6 children, and asked me to tell him what I suggested as a diet.

If you want to call Dr. **Andermann**, his telephone is 1-514-9373884.

Sincerely,

Liane Reif

LRL:a
enc.

LlANE REIF-LEHRER PhD
***Department** of Ophthalmology*
***Harvard** Medical School*
and
Department** of Connective **Tissue Research
Boston** Biomedical Research **Institute

Mailing Address:

20 Staniford Street
Boston, Massachmetts 02114

Telephone: ***617*** 742-6580 ***x326***

October 21, 1975

Dr. Frederick Andermann
3801 University
Montreal Neurological Hospital and Institute
Montreal, Canada

Dear Dr. Andermann:

It was of great interest talking to you on the telephone this morning. I have written to Dr. Stemmermann to let her know that **you** may be contacting her. As per our discussion, I am enclosing **a** copy of the work that originally sparked my interest in glutamate. A brief letter to the editor to the New England Journal of Medicine concerning 3 of the cases Dr. Stemmermann and I have found, is scheduled **to** be published within the next several weeks. I have also submitted for publication 2 manuscripts, one concerning our findings in the questionnaire study that I mentioned to you, concerning the prevalence of adverse reactions to ingestion of MSG, the second is a "mini-review" article attempting to bring together numerous published findings about the effects of glutamate in humans and animals, and my own thoughts on how these may relate to so-called "Chinese Restaurant Syndrome".

I would b most interested to hear how your 6 children respcind to a dietary regimen free of added glutamate.

The children (or adults) should be fed a diet of natural foods, prepared at home, and not containing any store bought products on which the ingredient label either specifies presence of MSG or specifies the more vague use "spices" or "flavorings". Commercial soups and commercial protein containing foods are most likely to contain MSG and should be avoided. Tomatos and all tomato products should be avoided. Use of seasonings in the home containing MSG must be eliminated. These would include "Accent", "Lawrys seasoned salt", "Adolphs meat tenderizer with seasoning", and other types of mixed spices. All meats and vegetables, gravies and salad dressings should be prepared in the home from freshly purchased foods. It is extremely important to spell all this out since many people do no seem to be aware that "Accent" is pure MSG, that many mixed spices contain this material, or that many packaged foods contain this material. One physician who called me in response to the enclosed request, who reacts very severely to MSG, thought he was avoiding all exogenous glutamate but got a bad "attack" one day. After investigating, he told me that he found he had eaten a salad prepared with bottled

cont. to:
Dr. F. Andermann

dressing which turned out to contain MSG.

A good way to do these tests would be to put somebody on such a **diet** for 1 to 2 weeks and then allow them for an equal period of time to go back to eating their usual diet which might presumably contain a fair number of commercially packaged foods. In the ideal situation the plus and minus glutamate diets should be identical in every detail from one week to the next except for the presence or absence of glutamate. Dr. Stemmermann is just starting such a study on a group of children whose diet could be meticulously watched. For purposes of your initial trial, it may well be possible to find what we want to know by being careful to avoid glutamate one ;-:eek and being sure that some exogenous glutamate is in the diet the other week. I hope this information has been helpful.

The child in Connecticut is named Jeff Brinen and lives in Stamford. This child is different from the other 3 in several ways; first of all he is older, being now.14; secondly, rather than ''shudder" at acks this child gets severe migrain attacks with vomiting and dry heaves. He was seen by a Dr. Resnick whose diagnosis was "migraine-type syndrome or seizure-equivalent". Skull films were normal. EEG was abnormal with slow wave accentuated on right side (but this apparently not unusual in children). This child appears to respond to MSG only in the presence of tomato products, but do.es not respond to either tomato products or- MSG alone. This could be either a RH factor or an additive MSG effect since tomatos are high in free glutamate.

Since this child is somewhat older, we hope to be able at sometime soon to challenge him with a measured dose of glutamate under controlled conditions, with serum samples taken before and after,i.e., when our human studies permission slips come through and if the child himself volunteers.

I would appreciate knowing if you plan to contact any of these people. I hope this has been helpful. I as happy to hear that you were interested in our ongoing work on glutamate effects in humans. I trust we will keep in touch, and I would be most anxious to know if any of your patients respond to the dietary regimen.

r;:·v2t

LRL:a
enc.

Dr. Liane Reif-Lehrer
Asst. Professor

SHUDDERING ATTACKS IN CHILDREN

an early clinical manifestation of essential tremour.

Michel Vanasse, Paul Bedard and Frederick Andermann.

From the Department of Neurology and Neurosurgery,
McGill University and the Montreal Neurological Hospital
and Institute.

Eight years ago a twelve months old foster child presented with brief shuddering episodes which were unexplained. She also had a slight tremour. The attacks were clearly related to emotion. They were filmed by the adoptive parents and were witnessed when the child was put under stress by having the mother leave the room. A variety of diagnoses were entertained and for some time an epileptic etiology was considered. She failed to respond to antiepileptic treatment and furthermore the brief shuddering attacks did not really correspond to any of the recognised myoclonic ynd omes encountered in this age group. A psychiatric evaluation was equally unrewarding,

Some time later a young woman with well documented essential tremour and secondary alcoholism brought her five year old son with a history of brief shuddering episodes which had started during infancy and he, like his mother, also proved to have an essential tremour.

The causal relationship between essential tremour and shuddering attacks was confirmed by three additional patients with similar history and findings.

Several pediatric neurologists were questioned regarding their experience with shuddering attacks and although some of them recognised these as a diagnostic problem they had not been able to relate them to any of the known neurological entities.

A typical example is illustrated in the first slide: a five year old boy presented with attacks of shuddering, during which his elbows and knees were adducted, the arms extended, the trunk and head

flexed and the head was occasionally turned to one side. Two or three shuddering movements were usually noted.

The attacks started at age three and a half, lasted two to three seconds and occured many times daily. At times these episodes were very frequent and he would have them almost continuously over a period of hours. He usually stopped eating or walking when he had one and when skating would occasionally fall. The parents noted precipitation by excitement but the attacks did not seem to be triggered by crying or by fear. No episodes were noted during sleep. The course was one of gradual improvement with only occasional episodes in strange situations at the age of five. On examination he showed an essential tremour best demonstrated by holding a full glass. In addition to his shuddering episodes he had a history of sniffing and throat clearing tics and he often handled his genitals.

The father's brother is a banker and has an obvious tremour. When he is at a cocktail party his wife has to lift a drink off the tray for him but his tremour then improves with alcohol. The father himself has a mild essential tremour arid there are other affected family members.

Next Slide

In our brief series of five patients certain features were found in common. These are the shuddering movements and the posture consisting of flexion of the head, elbows, trunk and knees as well as adduction of the elbows and knees. Less commonly head turning, extension of the arms, elevation of one arm and sympathetic changes were described.

Next slide

In their own words the parents describe these episodes "as if water was poured down the child's back" or "as if the child had gone into the cold" or "as if he needed to move his bowels". Our own impression was that the attacks were similar to what one might do when needing to void and being unable to do so because of the lack of suitable facilities.

Next slide

Three of the children began to have attacks of stiffening around five to six months of age. These became clearly recognizable as shuddering attacks only after the child began to walk but in two patients the attacks started only later at 3 and 3½ years of age.

Next slide

The duration of the attacks was always brief and the frequency quite variable. They occasionally occured over 100 times a day. Free intervals of up to two weeks were noted. The child would usually stop walking and occasionally fall or sink to the floor. In one patient the attacks were probably present during sleep.

Next slide

The precipitation of attacks was variable. Usually associated with excitement they were sometimes increased or brought on by fear, anger, frustration, embarrassment, meeting strangers, the need to move the bowels or to void.

Next slide

The course was one of gradual reduction in frequency and a complete remission was noted in two patients at the ages of 4 and 7½ years respectively. Other history included sniffing, nodding and thr.oat clearing tics in two children and in two more the history was not clear enough to decide if tics were present in addition. This seems to represent an unusually high incidence of tics and the reasons for this association remains unexplained. A mild tremour with the characteristics of essential or familial tremour was seen in two patients and in three children it was rather marked. The parents were often not aware of the presence of the tremour until it was pointed out to them but in one case referral to the pediatrician was prompted by the recognition of a tremour by the teacher in kindergarten. The neurological examination in all cases revealed no abnormality.

Next slide

Family history revealed essential tremour in a parent in the four cases where such history was available. In three cases the affected parent had a milder tremour than other, particularly older, relatives. Two of the four affected parents did not realize that they had a tremour until this was drawn to their attention by the examiner or by their spouse.

Next slide

The initial diagnostic impressions and the diagnoses on referral varried widely. Epilepsy was most commonly entertained but psychogenic

attack, tics, mannerisms, paroxysmal choreoathetosis, tetany and need to void were also considered.

Lights

The diagnosis can be made by history and confirmed by the findings of an essential tremour in the patient, a parent and other relatives. This disorder is benign and the prognosis is good with eventual improvement and remission. Unnecessary investigation can be avoided. We have not had the opportunity nor felt it justifiable to study the effects of medications such as Propranolol on these attacks. Phenobarbital which was occasionally given when an epileptic etiology was suspected was not effective.

The pathophysiology of shuddering attacks seems to represent an expression of the mechanism of essential tremour in the immature brain. It is subject to the same fluctuations and exacerbations but improves with cerebral maturation in contrast to the tremour which often worsens with age.

The ultimate nature of the mechanism of these shuddering attacks will undoubtedly be clarified when a neurochemical basis for essential tremour is found.

LIANE REIF-LEHRER PhD
Department of Ophthalmology
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and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

October 28, 1975

Dr. M.G. Stemmermann
Owen Clinic Institute, !nc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Thank you for your letter of October 24. Your comments about aging, freezing and thawing of urine specimens are certainly apt - although I did hear one person say that glutamate spotL,in urine tend to increase with time. I assumed that this was n-8rmally there is some glutamine and little or no glutamate in urine and glutamine of course would be expected to break down to **glutamctle.**

Apropo of the glycine spot in Mrs. Hager's urine, I think that Dr. Shih might be willing to run Mrs. Hager's serum if you want to send some.

Thank you for the comments on my papers. Enclosed please find a copy of the questionnaire on which the prevalence paper is based and also a revised form of the questionnaire which is being distributed to 5000 twins just about now. Apropo of your first point concerning 10% of the population answering "yes" to anything: I would like to think that since the largest part of the sampling went to Harvard faculty, that this might not be quite so true. That it is however at least a "little true", is attested to by the discrepancy between the number of people who wrote "no" to getting CRS and "yes" to symptoms, or, vice-versa. As far as the high incidence is c9ncerned, I can make two comments; (1) it is not clear to me that the d',a....r-rahe problem may not be physiologically different from what I think of as € 4- neurological type symptow, and when and if further work is done in the future, this question should be attended to, (2) another example of "high incidence" is the so called "aspa:iagus ___..effect" for waich the reported incidence is 46%. Tongue curling is also present in some .,>40% of the population. Maybe the problem is my use of the terminology "benign inborn error". Perhaps a better description would be "benign inborn difference".

In the pediatric group;I eliminated and did not question those who said they had never eaten CR food. However I did question individually all those who said they had "funny feelings" after eating CR food, and asked them if they ever felt the same feeling in any other restaurant or at home. A number of children said they had those feelings every time they ate in a restaurant. Those were not counted. If they said that they sometimes get these feelings at home, I did not count them.

cont to:
Dr. Sternmermann

I did also ask other questions, like , did their mother have a red and white box of seasoning called Accent at home and if the answer was yes they were asked whether they had seen their mother use it, and if so, was it sprinkled or measured out in a spoon, but, by and large by asking successive questions, I ''determined;' for each child whether I thought.their complaint was real or not. After these sessions, I really felt this data might be useless. It was only several weeks after; when all data w ein,..-I compiled my answers and found that the incidence was very similar to those that the computer had found for the adult sampling1that I began to have any faith in the answers I had obtained. It was also at this time that I realized that their childish complaints were very reminicent of many of the adult complaints.

Your question about whether the emotional state of the subject determines severity of MSG symptoms is extremely interesting and is difficult to answer in a letter. If we could replace the phrase "emotional state" with the phrase ''chemical state of the nervous system", I think I would be inclined to say that it is a question of& eatifinterest. I have been extremely puzzled1for exampl by some papers by Himwich, et,aL in the 1950s. They reported on various parameter) after feeding some 30 odd patients (mostly geriatric and all apparently psychopathic), and four staff controls , as much as 45 grams per day MSG. In none of these papers is there mention of the severe nausea and probable vomiting one might have expected. I called Dr. Himwich a few weeks ago to ask about this but did not really get a satisfactory answer. In looking again through some of the older literature making all manner of positive claims for the use of glutamate to alleviate hypoglycemi coma, elevation of IQ in menual retards, its use in treatment of epileptics, beneficial for petit mal but not at all for grand mal. The reports of its use all the way from treating convulsions to inducing them, have me wondering recently whether the literature is really as confused as it seems or is there a vague possibility that a particular glutamate concentration, at least in neuronal tissue is critical, and could it just possibly be consider that in those with a too low level, glutamate might be beneficial, whereas, those with a normal or high level, might be harmed by it. I believe that such dichotomous effects on different people are well established for some other drugs such as amphetamines. Also, it is extremely important to keep in mind that when I use the word glutamate in the above sense, I may not necessarily be referring specifically to glutamate, but, rather to some direct metabolite of glutamate, or possibly to some other molecule or molecules which may result from'\"elevated glutamate levels. Perhaps I shall try to find Dr. Funkenstein\. I would be most interested in what you find when you go back and check. your own raw data. There is so much of interest to be done, I really find it very hard to understand why this topic has been so neglected.

Your point no. 7 is a very complex one. See for example, the enclosed reprint, etc., etc., etc.

cont. to
Dr. Stemmermann

In the Spring I spoke to a Dr. Spector at Childrens Hospital. He tells me that there are probably saturable sites for glutamate in brain and retina. This would also tend to keep glutamate out of these areas. However, he also assured me that a certain amount of small molecules do enter these areas by diffusion so that a high serum level would presumably lead to a greater entry of glutamate into those areas despite the other protective devices. However, the real question is still whether the permeability to glutamate is different in those who do and do not get CRS. Also of particular interest is the enclosed table which appears in two papers by Waelsch which show that the disposition of free glutamate was quite different in four subjects and that these particular reactions were very tied up to what happened to glutamine in each of these people.

I finally had a chance yesterday to speak to a Dr. Field here who is an expert in **diabetQs** with a great interest in diabetic retinopathy. He seemed very interested in my question of whether diabetics might be more subject to entry of glutamate into their retinas. There are many interesting issues here since glutamate is known to be **gluCogenic.** He also pointed out that several amino acids are known to be insulinogenic, :euc&inebeing the most notable example. He could not remember whether glutamate fit into this group. However, he did feel that while /questioru of great interest and should be pursued, that it was in fact very difficult to pursue.

I have called a number of seizure clinics and have promises of being called back by both Rossman at Boston University and GC!l,=r?'IL c;ctsc..Ovl at Childrens Hospital, but so far a week has gone by and I have not heard.

The letter to Andermann came back because of the mail strike in Montreal, but I will try to mail it as soon as possible.

Thah's about all I have to report from here. I never did get a letter from Mrs. Daily. Do you have any news on her.

Sincerely,

Laine Reif

LRL:a

Sorry about state of this letter — great hurry today!

October 31, 1975

Liane Heit-Lehrer, Ph.D.
20 Staniford Street
Boston, Mass. 02114

Dear Dr. Heit-Lehrer:

Your high prevalence or MSG reactors (25 ,adults 1 children) bothered me. Therefore I reviewed the records or the last 100 school age children I have seen, exclusive or the severely retarded or severely physically bandicapped. I used a single oriterion, namely shudder or shiver attacks, apparantl7 related to MSG meals (none in Chinese restaurants). In my group headaches are so common, I doubt that they are a use.ful index SJ11ptom.

The five i'eactors include the Hager child but not the Dailey (too young) or the Rhodes (too retarded1. At least part, probably a large part, or-, amall numbers is lack ot exposure. Accent ia found in ve17 tew ot our kitchens. Ea,ing out generally means McDonald's, or equal. My cursory market basket inspectionsuggeats that the chief home MSG sources include canned soups, sausage, hot dogs, bolony. Incidentally, the last appears often 6n school lunches this 7ear, due to cut in Federal funding. Of oours• I don•t know it the bolon7 served contains MSG.

Sincerely 7ours,

M. O. Stemmermann, M.D.

Ebert

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: *617 742-6580 x326*

November 3, 1975

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemmermann:

I called Dr. Ebert immediately after speaking to you and he was very agreeable to several of the things we spoke about. First of all, he will arrange for a laboratory, probably in Chicago, to analyse a variety of sausage products and pay for all the necessary expenses of buying the things, shipping them, and analysing them. However, before we do that, we need to know several things: - (a) are these products shelf-staple, that is, do they come in cans or do they need to be refrigerated; (b) is there an express parcel service out of Huntington so that we could arrange to have any refrigerated goods picked up, taken to the airport, and delivered to Chicago within 24 hours; (c) what is an approximate average cost of a package of sausages.

Dr. Ebert would be happy to make up a variety of canned foods with and without MSG for the Hagers and whatever other families you could get to do these tests. However, he would like to know for each of the children several foods that they would like to eat- so could you find out from these families by any chance say two kinds of soups that the children would eat. Would they like things like deviled ham, chicken spread, etc., etc., spaghetti and meat sauce? As soon as I hear from you about these, I will get this information to Dr. Ebert and will see if we can formulate a reasonable diet out of the lists of foods that the children like.

The foods would arrive in cans labeled A or B and the parents would simply have to make sure that the child eats only A foods one week, and only B foods another week, and keep• written records of how the child is doing. None of us will know whether MSG is in the A or B food until after we get the returns. Does this sound OK. Please let me hear from you.

Sincerely,

Liane Reif

LRL:a

November 4, 1975

Liane Reif-Lehrer, Ph.D.
20 Staniford Street
Boston, Mass. 02114

Dear Dr. Reif-Lehrer:

Many thanks for your "comments" on "comments". I especially liked your col'Notion of my phrase "emotional state". You are correct (I believe) but sometimes old semantics have a difficult time catching up with newer insights.

The older literature is confusing and probably should not be taken too serioual7 because:

1. chemical analyses were primative by today's standards and,
2. controls, if used atall, 1"'1'9 auspect--certainly not as sophiatioated as we use now. Inoidentall7 the words "glutemine", "glutamio acid","glutamate" are tossed around aa if their metabolic end points in brain were identical. Is that tiwue? Or is that really what we are talking about? Doubtless a naive question, but bioohemiat17 is not 1lI1torte, as you may have gueased.

I have unearthed *yll'* old work on autCllOmic t•sting and am enclosing three:r eprints. Some of the comments seem naive 1n the mid-1970's. Mentioned only briefly in the :eprints, but *ot* conside:rable interest, was the marked variability in subjective :response to methacholine, roughly paralleling the degree of drop in blood pressure. Objective "shivers" were commonJ shaking chills rare, usually in pre-menstrual .females.

The November issue *ot* ARCHIVES OF NEUROLOGY has just arrived. You will be in··;erested in P. 752. "AlttDo Acids in Human Epileptogenic Foci."

Sincerely yours,

M. O.Stemmermann, M.D.

MOS/blm

Enclosure

Liana ?ei.f-Lehrea,, Ph.D.
20 Staniford St eet
Boston, Massaohuaetta 02114

Dear Dr. Bei.f'-Lehrera

Many thA.nks to:r your l•cid explanations of glu emate and related compounds. One more question. Is pyridoxine involved, diNctly or indir&otly, in glutamate to glutamine. It 7our anawei.1s "yea", I v111 give 7ou another Ve1!J small group ot children to chew on• An apparnnt !:-!SGreacto1 , pos sibly p:rotactod by pyridoxiaJ. Lots of "ifs" he .

If I seem oool towards Ebert, thaN are two reaeons. First, in our telephone oonversation several yea:ra ago, he completely loat interest when I a•s-or&d him that '.1SG did not cause ~~i:ileptio~~ seizures. Second, mr expe ience with coal company inve st gators leaves me completely disenchanted with one who receives his sa!acy frOM industcy. Ext!'apolating .f:romcoal to MSG is r1sky and becy probably unjust. So be .t. The problem is not in twisting experimental data to please ones employer, but rather to omit experiments alt ether that might tend to diseredit a preconoieved notation.

I spent my promised hour in the supemarket with interesting results. All our lo•a117 produced sauaage under the brand names: ''Gunnoe', "Jimmie Dean", „Ballards" contains MSG. Pasta products or sauces are variabb, Rago-NoJ Franco-American-generally NoJ Chet Bo7-ar-dee-generally yos. Many producte do not list MSG but tome the term "natural .flavoring" sounds suspicious.

Amounts of MSG are never given. I am sure Ebert wol'ld check this out but I would want •oaimilar batch or sausage to go to another laboratory. I am not usually thie parRnoidl It would be sasier to go to Jinlmie Dean's--jtst up the road a piece--and observs for myself. I may even do that or delegate a responsible triend.

B7 tho way, bread or biscuits and gravy, a comJl'lonbreak.fast here, ismade with bacon grease and flour. So nuoh tor my latest thoughts of the day.

Sineeral7 7ours,

M. O. Stemmermann, M.D.

MOS/bl.JiJ

LIANE REIF-LEHRER PhD
Department of Ophthalmology
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and
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Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
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November 6, 1975

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va.

Dear Dr. Stemmermann:

Thank you for your letter and your 3 reprints which I have iust received. To answer your question about the glutamate te minology:- assuming we are talking now about L forms, glutamic acid in the dry form is a different compound from sodium glutamate in the dry form. However, in physiological pH both the salt and the acid would exist in the ionized form so that glutamate is really the correct term to use and in fact, although I sometimes use it for literary reasons, it does not make sense to talk about MSG inside the physiological system since one cannotdisti guishthe sodium ions from all other sodium ions that are floating around. Glutamine on the other hand is a different compound with an additional NH_2 group. It is in fact "my" enzyme, Glutamine synthetase (which has got me into all this) which converts glutamate to glutamine,- It has been conjectured in.some of the older literature that the high concentrations of this enzyme as well as glutamate, especially in neural tissue, serves the function of detoxifying these tissues of ammonia since the enzyme can useammonia to convert glutamate to glutamine. Glutamine in turn is sometimes considered a sort of inert storage form of ammonia which can subsequently be used to convert keto acids to amino acids.

Apropo of Ebert: Ebert is basically an administrator at this point and has offered me the possibility of some research money for some of my work, in which the company is very interested. He tries to get information through me and other investigators and does not really care where it comes from. If I find some children to test in Boston, I am sure he would also provide testdiets for them. The whole situation is too complex to explain in a letter but perhaps we will meet sometime yet.

Thank you for the reference in Archives of Neurology. I really appreciate your pointing out any pertinent things of this nature to me. I have a computer service contract which scans the basic literature for me, but I do not have ready access (without going cross-town) or the time to scan the clinical literature, so I very much appreciate your keeping me up on these references.

Sincerely,

L,

LRL:a

P.S. I called Dr. Funkenstein at Mass Mental Health last week. He seemed rather curt and disinterested, and told me that he hasn't done anything with acetylcholine for 20 yrs, was no longer interested in the subject,

cont. to
Dr. Stemmermann

and didn't know anyone who was. I did not quite know what to make of his reaction but at any rate he is not a source of information!

November 12, 1975

Frederick Andermann, M.D.
Associate Professor of Neurology
McGill University
3801 University Street
Montreal, Canada H3A 2B4,

Dear Dr. Andermann:

Many thanks for your letter and accompanying paper. My patients and yours apparently have similar, although not identical attacks. The little girl, whom I have studied most extensively, was mis-labelled "epileptic" on the basis of her mother's diagnosis. When I had the opportunity of observing the "shudders", six in a fifteen minute period, they had none of the characteristics of the usual epileptic manifestations at this age, notably no disturbance of consciousness. She was eating a doughnut and fascinated by the fish in the office aquarium, when there was a one-second shiver involving the neck and trunk, as if a chold draft had blown across her shoulders. She neither dropped the doughnut nor ceased watching the fish. Flexion of the head was minimal. Adduction of the extremities was only slightly greater than her normal posture. Temperature was normal, but the mother stated that on bad days (usually afternoon or evening) temperature was lower than usual, 96° or so.

Neither the parents nor the two older brothers had anything similar or tremors. Attacks were never activated by temper or frustration. Rather, they were most prominant when the child was especially healthy, happy, and eating well. The latter was my clue to investigating food and the relationship of MSG and attacks was established--at least to my satisfaction and her mother's.

Whatever etiology, this is an interesting group of children. If you are in N.Y.C. in December I should like very much to discuss the problem at greater length. I will be staying at the Roosevelt and, at the moment, I am planning on all three meetings. "God willing and the crock don't rise."

Sincerely yours,

M. G. Stemmermann, M.D.

MGS/blm

cc: Dr. Rait-Lehrer

BOSTON BIOMEDICAL RESEARCH INSTITUTE

DU'ARTMENT or
CONN[CTIV[TISSUE R[S[ARCI-I

20 STANIFORD STREET, GOSTON, MASSACHUSETTS 02114
Arca Code 617 • 742-6581

Novewber 17, 1975

Food & Drug Administration
585 Commercial
Boston, Mass.

Dear Friends:

I wonder if you corild answer the following questions apropos of Monosodium Glutamate used in foods for its flavor enhancing properties.

(1) Is there a limit to the amount that can be put into foods and if so what is the limit.

(2) What is the usual amount of this, added to foods in which the ingredient label states that Monosodium Glutamate is present.

(3) Is it required that Monosodium Glutamate be listed specifically as such or is it possible that packages whose ingredient labels end with the notation "and flavorings" or "spices" might also contain Monosodium Glutamate?

Thanking you for an early reply, I remain,

Sincerely,

Liane Reif-Lehrer

LRL: a

Dr. Liane Reif-Lehrer
Asst. Professor
Harvard Medical School and
Staff Scientist
Boston Biomedical Res. Inst.

11/21/75
Will call you this pm to discuss other matters in your letter

November 28, 1975

Laine Reif-Lehrer, Ph.D.
20 Stanitord StNet
Boston, Mase. 02114

Dear DP. Reif-Lehee:r:

HeNwlth a tew clinical tacts :regarding P,Jridoxine. Recommended daily allowance: children: *0.5.1.5* mg•

Treatment • Infant dependant up to 10 mg. Adult $0-1 00 mg.

Co:rNotion ot convulsions b7 20 mg. is said to be diagnostic o€ pyr1doltine dependancy.

In PJ'l'fidoxine detii\ient intant•, there may be 1m :reaae in w-i ary Kyne:renine and xanthu:renio acid.

Avenage "over the counter", multivitamin tablet contains 2 mg.

The enclosed omatograph7 Report ma7 be ot some interest to you. It may be ot aome intereat to 7ou that these are on the patient who ma7, tie protected by B-6.

Since:rel7 yours,

M. G. Stemmermann, M.D.

MGS/blm

Enclosures

BOSTON BIOMEDICAL RESEARCH INSTITUTE

DEPARTMENT OF
CONNECTIVE TISSUE RESEARCH

20 STANIFORD STREET, BOSTON, MASSACHUSETTS 02114
Area Code 617 • 742-6581

December 1, 1975

Dr. M.G.Sternmermann
Owen Clinic Institute Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Sternmermann:

Thanks for your letter of the 28th and also the chromatography reports. They are indeed interesting. I am most anxious to hear what happens if and when you decide to try B6 on Hager and Rhodes.

I will keep you posted on any developments.

Sincerely,

Lilaine

LRL:a

HP.RVARD UNIVERSITY

SCHCOL OF PUBLIC HEALTH

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(617) 734-3311 (MT::'R HOURS)
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DEPARTMENT OF NUTr,11 ic.@
66!5 HUNTINGTON AVENUE
BOSTON, MASSACHLISCTTS 02115

December 4, 1975

Dr. Liane Reif-Lehrer
Assistant Professor of Biochemical Ophthalmology
Boston Biomedical Research Institute
20 Stainford Street
Boston, MA 02173

Dear Dr. Reif-Lehrer:

While I don't recall that we have ever met, I do recall Dr. Mayer telling me some months ago about your work and asking if I could be of assistance in finding funds to help support it. If ny memory is correct you were cultivating chick retinal cells in vitro and thought that MSG at physiologic levels had some kind of a toxic effect. I remember asking Dr. Mayer if any of this work had been published and he said not yet, but that it was in press. If these findings have now appeared in the scientific literature, as distinguished from any comments in the public press, I would appreciate receiving a reprint or at least the specific reference or references.

However, the main reason for this letter is to comment on your Letter to the Editor in the December 4 issue of the New England Journal of Medicine which I have just read. In Case 1 you refer to "shudder attacks", in Case 2 to "shivers", and in Case 3 to a "migraine-like syndrome or seizure equivalent". Then, in the second last paragraph you state: "The cases reported here may be a severe childhood form of Chinese-restaurant syndrome."

While I do not pose as an authority on the Chinese-restaurant syndrome, I have read most of the papers on this subject and I do not recall "shudders, shivers, or migraine-like syndrome or seizure equivalents" appearing in any 0£ these papers. Also i11 the Chinese-restaurant syndrome the MSG is received in a large concentration on an empty stomach.

So little data is given in your letter, essentially none, that I don't see how one can conclude that the observations are in any way related to added MSG. True, you mention "attacks" stopped when "all foods containing added MSG were eliminated from the diet ... no attacks have been observed except during several deliberate trial feedings".

But surely if one incriminates MSG or any other dietary component one ought to give a reasonable description of the diet, an estimate of the added MSG, how much "natural" MSG might be formed from the metabolism of the protein of the diet, were the individuals evaluating the "attacks" aware when diet changes were made, etc. etc.

Since you are a biochemist and your co-author, Dr. Sternmermann, a physician from West Virginia, am I correct in assuming that the three cases were all from the Owen Clinic in Huntington? f any of the three cases were from Boston who was the physician responsible for the diagnosis and case descriptions?

The untoward effects of food composition and "additives" are a matter of great interest to all of us engaged in nutrition research but I don't see how even a preliminary communication of such a skimpy nature as your letter accomplishes anything but to add more confusion to the hysteria that so many people have as to the safety of our food supply. This is not the kind of co1mnunication I expect from one having an appointment in any division of the Harvard Medical School and I am quite surprised that a publication of the quality of the New England Journal of Medicine would have given it any space.

In due time I will be interested o see in any standard medical publication the data you and Dr. Stemmermann have to support what you readily term your "conjecture".

Sincerely yours,

Fredrick J. Stare, M.D.
Professor of Nutrition
Chairman, Department of Nutrition

FJS:cm
cc: Dr. M. G. Sternmermann
Dr. Jean Mayer
Dr. Franz Ingelfinger

HARVARD UNIVERSITY

SCHOOL OF PUBLIC HEALTH

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DEPARTMENT OF NUTRITION
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December 9, 1975

Dr. Liane Reif-Lehrer
Assistant Professor of Biochemical Ophthalmology
Boston Biomedical Research Institute
20 Stainford Street
Boston, MA 02173

Dear Dr. Reif-Lehrer:

It was good of you to telephone me yesterday in response to my letter of December 5. It would be helpful not only to physicians but also to the public if in the future you had some hard data rather than testimonials and hearsay information about the dramatic improvement of such vague complaints as "shudders, shivers," etc. by removing foods with added MSG from the diet.

With my compliments I am sending you a copy of a recent book of mine, done in collaboration with a former student. It is called PANIC IN THE PANTRY. And the gist of the book, as you might guess, is that in our opinion there is no reason for panic in the pantry. You will find several comments relative to MSG, none of which you will agree with, but if you find any errors of fact, I would appreciate your calling them to my attention in writing. "Shudders and shivers" are not dealt with but we may well include such comments and reference to your recent letter in the New England Journal of Medicine in a revised edition. Incidentally, the book is selling well and shortly will go into a third printing. And for your information, my portion of royalties all goes to the Nutrition Fund of this Department.

Sincerely,

Fredrick J. Stare, M.D.
Professor of Nutrition
Chairman, Department of Nutrition

FJS:cm
cc: Dr. M.S. Stemmermann
Dr. Jean Mayer
Dr. Franz Engelfinger

LIANE REIF-LEHRER PhD
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and
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December 17, 1975

Dr. Fredrick J. Stare
Professor of Nutrition
Chairman, Department of Nutrition
Harvard University
School of Public Health
665 Huntington Avenue
Boston, MA. 02115

Dear Dr. Stare:

Thank you for your letter of December 9th and the complimentary copy of your book, "Panic in the Pantry". Needless to say, I have not had time to read the book, but I have read some sections, and in particular, those concerned with Monosodium Glutamate, and I would like to make several comments: - First of all, I think we are both working from the same data base and coming to different conclusions as to how to cope with the data, i.e., real knowledge about nutrition in depth is, in fact, not yet available, and I simply choose to take a somewhat more conservative view about how to cope with this lack of definite knowledge. I am, however, disturbed by some statements in the book which I feel could be misleading, especially to lay readers - and I suspect your book will get to many more non-professional people than my letter to the New England Journal. On page 19, it says that MSG has been used for hundreds of years. MSG, for commercial use, was not, in fact, produced before 1910. Before this time, the Orientals were cooking with a seaweed called Laminaria Japonica and it was not until 1908 that Ikeda isolated MSG as the active flavor enhancing ingredient in this seaweed. It is difficult to imagine that the quantities of MSG used in the process of cooking with Laminaria could compare with the amounts recommended on the back of a package of ACCENT.

Apropos of pages 172-174, I have several comments: - There is a rather large literature which indicates that absorption of amino acids is strongly dependent on other amino acids and other substances which might be present concurrently. Some amino acids appear to share transport agents, and this becomes an extremely important issue which has been well documented. Moreover, it would seem clear both intuitively and from the data in the aforementioned papers, that ingestion of glutamate in the form of protein which would slowly be hydrolyzed and released is quite a different matter from ingestion of several grams of free glutamate in a short time period. In fact, it is a well known phenomenon that people with "borderline" cases of "Chinese Restaurant Syndrome" may respond to MSG on an empty stomach when it is ingested in a protein free and lipid free medium (e.g., wanton soup), but may not respond to ingestion of a similar quantity in the presence of protein and/or lipid.

Apropos of the comment on the bottom of page 172, which compares sensitivity to M[illegible], that [illegible] exhibit to strawberries and tomatoes, it is important to distinguish between an allergic reaction to food which I believe is the case for both strawberries and tomatoes, which is a well defined biological phenomenon, involving very specific cell types with well defined physiological reactions. The adverse response to MSG has been shown not to be an allergic reaction. It has no symptoms common to allergic reactions, and does not respond to antihistamine drugs (see Schaumberg, et al., 1968 and 1969). The particular case of tomatoes may be bi-faceted: some people may have an allergy to some component of tomato; on the other hand, tomatoes are known to be very high in free glutamate and may cause an MSG response in individuals who are particularly sensitive to very low levels of MSG.

Apropos of the comments on the top of page 173 about Olney's single monkey, Olney had another paper published in July 1972 (reference enclosed) which reported on nine monkeys, three controls and six treated with MSG (one of the six was probably the original monkey reported). Although several groups challenged this report, the enclosed article from a 1972 Science makes one wonder whose data are, in fact, correct. I have personally tried to investigate Olney's reputation and I have heard from a number of people that he is a worker of some integrity and that his EM work is, in fact, good and reliable. In fact, I have recently called Dr. Olson, who used to be in your department, and who you mention in your book, and although he felt that some of Olney's comments to the press are excessive, he assured me that he has seen Olney's sections and that the work appears to be good. I have also recently sent Olney's 1972 paper for evaluation to an electron microscopist at Harvard whose judgement I greatly respect, and I am currently waiting to hear his assessment of the paper.

Apropos of your comments on page 180 about aspartame, I am sitting here looking at the only thing that I have seen in the press about this: the February 17, 1975 issue of Moneysworth. Nowhere in that article does it say that Olney has evidence that aspartame causes brain damage in children who eat it in conjunction with other additives. The article does, of course, overdramatize the situation greatly; however, if my own limited experience with the press is any indication, this may have nothing whatsoever to do with John Olney. We, of course, have also been doing work with Aspartame and all I can say so far is that, like MSG, it inhibits induction of glutamine synthetase in cultured chick embryo retinas by about 70% at a concentration of 2.4 mM. Moreover, we have just gotten our first sections back from an aspartame experiment (one sample only so far). In this single sample 3-1/4 hour treatment of a 12 day embryonic chick retina with 2.3 mM aspartame, showed some very distinct disruption of the inner nuclear layer of the retina: very reminiscent of what we have seen with glutamate, yet different in a way I would hesitate to say until we section further samples. I would certainly be personally concerned about aspartame, especially in conjunction with MSG: I would guess that (and plan to get data) aspartame may induce Chinese Restaurant Syndrome in people who respond to low doses of MSG with these symptoms. Secondly, one of the groups that concern me viz-a-vis excess MSG consumption are diabetics because (a) they have been shown by fluore ein angiography studies to have leaky retinal vessels (b) glutamate can be converted to glucose -- and (c) it is specifically diabetics who might tend to use a new artificial sweetener. Another concern about aspartame is that, as far as I can gather, insufficient data has been accumulated on the effects of 2,5-ketopiperazine,

the thermal decomposition product of aspartame. In the meantime, it is my understanding *from* an article in a recent Wall St. Journal, that the ultimate halt on aspartame came not because of the objections of Dr. Olney, but rather because of the findings of other researchers that aspartame causes uterine polyps in rodents. If this information is correct, its omission on page 180 would appear to put the total ''blame" on Dr. Olney which seems, under the circumstances, unwarranted.

I would also like to say that as a result of a news release from Harvard concerning my initial paper in Investigative Ophthalmology of February 1975, (copy enclosed) I received numerous letters and phone calls. A number of the individuals who contacted me (including several physicians) complained that physicians in general do not seem to be sufficiently aware of the effects of glutamate on some adults. I am enclosing some notes I took of a recent discussion which is rather typical of this complaint; hence, at the very least, I think it is important to make the medical community and perhaps the public at large aware of the fact that these symptoms do exist in some people and that as far as we know, they are generally benign although they can apparently be extremely frightening to some people.

I think one of the main problems in the MSG field, is that there have been a lot of misunderstandings of peoples' motives. For example, I do not for a minute believe that MSG, in any reasonable amount, is harmful to most "normal" individuals. However, I do very strongly feel that there may be a small number of individuals around, who for one reason or another, should perhaps not be eating appreciable amounts of excess glutamte. I am well aware that proteins contain large amounts of glutamate and that some foods, tomatoes, mushrooms, beets, etc., contain high levels of free glutamate. However, whether one cares to increase the consumption of free glutamate above and beyond these levels is questionable. The argument that something has been used for a long time is not really a very good one. In fact, I am currently writing a paper in which I try to point out that not only are food additives of interest, but that certain natural foods which have been around for a long time may also produce some cumulative undesirable effects. To give just a single example, tropical ataxic neuropathy, which is found in certain regions of Africa, has recently been traced to cumulative effects of residual cyanide in the cassava plant used so extensively in the diets of the people in that area. The whole point of my paper is, in fact, the question of how man might have determined which foods were edible and which were not, and I would maintain that the conclusions were based on rather gross, overt, short term observations. Real knowledge about the long term cumulative effect of ingredients of so-called natural foods are yet to be determined; so basically, what I am saying, is that, in my opinion we do not yet, and probably will not know for some time to come (if ever!) the total complexity of the interaction of ingested materials with the multiple biochemical functioning of an organism.

In the meantime, one can choose to err on either the side of conservatism or the opposite. I would like to comment apropos of the statement on artificial sweeteners made in the book that my own conservative view is that the best way to "salvation" is through "moderation and diversification''; what I mean by that is that if it is true that excess glucose or sucrose may be harmful, do we really need to eat so much of it?

I cannot for a moment understand why anyone other than a diabetic or someone who is excessively obese, would want to use an artificial sweetener rather than an occasional teaspoon of sugar. Likewise, in my system of values, if I had to use artificial sweetener, I would certainly choose saccharine which has been around for over 100 years rather than something which has only been tested for a shorter period of time.

Apropos of some comments on page 174, I can only say that there have now been numerous studies of MSG by ingestion as well as injection. As soon as I can dig myself out from under the multitude of papers of trying to get the necessary permission from four different Human Studies Committees, I certainly hope to get some hard data on the whole MSG story. In particular, of course, I am interested in precisely what Dr. Stemmermann mentioned in her letter to you, namely what is the mechanism of the action of glutamate that causes the "Chinese Restaurant Syndrome" symptoms. I am sure that you are aware of an increasingly large literature which clearly defines glutamate as a neuroexcitatory amino acid. There also have been numerous conjectures that it may, in fact, be a neurotransmitter in some lower forms and possibly in some cells of some higher forms. Moreover, there is increasingly good evidence that cells, especially nerve cells, contain at least two separate pools of glutamate, one which appears to be used for general metabolism and the other which may contain glutamate used for possible neurotransmission purposes. There are an increasing numir of papers which give evidence for such compartmentalization of glutamate in cells. My own original interest in the enzyme glutamine synthetase which appears in high concentration in nervous tissue and in highe concentration in the neural retina than anywhere else (on a per milligram a is) has long intrigued me and since one of the functions of this enzyme is to convert glutamate to glutamine which is benign with respect to neural excitation as well as causing damage to the neural cells, and since glutamate also converts to GABA which is present in high concentrations in neural tissues, there are some interesting possibilities for some unique functions of glutamate.

In closing, I would like to say that I try very hard to keep all things in perspective, and I agree with you that there is no reason for "Panic in the Pantry". However, I feel that there may be rather good reason for exercising some "caution in the pantry" especially with respect to children. As a last example, I have spoken to the group in Pittsburgh who are under contract (under the consultation of Dr. Benjamin Feingold) to study the possible connection between certain food additives (in particular, food coloring) and hyperkinesis. They tell me that there does seem to be some finite connection between hyperactivity in children and the red and yellow food colorings. One can argue that the data are premature and sparse. However, one might also wonder, in the absence of any positive data on this matter, why use any food coloring at all. I am not generally terribly puritanical; however, I find that my children enjoy natural colored cookies almost as much as the colored ones and I must say that personally I feel completely revolted by the intense artificial coloring in some of the foods I have seen, for aesthetic, if not for scientific reasons. The same sort of thing, of course, applies to the now resolved questions of MSG in baby foods: why would anyone want to add anything to the diet of an infant who has no preconceived ideas of what to expect - As far as I am concerned, this would even include addition of sodium chloride, which I am told by a number of physicians, like sucrose, we eat much too much of.

I hope this letter has clarified my position as well as answered some o the p0i ts in y0ur letter. I h ve two other papers on MSG which have been submitted for publication, which I would be happy to send you if and when they get published. One reports the results of a questionnaire study that I did concerning prevalence of human reactions to MSG, the other is a kind of mini-review article of current data in the literature concerning MSG.

Sincerely,

Liane Reif-Lehrer

LRL/fg
CC: Dr. Stemmermann
Dr. Jean Mayer
enclosures:
1. LRL reprint Invest. Ophth. Feb. '75
2. Science article 177 Sep. '72
3. Olney reference on nine infant primates
4. Mrs. Dailey's letter
5. My notes on 11/18/75 discussion with Tuf student

LIANE REIF-LEIJRER PhD
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and
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December 22, 1975

Dr. Fredrick J. Stare
Dept. of Nutrition
Harvard University School of Public Health
665 Huntington Avenue
Boston, Mass. 02115

Dear Dr. Stare:

Although I understand that administering your department must be a gargantuan task, I was somewhat dismayed by your letter of December 19.

Upon receipt of your letter of December 9 asking me to bring to your attention in writing any errors of fact that I may find in your book, I essentially stopped what I was doing and took an evening and the better part of the next day to read some portions of your book and comment on some matters which I felt were erroneous implications and to gathe such material as I thought might be of interest to you apropos these matters. Although I too am extremely busy, I felt obliged to put some time and thought into this matter since you had been kind enough to send me a complimentary copy of your book. After all the time and effort I put into answering your letter to have it simply filed in your "rather thick","to read when I have time file", makes me feel that I could have used my time to better advantage. I do think my comments are worthy of consideration,althoI would hardly expect you to drop what you are doing to consider them. I would appreciate it if you could find the time in the next month or o to consider my comments and perhaps answer my letter.

I too hope that there will be data with adequate controls forth-coming on the MSG problem.

Si cerely,

I ,a,{,.J! Reif-Lehrer

Dr. ***Liane*** Reif-Lehrer

LRL:a
cc: Dr. Jean Mayer
Dr. Stemmermann
Dr. F. Ingelfinger

Laine Reif LehJ.'-er.lh.D.
20 Staniford Street
Boaton, Mass. 02114

Dear DI'. Re1f-Lehre1":

Your letter to .OZ. Stare has **given** me many pleasant minutes, and another chuckle on each re-x-eading. It is the sort of letter I would have written when I was JOU1' age,.-and did. Not that it ever accomplished muob at the time. Accumulated evidence through the years was much moN persuasive, although after so long the "STARE'S" al'S usually **"Buwied"--on&** way or another.

Except tor a minutia, I agl'ee completely with your opinions and conjeotuNs. While I em reasonably certain adult O.a.S. is benign, I still have an uneas7 feeling, without any solid evidence, that this may not be true in ohild:ren. A long list of agents, organic and inorganic, are more destructive to the unmyelinated or partially 'llnm)'elinated brain than th$ adult. Perhaps one way to find out is a long em study of offspring ot mothers whose diet includes MSG, or doe$n•t. In Boston one could compare the baked beans and oodt'iahers, the, chip sueys. and the sausage pizzas. The logistics of auoh a study would probably be insui--mountable.

I had a briet but interesting meeting with Dr. Andel"man in NEw York Cit7. He is presently president of: the Eastern EEG society. He is gaing to look at MSG and I am goint to look at ubgerutanoe. I have done this previously, but have not included collaterals. I still think this is stPetching a bit. He will be sending me a reprint as soon a• his paper 1a published ••

Sincerely youx-a, or "moderation in the jSant17".

M. G. Siemmermann, M.D.

P.S. Does Dr. Stare noeive reseattch .funds trvm "Companies"? Money does not necessarioy close a person's mind, but it helps.

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December 24, 1975

Dear Dr. Reif-Lehrer:

Thank you for sending me a copy of the very interesting and entirely reasonable letter you sent to Dr. Stare in response to his letter of December 9th.

With best regards,

Sincerely yours,

Jean Mayer
Professor of Nutrition
and
Master of Dudley House

Dr. Liane Reif-Lehrer
20 Staniford Street
Boston, MA 02114

LIANE REIF-LEHRER PhD
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December 29, 1975

Dr. M.G. Sternmermann
Owen Clinic Institute Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Sternmermann:

It was good to talk to you on the phone last week - by now you've no doubt received all the letters to and from Stare. Enclosed is a copy of an encouraging note from Dr. Mayer, which helped soothe my "ruffled back feathers".

When you spoke to Andermann in New York, did you mention the Vitamin B6 boy at all? This is of great interest to me and there really is no very good way to check this out other than in Humans. I can't wait to see what you find apropos of this in Hager and Rhodes.

Hope Dailey showed up for the Holidays. - Trust you got a chance to relax.

Best regards,

liane

LRL:a
enc.

1P.S. Just got your letter, glad you enjoyed mine to Stare.)la.-, My technician suggested GAUTIDQN IN THE KITCHEN as a counter title. I don't know the answer to your question about where Stare receives research funds, but I certainly gather from Olney that there has been a lot of (pardon the pun) monkey business in the MSG field. By the way, please call me Liane - I am still trying to figure out with your first name is although I notice that you sign it Sternmie - is that what you are callfed?

LIANE REIF-LEHRER PhD
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December 29, 1975

Dr. Frederick Andermann
3801 University
Montreal Neurological Hospital and Institute
Montreal, Canada

Dear Dr. Andermann:

I understand from Dr. Stemmermann that you had a chance to meet and at least talk briefly at the New York meeting. It is really important to get some "hard" data on this glutamate story, and, I am in the process of completing various arrangements, including Human Studies Committee permission forms, to allow me to proceed. Meanwhile, I would be very appreciative of hearing about any results you may get from diet testing your six children. I presume you received the two earlier communications which I sent off several times but which came back several times because of the Canadian mail strike.

I look forward to hearing from you about this matter.

Sincerely

Ira t[us]. -Lt2

Dr. Liane Rei -Lehrer

LRL:a
cc: Dr. Stemmerman

HARVARD MEDICAL SCHOOL THE CliLDREN'S HOSPITAL IVIEDICAL CE,\TFR

CESARE T. LO\IBROSO, t\LD., Ph.D.
Professor of Neurology

CHIEF, SEIZURE UNIT AN'D
DIVISION OF :-.'EUROPHYSIOLO<;Y
300 Longwood Avenue
Boston, Massachusetts 02115
(617) 734-0000

February 2, 1976

Liane Reif-Lehre= , H. D.
Asst。 Professor
20 Staniford Street
Boston, Mass. 02114

Dear Dr. Reif-Lehrer,

I apologise for the delay in answering your letter of December 16th, concerning your study - which I found extra interesting - and interest in the possible role played by free glutamate in mimicking seizure disorders in children. I would be very glad if we could cooperate in any way you may find effective and perhaps we should meet, together with some of my associates to discuss this further. I am in the process of writing up a small series of young infants who could be easily misdiagnosed as having "Infantile Spasms, or myoclonus", but instead have entirely different correlates in terms of progress and EEG. I sort of doubt that they would fall within your group in view of their age, but we should take a look into this possibility also.

Please contact my Administrative Assistant, Mrs. Sara Korvitz to set up a convenient date.

Very sincerely yours,

!_ L, t1
Cesare T. Lombroso, n.D.

CTL/sb

Dear Dr. Stemmer — this finally arrived today (2/3) & I have an appt w him + a Dr Erba on Fri 2/13.
Liane

LIANE REIF-LEHRER PhD
Department of Ophthalmology
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and
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Boston Biomedical Research Institute

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February 26, 1976

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Thanks for your call yesterday. After talking to you, I went through the manuscript several more times and made a few more corrections. For example, page 3, line 10, should read "added" instead of "a great deal of unbound", page 3, line 16 should read "excess amino acid" instead of "chemical". I also suggested that on page 4, line 2, she add something to the effect that I had found 2 possible cases (primarily with a view to not having the reader think that this is somehow indigenous to West Virgina). I also suggested that she add a sentence at this point, to clarify the fact that my particular interest in this was in the mechanism of the action of MSG in these individuals. Lastly, I suggested that since the purpose of this article was to alert physicians of what sorts of things to look for, I suggested that if possible, she add a sentence to the effect that in some cases migraines and hyperactivity may also be of interest to look at in this regard. If you have comments or changes about any of this, please give me a call or call her directly. She was not sure how the final editor would feel about some of these changes, and I left it that I really did not feel very strongly about any of them. She did however, promise to call me back to check out the Headline with me when she gets it.

Enclosed are copies of my letter to Lombroso and his letter about the possible MSG child. I called Dr.Packard yesterday afternoon; he had not yet received Lombroso letter but when I briefly told him about the possible involvement of MSG, he said, "well I'll be damned"! I am sending him some suggested dietary restrictions and he seems very interested in cooperating.

Sincerely,

L,a

LRL:a
enc.

[illegible]: HE/FU:JJJ1EH PhD
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[illegible]nrrarcl /11cdil'11/ School
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February 23, 1976

Dr. Cesare Lornbroso
Childrcns Hospital
Dept. of Neurology
Longwood Ave.
Boston, Mass. 02115

Dear Dr. Lombroso:

It was most ki d of you and Dr. Erha to meet with me on Friday, February 13 to discuss the matter of MSG. As per your request, I would li e to su@narize here the kinds of things to look out for and then to describe the type of simple diet testing which might be useful to detect MSG intolerance in individuals.

1. individuals 10 have shudder or shiver attacJ s but who maintain all sensory function during these episodes, and who have normal EEGs

2. individuals in '\·Jhomdilantin does not alleviate "seizures".

3. individuals with migrain attacks (especially if vomiting also occurs) - if the episodes seem to come on within 20 to *GO* minutes after meals.

4. children Kho appear to become hyperactive within 20 to 60 minutes after eating

I would be interested in individuals in any age gro p, but the most interesting cases for us would be more likely to occur in pre-school age children. I would be happy to •question or speak to possible candidate:c of interest. If you see a patient w·ho appears · to fall. into one of the above cat gories, you could suggest the use of the following diet for two weeks and then have them report back as to whether symptoms hilve decreased or disappeared, If the answer is yes, we could tl1cn do double-blind diet testing on s ch individuals with identical foods, with or with6ut mea ured amounts of MSG.

cont. to Dl:. Lombro jo

Sugg0sted diet: The following items arc to be eliminated from the dint *[or* 2 weeks:

coimncrciu.l foods that mention MSG on the ingredient label, commercial muyonnaise, salnd dressing or french dressing, l\CCENT, MSG or Monosodiurn Glutc1mc::1tc
Adolphs' Ment Tenderizer with spices added
Lawrys Salt or c1ny other mixture of spices which might contain MSG.
tomatoes, mushrooms or seaweed

All Restaurant food; note: this includes hot dogs, etc. (however, ice cream, candy and fruity things are alright.)

If jou have further questions, please let me know.

Apropos of the question you asked about human breast milk, in two reports, one from Industry and another not yet published but presumeably in press, it is stated that human breast milk contains of the order of 20 11q free <Jluta.1"1alpeer 100 grc:tms of milk, and that glutamate plus aspartatc comprise about 45 of tl1c total free amino acids in this fluid. I do not at present know of a reference in wbich changes in composition of breast milk were measured as a function of maternal intake of free glutc1raate.

Thank you again for your cooperation.

Sincerely,

Lo -U

.LRL :a/f

Liane Reif-L hrer, Ph.D.
Asst. Professor

P.S. 2/25/76 I have just received your letter to Dr. Packard and will try to call him this afternoon - this certainly sounds very interesting - especially since either sausage or spaghetti sauce have been the "culprit" in our other 5 cases. Thank you very much for calling this case to my attention.

l.,//\NEl<.EIP-u:11n,m pf,])
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1'clcpl101161:7 742-6580 x326

February 26, 1976

Dr. Thomas J. Packard
279 ,1)cas&nt st·.
Concord, N. H.

Dear Dr. Packard:

I was glad to have the opportunity to speak to you on the telephone yc-·sterday, and lior,e to hsar from ye u further about Michc1el Sargent at your convenience. I am enclosing a copy of the letter from Dr. Lombroso to 1 ou just in case you still have not received your copy. I am also enclosing a copy of my letter to Dr. Lombroso since it lists the informal initial dietary restrictions that I would suggest. As 1 mentioned on the phone yesterday, if this informal diet re:·tr iction helps to alleviate or eliminate symptoms, we would like very much to do a double blind stud on this child with foods identically prepdrcd except for the absence and presence of the glutamate. *(An* important consideration in doing the preliminary informal diet testJng is an asses2rncnt of how faithfully the parents - as well as the c',ild- will stick to the diet. Do you have any feeling for the intellect11al capacity and conscientiousness of this family in thjs regard?) Rcgarcrl ess of whether the diet testing does or does not give any results, there is some reason to see whether a Vitamin B6 supplement might be useful in this child, but it is impor ant to do only one thing at a tim?. I would also like to add (with respect to something in Dr. Lombroso's letter to you) that it is my conjecture that if Michael w0re to turn out to be a MSG sensitive child, that dilantin might not only not help, but could, in fact, conceivably be making matters worse.

I would be interested to know (1) whetLer there is any history of diabetes in Michael's family, (2) has Michael had any visual difficulties? (3) has he had a fundus examination: does his retina look normal?

I am enclosing a copy of a letter to the editor of the New England Journal of Medicine which we had in the December 4 issue (unfortunately they goofed and left out the references). If you have any questions, I would be happy to talk to you further about this matter. In the meantime, if you have any other cases that might.fall into this general category and could be of interest to me. I would be most appreciative rJ\- hearing about them.

Sincerely,

Reif-Lehrer

Liane Hcif-Lehrer, Ph.D.
Asst. Professor

J,HT,:,l
enc.
cc: Dr. Lornbroso

The Children's. Hospital Medical Center

300 Longwoo Avenue, Boston, Massachusetts 02115, Telephone: (617) 734-6000

Depactment of Neurology- Seizure Unit

February 20, 1976

ThoMas J. Packar<l, H.D.
27 Pleasant Street
Concord, ;1.II.

Re: Si\RGI:llT, ?lichael

CIU!C# 85 53 69

Dear Ton,

Thank you for referrinq to me nichael and his parents, when I found a very nice family. I need not go into the details or his history, \•ihich are well stu:lr.larized in your notes and in the material that you sent along. I am not entirely sure about the present status of his so-calleu dyslexia, but it appears that he still is about 2 grades behind in reading anri that r.iay require sone nore active intervention. However he <.locs ver:• well in math and science; he is active in sports and seems to be well adjusted in terms of social activities and lean.ership.

The episodes that brought him here go hack to sonetir.'.e ago, but they becane more frequent about 8 months or so ago, at·which tiMe they were brought to your attention. As far as I could determine, in discussing it with Michael, they occur usually after he either tries to go to sleep and cannot, or after he has awoken for some reason or other. He has soIT\e kind of finger sensation which he could not quite describe and apparently says that it is not like true tingling and then he may have ringing in his ears and feel like trembling and somewhat clammy, although rather warm. His parents, whom he would call, find him in a diffused chill involving ams and legs, but J.,ei:fectly conscious and able to-understand and converse and within a minute or Uf' to 15 minutes of such activity, and a good deal of reassurance he would go back to sleep, · with in the morning remembering very well what had happened. They hav occurred at various times, sometimes, as I say early in the evening, at night and sometimes rather late in the morning. He has had one or two of the finger feelings or warning in the day time, but none of the rest. They have occurred at about the rate of once a week although they have not been quite consistant. As you mentioned Phenobarbital did not help and Dilantin, if it nid help, only for a couple of weeks and even with it increased now to 200rags it does not seem to have done a great deal.

rtichael is one of four children, beinq the product of the 3rd pregnancy; when the mother was exposed to German Measles at 2nq month of preqnancy, but evidently there were no complications from that. His milestones \-;ere all quite normal. He has had some past history of niqhtmares and still has some fears of the ark but no other fobias or unreasonable fears. 1\s I r.ientioned he is q:uite active in sports and he is captain of his basketball team. In reviewing the fami.1y

SARGF.:HT, z.tichael

history there is a brother of the mother, who as a child had, ar ar ntly petit mal which she had too, and there is a fairly stronq !listory of !1igrciine headaches; there is nothing positiv on the father's side o-: the fanily. He has had sor.tc hallucinatory experiences with high fevers. I coul<l not obtain any other history that would, in my opinion suggest an epile!"'tic syndrorne or some other neurological problem. ·I forqot to mention that 1,:;1 nI spoke \·1ith Michael alone, he seemed to agree that ·:I:.:seepisodes often occurred when he was thinking about them or when he was thinking about SOI'cleworrisome thoughts. However, the nether later suggeste<l that.occasionally they seem to be in relation to his dietary intake and particularly larqe consu.-:iption of spa(1hctti. possibly with sausage opened from cans.

On neurological examinatio he appears as a bright,'pleasant '1ell adjuste<l boy who could give a good account of his symptoms'· and did not seem too anxious, but he easily adnitted to fears that axe commnon at his aqe. There were no abnomalities otherwise in his neurological exanination. A full EEG study was done here in waking with natural sleep 3 hrs. post prandium which shows normal background patterns in :,oth states with good alpha in waking at 9-10 hz. with norri.al distribution and reactivity with no excessive ru:iount of slow wave activity, but with normal sleep patterns up to stage II or III of sleep. There wereno focal abnormalities and no discharges in either state nor any activated by hyperven ilation nor by photic stimulation.

I do not know what these episodes really consist of. I doubt that they are evidence of hypoglycemia, but possibly some fasting blood sugar might be obtained. I do not think t. at there is any evidence here to indicate an epileptic disorder, in my opinion, and I do not find evidence to suggest a neurological disease nor do I think that further studies in this direction ·would be advisable Whether or not this is all psychosomatic in origin remains to be seen, but there is some suggestion that it might be. There is a recent report that refer to so-called "shudders" attacks in children who might have some sensitivity to high glutamate ingestion and a very superficial inquir . with the mother brought up, as I mentioned a qu stionable relationship to his high consumption of spaghetti with possible sauces rich in ·HSG and I thought that this is another possibility. I will take the libertv of referrinq his name to Dr·. r...Reif-Leher who has been interested in this pr blem ancl uho-mic,yht contact the family for further dietary investigation. This is something akin to the "Chinese Restaurant Syndror.,e".

Yours sincerely,

tr;-5'-t,_q
Cesare T. Lombroso, 11.D.

cc. Dr. Reif-Leher

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

***Telephone:** 617 742-6580 x326*

March 2, 1976

Dr. M.G. Stemrnermann
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemrnermann:

I had two meetings today, one with Dr. Ganz, Pediatrics, Mass General, and another with a Dr. Ray Adams, Head of Neurology at Mass General, to tell them about the glutamate story, and asked if they could help us find more cases. Dr. Ganz asked a number of questions about how the EEG work on Dailey was done which I could not answer. For example, he wanted to know whether a sleep study was done as opposed to just a waking EEG. Maybe, you can say a little bit more about this.

Has anything new developed vis-a-vis the Hager or Rhodes children. For example, did you ever try giving either of them Vitamin B6. Please let me hear from you at your earliest convenience.

Sincerely,

Liane Reif

LRL:a

Clayton Ferguson
Allen Braun

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: *617 742-6580 x326*

March 16, 1976

Dr. M.G. Stemmermann
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va.

Dear Dr. Stemmermann:

I have made tentative arrangements to get some food samples (sausage in particular) analyzed for glutamate content. Before I can finalize the arrangements, I have to know on what date they will be shipped, and I have to know this 7 days in advance. Would it be possible for you to buy several vari't:.ies of sausages which are popular in your area and ship them frozen directly to the laboratory after I make the appropriate final arrangements?

1. Do you have access to dry ice?

2. Do you have some sort of appropriate shipping container?

3. Would you have time or is there someone who can purchase and pack these things.

I would be happy to pay for the sausages and shipping. Should I send money in advance or "after the fact" Are there any other problems? I realize that you do not have help so I would be happy to send shipping labels or help in any other way. I did suggest that we would get the samples to them within the next 2 weeks or so. I hope that is feasible and does not put you out. Please let me know at your earliest convenience.

Sincerely,

LRL:a

March 30, 1976

Laine R●it-LehNr, PhD.
20 Staniford Street
Boataa, Maaaachuaetta 02114

Dear Dr. R●it-Lehrer:

Dr. Steano**rm**ann **ask me** to **write** you and let you know that the a●usage got in the **ma**11 on Monday, March 29, 1976 out *ot* our local air,port at 5:41 P.H. W● had the sauaag● froz●d and then packed in **a** starotoam oontainer and then in the ice with **n●**wspaper around it in a lal'Se box. We sent th● package AIRMAIL SPECIAL DKLIVERI and th● poat o1't:tce intormed us that it would arri**v**e b7. early **m**otming th● next day (**M**arch 30th).

Th● thl'ee kinds ot •●usage ve sent were all **mad●** in West Virginia and included: Ballards Hot Whole Hog $1.$9 per lb.
Gunnoe•• Sau●age at $1.$9 per pound.
W. Va. Mild Sau●age at $1.39 per lb.

All three pere processed in the **Hu**ntington Area and all have the a●m• label except the cheaper brand that was not l●bel●d "whole **ho**g" and **uses** dextrose instead *ot* sugar.

W● will be look **OoNard** to hearing the results *ot* these tests and thank you *tor* your eooperatin in this matter.

Sino●rely yours,

Betsy Matth●we, Seoretal"J
M. G. Stemmel'ID&nn, M.D.

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

March 22, 1976

Dr. M.G. Stemmermann
1319 Sixth Avenue
Huntington, W. Va.

Dear Dr. Stemmermann:

Could your Secretary please call me collect on Friday between 10 A.M. and NOON to let me have the exact flight information on which the sausages are going out, how many different samples there are and when they are to arrive in Minneapolis. The people who are taking care of this will arrange to have them picked up at the airport if they have all the necessary information. Thank you.

Sincerely,

Liane Reif

LRL:a

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

March 22, 1976

Dr. M.G. Sternmermann
owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, W.V .

Dear Dr. Sternmermann:

I have just received a telephone call from the Mother of the child whose case study Dr. Lombroso sent me; she informed me that the boy has had no symptoms since he has gone on the diet to eliminate foods with exogenous MSG. I am very excited about this news.

Sincerely,

Liane Reif

LRL:a

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

March 29, 1976

Ms. Betsy Mathews
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, W. Va.

Dear Betsy:

Thank you for sending the biography on Dr. Stemmermann. Do I presume correctly that in the 3rd line M.G. should read M.D.? Did Dr. Stemmermann really get through medical school in 2 years? Dr. Stemmermann mentioned to me that she was Board Certified in Internal Medicine; that should have been incorporated in the biography. Can you please tell me what year that was? Other than that the information is exactly what I need. Thank you very much.

Sincerely,

Liane Reif

Dr. Liane Reif-Lehrer

LRL:a

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

April 2, 1976

Ms. Betsy Matthews
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Ms. Matthews:

Thank you for your letter of March 30 with the information. However, you neglected to tell us how much you paid for mailing the sausages. Please let us know and I will send you a reimbursement for the total amount. Thank you.

LRL:a

Dr. Liane Reif-Lehrer

April 10, 1976

Laine Reif-Lehrer, PhD.
20 Stanitord Street
Boston, Maasachusetta 02114

Dear Mr. Reif-Lehrer,

Thank you for your recent letter and the reprints on the aritcle you sent us. I am sure Dr. Stemmermann will putthem to very good use.

I am sorry I did not let you know the price tor mailing the aauaage. The total coat of mailing vas $8.61. I have the receipt bare 1• you need it.

How long da you think it will take until weh bar about the sausage results. I am just cui-loua to know 1r thel arrived froz•• and aate.

Dr• Stexmaermann has enclosed a note on the Hager child for you• Hope this on give you some additional intormation. Stemmie and I were both surprised to find out about Glen's eating habits now.

It you nsed anl more intormation please let me know and I will tl"J'to aupplJ it.

Sineerely -, urs,

Mias Bets7 Matthews
Secretar,

Enclosure

DE LA
RECHERCHE SCIENTIFIQUE

CENTRE DE NEUROCHIMIE
11, RUE HUMANN
67085 STRASBOURG CEDEX
FRANCE

Strasbourg, le April 9. 1976
Telephone 36 06 05

Professor Liane REIF LEHRER
Department of Ophthalmology
Harvard Medical School
Boston Biomedical Research Institute
20 Staniford Street
BOSTON, MASSACHUSETTS
U.S.A.

Dear Professor Reif-Lehrer,

Thank you for your letter of March 16 and for the communication of the very interesting results you enGlosed.

The results concerning glutamate were particularly interesting. Glutamate that hardly crosses or does not cross at all the brain blood barrier, can pass to the hypothalamus level, due to particular circulatory system and produce primary and secondary effects of the kind you related. But in this case as in others, I think that the consequences are the results of a connection of a genetical predisposition and of the effect of an external factor.

Obviously, 1 would be very pleased to meet you during my next stay in Boston or better, at the o casion bf your trip to Europe.

With best regards,

Sincerely yours,

ProfessoL P. MANDEL

April 13, 1976

Laine Reit-LehNr, Ph.D.
20 Stani:tol'd Street
Boston, Mass 02114

Dear Laine,

Herewith "Clayton Ferguson" an "Glenn Bl'Own." Glenn is my newest and improtant becau e he oon:tima the pl"Otoool I have been using tor lsu•peots." (See note attaohed to his aumma17). In this way, I can personall7 obsel"Ve any unusual SJJDPtoms dUl"ing the application ot electi-c,dea and subsequent EEG exwaination. The lunch (or b:reakfast) challenge depends upon tho child's p:referenoeJ but, of course, th-, amount o:t MSG is unknown.

Dt, let me know 1:t B6 pl"Otecta the Packard/Lombaoso patient. It did nothing *tor* Olen Hager--or is he complicated b7 being a heteJ:10z7gou.s hJP8rgl7c6nemim1•·.? (You may remember that his mother is homoz7goua tor thie condition--probabl7) • Delighted 7ou have met with Lombroao. He is one or my .favorite people, although I do no know him personall7.

Should the question evo arise again, 95 **or** m7 EEG's include waking and aleepi . In tho pediatric group, 75 go to sleep naturall7J 2 require medication (diazepam or nemhutal)J S nothing works. In addition, photio or auditor"J stimulation is uaed depending on the problem.

Reoentl7 one **ot** the editors o.f the SCHOOL PSYOHOLOGIST'S DIGEST? has aakod me to write an MSG piece tor the November iaaue. This issue will teature medication. With J'OUl" permission I will attach 7our name tc th& report, a:tter you have read, digested, oorrected--and hopefully not lengthened Anything biochemical you would like stressed?

Thia rather rambling latter I trust wovers the questions 7ou have asked during the past month. It. in the tuwre, I do not respond aa quick.17 aa 7ou might like, 7ou will know I am up to my eyebrows in r.on-MSG-related lll'Oblems.

Ever yours .for more and better sausage.

M. O. Stemmemann, M.D.

P.S. The article in EMEllJENCY, April issue, just arrivod. Did the publishers send you the issue?

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

April 15, 1976

Dr. M.G. Stemmermann
1319-- 6th Ave.
Huntington, West Virgina 25701

kv $13.18

Dear Dr. Stemmermann:

The sausages apparently arrivea-irozen at their destination. We have put through for a refund/which you should be receiving in 4 to 6 weeks. As far as the results go, it is hard to say when they will come. I got a call yesterday asking what we could provide as a control without MSG, and that may turn out to be a slight problem, but I do not think it will hold us up very long. I think it will be very difficult to find a really good control. I will of course let you know the results as soon as I get them.

Thank you for your note about Glen Hager. I would like to have more details about how much pyridoxine he got, for how long, and how much Accent was he given and in what form during the five days. Does he consistently get the shudder attacks after he eats the MSG, and did you witness any of them? I realize how little time you have, but it is really very important for me to know these details.

I will keep you posted about our end of things. Thank you.

Sincerely,

Li Reif

LRL:a

April 16: - Just received a letter from the Pediatrician of the New Hampshire child corroborating what the Mother told me, and also telling me that in checking back through his records, this child began to get shaking episodes in 1972 at the age of nine. The first episode having come when the child had "regular measles". Do you know anything about whether the virus that causes measles might be likely to cause long term, or permanent permeability changes in the blood brain barrier? Is anything known about this?

Please let me know when you receive your check.

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

April 20, 1976

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Enclosed is a copy of a letter I received today which is very interesting apropos of what we have been talking about.

Just got your letter. Thank you for the 2 case histories which arrived just after I dictated the above. I will try to answer some of your questions, but I'm off to the ARVO meeting tomorrow so things are kind of hectic. We have not yet done any testing on the Lombroso patient but hope to do that this summer. As for the article for SCHOOL PSYCHOLOGIST'S DIGEST, I would be happy to read and make comments, and you're welcome to put my name on it. I did get a copy of the EMERGENCY MEDICINE and was happy to see a reasonably tasteful headline - I almost had a fit when they called with their first title, which was something like,"Chinese Restaurant Syndrome & Seizures.

Your cases sound interesting. I look forward to hearing more. That's all I have time for now.

Sincerely,

Liane Reif

LRL:a

April 24, 1976

Laine Reif-Leijrer, Ph.D.
20 Staniford Street
Boston, Masa. 02114

Dear Laine:

MEASLES
NOTES-4.2[.76

(Also applies to chioken pox, mumps, Ger.man measles, with some variation in morbidity, mortality, and EEG's).

EEG changes occur in prodromal and post-enptive stAges in almost all casea. In uncomplicated oases these changes have usually resolved 7-10 da7s after the acute phase. Whatev r affects the cerebral hemisphere is likely to affeot the capillary blood brain barrier, ale9. Howevei-, I !mow of no data that proves this or its p&l'Dlananoe.

As you probably know measles enoaphnlitis is a serious complication, varying in ultimate expression from death or severe retardation to mild byperkinetic behavioral disorders. Coulf your Naw Hampshire child have had one o the minor \rarieties? Or ai-e his "shivers" coincidentnl \lith a change in diet fo1lowlng the acute illness?

Thia is one r9ason why the Dailey child is so porcious. e was (and is) an entirely norma child who hns never had a serious illness or measles.

This is unlike Glerm Hager whose problems started with hat was probably encephalitia (moaales or something similar) •t 6 7 Mon hs, verrr 111 for almost a mo th. At 10-11 months allting, hyperactivity and adult foods rtad s11Tlultanelusl7 •hivera" az-e a minor feature of Glenn's MSG sensitivity. 'l'bose I have observed (examination within one hour of nnusage) e e atypical or conta.rainated by his marked byporkines:t . The lfl'1al of B-6 (25 mg. daily) + MSG (amount Accent usad unknown) aa five da7•s in duration.

M. G. Stemmermann, M.D.

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Haillard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

May 10, 1976

Dr. M. G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Dr. Stemmermann:

Enclosed is the report from Medallion Labs. I am just back from a meeting today so I know no more about this than what is on the sheet. I gather they purchased a local sausage with MSG to use as a control. They also give no indication of the margin of error on the analyst's. I will try to find out about that, but thought you might like to see this in the meantime.

Sincerely,

LRL:a
enc.

P.S. I am enclosing an article from April 1976 Playgirl (!!!) which was brought to my attention recently and am wondering where the author got the details. Were you by anychance contacted? If not, where could the information have come from (see red arrow on enclosed copy) I am also enclosing an article from a recent Globe which I thought you might enjoy seeing. I heard via the grapevine that there was also something in the DAILY NEWS several weeks ago which horrified me. I have not been able to get hold of the item and am having "nightmares" about what it might say.

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

May 13, 1976

Dr. M. G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Stemmie:

You certainly are correct, if the MSG action is hypothalamic, the blood brain barrier would probably not play an important role. I really did not completely comprehend this myself until I got the letter from Mandel. Perhaps you can suggest a reference so that I can learn a bit more about which parts of the hypothalamus are, and which are not under the control of a BBB.

Sincerely,

*L rtz,v<-Z_*

LRL:a

P.S.- Dr. Stemmermann:
Please note spelling of Dr. Reif's first name.
Ame Hoffman
(Secy.)

LIANE REIF-LEHRER PhD
Department of Ophthalmology
Harvard Medical School
and
Department of Connective Tissue Research
Boston Biomedical Research Institute

Mailing Address:

20 Staniford Street
Boston, Massachusetts 02114

Telephone: 617 742-6580 x326

May 18, 1976

Dr. M.G. Sternmermann
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Sternmie:

I got a letter from Beatrice Truro Hunter today which answers the questions that I asked in my recent letter. She apparently must have spoken to you in 1973-74. I was not aware of the 1973 Medical World News report on Dailey. If you have a copy, and could send me one, I would appreciate seeing it.

Sincerely,

L (a"—'-Z

LRL:a

April (1976)
Playgirl

YOU ARE POISONED!

WARNING:
THE FEDERAL GOVERNMENT
HAS FAILED TO DETERMINE WHETHER
OR NOT FOOD ADDITIVES ARE DANGEROUS
TO YOUR HEALTH

by BEATRICE TRUM HUNTER

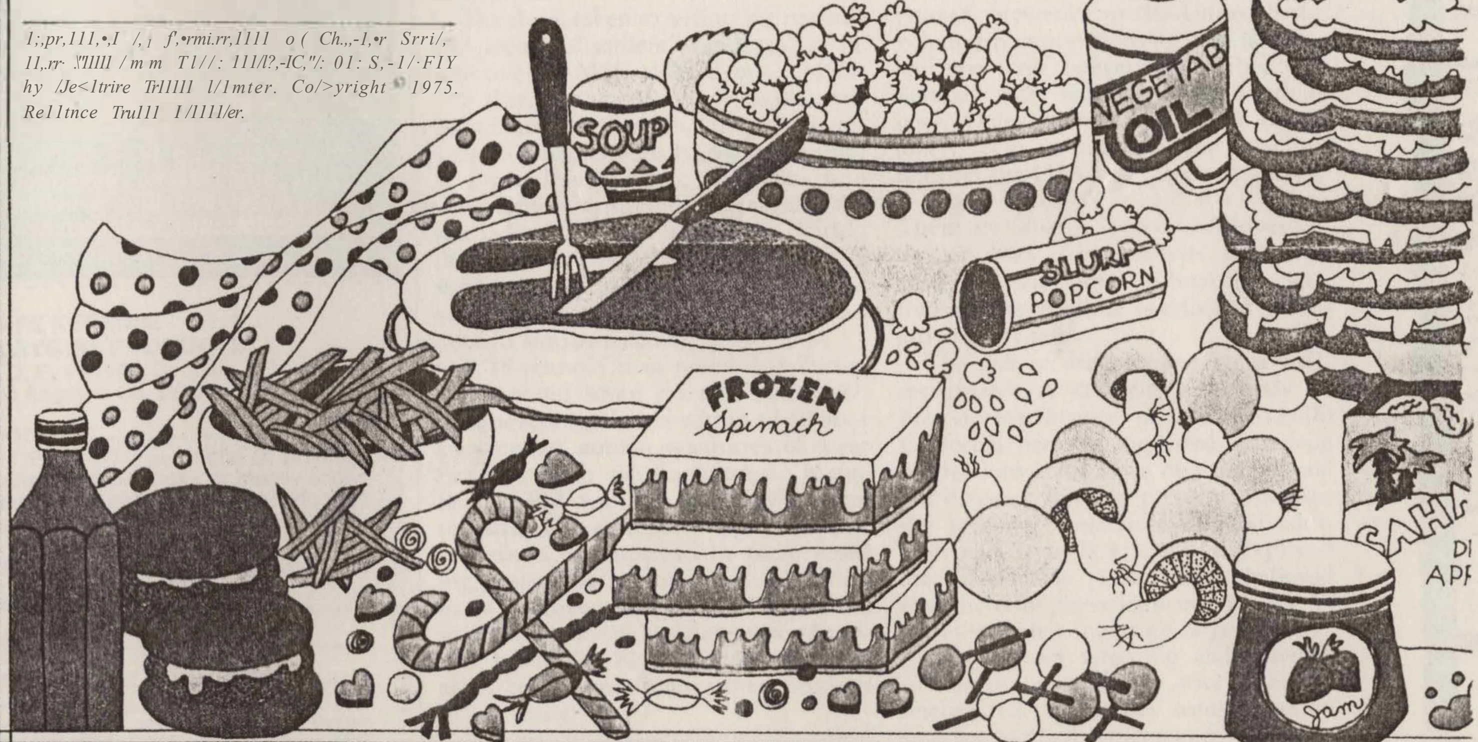
"People are finally waking up ro rhe facr 1h1r thl' awr.1gl' Amcril":111 d.1ily diet 1s suhsc1nri.illy ,1dulter.1tcd with unnecessary and poisonous chemicals and frequenrly filled with neutral, nonnurririous suhsrances. \V/e are being chemically medicated ;1gainsr our will and d1eared nf t,,lld v.d11t' hy lmv-11urri1io11 fonds. Ir is time to rak(' a c1rt.ful look at 1hl' prolifil" use or additives pcrme,1ri11g our foods." Senaror Gaylord Nelson made rhar srarenwnt on rhe flodr of illC' l Jnired St;1tt·s.Sc11atc 111 1972 when i111rotluci11g legislation to eliminate the use of unsafe, unresred, and unnecessary chemical additives in rhe food supply.

In recent rimes we've had an enormous rise in rhe production and consumption of convenience foods, which in rurn neared a sharp incrc.1se in rhc use of food addirivcs. Higher remperarurl'S, gre.ucr pressures.. incl more agi. r.1rio11 are required 10 prepare rhese highprofir convenience foods rhan rnnvenrionally prepared foods. Because of this, rhe convenience foods require many ad. dirives ro make up for the flavor, color, tt·xt11re, and other properties losr during the processing. And since rnnvenience foods are nor necessarily eaten immed iarely after they are packaged, an array of preservarivcs, anrioxidanrs, and mhcr addirivcs is 11cl'lkd w cxrcnd rheir shelf tile and keep rhem marketable for long periods of rime.

The Food and Drug Administration (FDA) and the Unired Srat('S Department of Agriculture (USDA) are the federal agencies responsible for assuring rhar chemical :iddirives used in the Ameri::111 l<i,hl supply are s.1te. Bur these agencies have been lax and ineflecrive. As a result, American consumers have been inadequately prorecred by two agencies that have allowed rhe food ancl beverage processing indusrry ro use legal loopholes anti del.1ying rncrics ro weaken governmem comrol over· food and beverage aiklirives.

The follow111g incidents are linkec.l to-gerher by a common bond: the: adverse re:iu ions resulri ng from exposure.: to :i chemical additive intentionally introcluced inro food. In each case, the assumprion was macle that the additive was safe. Adverse effecrs were found only after public exposure. In some cases, highly

1;,pr,111,•,I /,1 f,•rmi.rr,1111 o (Ch..,-1,•r Srri/, 11,.rr· .'\'11111 / m m T1//: 111/l?,-IC,"/: 01: S,-1/·FIY hy /Je<1trire Tr11111 l/1mter. Co/>yright 1975. Re11tnce Tru111 I/1111/er.



Ilh1,lr.11t,I b\ Al IX\'1)RA \\ Al INI R

sen s ltlvc individuals sulk·1LLI temporary allergic discomfort or pt't>plc sufk·red radical personal icy ch;in/.!es. In ocher cases. the effeccs were gr.1,Tr. resulting in roxiciry or even in de,11'1. These imidcnrs are well-documen1l'li. Bur rhey lorm only rhc rip or an ilcherg thar is srill largely submerged. i\s it surfaces, we arc learning its enormous size.

- A pediatrician cxpcrienlcd a strange scr o(symptoms whenever he alt' in 01inesc restaurants. Fili:ecn ro rwcmy minutes after earing rhc first dish, he would experience symptoms closely resembling a hearr arrack: general weakness, palpirarions, and a numbness at the back of his neck which would gradually radiate co his arms and back. The physician described his symptoms in a lem:r to rhc editor o(a medicd journ,d and pret ipir.ued a llo\ld \l(uirrespondenu· wl m(H1osodium glu1.un.11c (1'l C), i ll.l\m e11h.111tcr use! extensively in Chincse rcsrauranrs, as well as in protcsscd fi>cds and in many homes. The physician was surpri sed m learn that many people suffered similar S)'mproms, and other symptoms: profuse c)id swearing. a righv.ncss on borh sides ol the he,ld, and rhrobbing sensations in the he.id.
- [n dw 1970's, a six-llH)Jllh-old girl began to cat the regular family food. The child scarred co h,we seizures, resembling shuddering fits. The seiwrcs grew in frequenly, and by rhe rime she reached one year of age, the child was experiencing more than a hundred seizures daily. She showed no signs of losing consciou sncss. Repeated clecrroencephalogram rests revealed no conical disrnrbance.

The child, rakcn co a clinic for nervous and menral disorders. was found m be sensitive to l\[SG. Placed on a t-ISG-free diet, supported heavily with anti-rnnvulsanr medication, the child lesponded well. Gradually, the medication was withdrawn. Then, ,1frer the child was without symproms for a)'car. she w,l, led 011e-half of a frankluner. \'v'irhin three hours, rhe child experienced a shuddering seizure. A week later, a bit of spaghetti sauce containing MSG induced a similar reacrion.

- A 58-year-old man noted that during rhe previous seven years he had developed severe headaches within a half hour after eating normal quantities of meat products such as frankfurters, bacon, salami, and ham - all of which are sodium nirri re-treated. These attacks, sometimes accompanied by facial flushing, lasted for several hours. No other filods or beverages produced headaches in the man, nor did he otherwise l'xpcril'llle headaches. Nor had recurring he.id. aches been nored in any other memlx·rs of his family.

The man undcrwcm a series of 111<dicl rcsrs ro determine whether rhe sodium nitrite was the cause of what he now termed his "hot-dog hcad:1d1cs." 1 lc.1d-athes octurred eight our of the thirteen times the man ingested sodium nitrite. They ncvn onu/rl'll .1(1er he ingested the sodium irirrirc-free comrol solution.

llr CXliuding nitritc-Cllrl'd llll',IIS from his diet. rhe m1l1 wa !'recd o(hcad.1d1es. \\'lic11 he i11,1dvcne1HI)' u>1ls11111rl ,1 1litritc-lurnl)'roduu, thl' he.1dati1l' would I'l'I 1lr1l.

- At bre,1kfost one 111oming a child ate a spoon(ul or rnrnHakes without any other food or beverage. \'v'irhin minute, rhe uvula (the pendant flesh! ' lohe in the middle o(the posterior border o(the soft pal arc) in the Fiack of her throat swelled. She felt extreme fatigue and moved her limbs only wirh great effort. ·11le thild was rested for liiod allergies. Tests \\'ere lll'l a1ivc. 011 .111uthn t;ll,l-sio11. she ,lll' i>11ll' rl-u>11 1i1utc,l 111.1shlli potatoes: the ,r1111,1oms o(s,"ilk11 11ntl,1. exrreme forigue. and weaknc,s returned. Tests for pmaro allergy were negative. The antioxidants nI ITand HI IA, present in hoth rhe cornfl.1kcs :111d)'\lt,1t\lt'S, wn1' the common L\cnornin:ttor. As long as tllL' girl a\'(Hded loods rnnra1n111g rhe c rno additives, her artatks did nor remr. .
- As reLt111ly a J<)(1(i. outl1rt".1b ol l11.tl heart disease among heavy beer Lirinkers in rhe United Sures, Can.1d,1, .111Li Belgium, were attributed to rnbalrous salts. Used in beer to srabilize the foam and ro prevent gushing, chcse rnbalrous saJrs had been judged sale. They had been used in European beers since 1956 and in rhe Llnircd St,J[es and Canada since 19(i1. A1ter the dc.11hs \\'l're rr,tCld to the cardimoxic action of these compounds, breweries in the United States volunrarily stopped using rhc additive and one large brewery in (Jucbec City dumped more than $(i00.000 worth o(hccr. Only :1(1er a 111mher o(de.1th finally were attribuced 10 the u>h,tltous salts.did the FDA ban these compounds.

There arc other \\'ays lixid :1ddi1ivcs t-ndanger lives; for example. rhey may interacr with other subsunces. Such interactions may be overlooked in additive safety resrs.

The risk of drug interaction is well-rccognizcd. A computerized smdy of prescription hisrory o(nearly ,12,000 California patients suggested char drug inreranions could have occurred in one our oi every th ineen prescri prions. But the possible inreraccions or food additive and drugs is a largely unexplored area. For many years, ir was believed that the Olli)' physiologic effect of cycla-111lllS w,1, tli11 i1lgsl i1lg large :111m111s pn>dllle,I swol sol tl'1li1lg ,ind di.1rrlll',1 in 111111,11s Ir was only ,1frcr exrcnsin• testing th11 cyda111.11cs were liiund to i111cdi..n· with the thl'r.q,eutic d'it·uivcness of co111110l1ytco11i1111cd *011* />.igc68)

(*co11ti1111cd from page* 66) used drugs such as diuretic drugs (rhiazidc), arnicoagulanr drugs (coumarin), cenain drugs that are bound co plasma protein, an,I :111 :111tibimic (li1lom)'ci11).

One c1se o(a food additivl' decreasing drug activity was observed in an English hospiral. Several patierns on antirnagularn drugs cominued w show abnormal coagulation. Test results seemed co indicate drug underdosage co a consider:1ble degree.

Before arrempring co increase rhe dosage, rhe phys cians questioned the patients abour rheir diet. All of them had been earing French fried potaroes. Upon investigation, rhe physicians discovered rlut the cooking oil used to fry rhe poraroes contained methyl polysiloxane. This substance, which is added to some cooking oils to give poraro chips a crisp, dry, and attractive appearance, was suspected of having interfered with drug ,1bsorptio11. About a week afrer thl' patients sropped ingesting rhe oil, a repeat blood test showed a rerurn co normal rherapemic values of the amicoagulant drug.

This kind of imeranion of food additives and drugs also needs co be viewed within a larger framework. Some food consriruenrs also comljine with certain drugs in the gasrrointesrinal tract. These combinations may be harmful - or even fatal - co rhe patient. Food-drug combinations which are already recognized .ire cheese, wine, beer, or liver with a group of tranquilizers (monoamine oxidase inhibirors); dai ry products with an antibiotic (terracydine); fats with cerrain antibiotics (griseofulvin and neomycin); leafy green vegetables with amimagulams; and vitamin C with a sedative and anrinausea agent (pemob,1rbiral) or an anesthetic (procaine). Such findings further demonstrate the limitations of any safory resting program rhar examines a single substance wirhour considering rhe total environment.

Even more alarming is the possible connection berween an increase in rhe use of artificial flavoring and coloring and a dramatic rise in the number of hyperaaive children.

• A seven-year-old boy stomped around, slammed doors, kicked walls, and charged oncoming cars with his bicycle. Ar school, he was disruptive, and his hyperaaive behavior affected other children. His scholastic achievement was poor, and he was placed in a special learning class. Numerous ped iarricians, neurologists, ps)'chiatrisrs, and psychologists were consulted. In reviewing the child's diet, ir was found that he was eating large quantities of convenience foods containing artificial colors and flavors. Many of these additives contain salicylates: 'foe child was placed on a salicylate-free diet. Foods with naturally occurring salicylates, as well as those foods containing salicylates in artificial colors and flavors, were excluded. Alter a few weeks on chis dier the bo), clisplayed a dramatic personality change. He was well-adjusted both ar home and at school.

Ben F. Feingold, M.D., allergist and pediatrician, traced a parallel between sharp increases in hyperacriviry and ocher learning difficulties and the rise in the sales of synthetically flavored and dyed foods and beverages in the past decade. Although there are only eleven basic synthetic colors, there are some 2,500 to 3,000 flavoring agenrs.

Feingold cited a California study that showed the incidence of hyperkinesis in certain school populations increased in the lase ten years from an average of rwo percent up co 20 to 25 percent, and in some cases, up to 40 percent.

To dare, Feingold has created successfully a number of hyperkinetic children, and his results have been duplicated and confirmed independently by other physicians. Feingold reported char even a slight violation of the diet can cause symptoms of hyperkinesis to emerge within a few hours and to persist for twenty-four co forty-eighr hours.

There is growing awareness of the assault from an ever-expanding number of chemicals on rhe body and their porenrial harmfulness. "In the past forty years, the environment in which we live has been altered to an extraordinary ex. rent," wrote Dr. E. Cuyler Hammond and Dr. Irving J. Selikoff jointly in a background paper for the American Cancer Sociery's annual seminar for science writers in 1974. Among rhe environmental changes, the rwo docrors singled our food additives for special comment: "Our food has chemicals, designed co improve irs caste, freshness, appearance - bur which are strange to our intestines, livers, kidneys, blood."

This awareness should alert food processors, as well as scientists and regularory agencies concerned with food additive safety, to a broader view of their responsibilities. Food processors must regard qualities such as attractive appearance, uniformiry, and long shelf life as minor facrors. Nutritional food values must become the prime concern. In order to better serve consumer needs, food processors muse rechannel their energies. Food processors already possess enormous technological skills and facilities, in addition co operational efficienly. No drastic alterations would be required to redirect present research ro emphasize the nutritional qualities of food rather than the further extension of shelf life, color and flavor uniformity, and ocher features char require numerous additives. Food inreresrs could edu. care and train their researchers to have a scienrific awareness of important concerns, rather than have them view food manipulation and engineering merely as subjects of physical and chemical technology. ■

Food	Chemical added	D_angers
Fr,tnkfurtl.'rs, bacon. lunch 1111at; and han1	Sodiun1 ni1 rit1.:. a curing agl·nt	i\lay cotnhinl' with a111ine'i in food and forn1 cancer-i11di1 ing lOmpound .
Maraschino cherries	F D & C r<d No. /4	1::xperi111entally cla1nagecl ac.ln•11d cortL·x of dogs.
Fro1,l'l1 spinach	E D T A , a sequestrant	Ties up iron and oth<·r valuable rran: l·le,nents whid1 may bt· prc,ent in th< food.
lt:l' cn:an1	Polyoxyl.'l h:vlL'11L' t0111pou11d a L'1nulsifit•rs	Can ,ilter ,thsurption of food from intl'lin1...s.
Fresh nn1shroon1s	OisulfilL', an antibrowning agl.'lll	InterfL·rt· with Iht• g<•neti<· hlu<.•print of th< body.
Cheese	Sorbic acid, a pn:sc:rvat ivl.'	Interferes wi1h functioning of 11un1L·rous enzyn1e ySll'l11.
i\ll',ll	DES (dic·thrlstillwstrnl), J grow1h-pronuuing hor11101H'	Susp1.e11.d as a hun1an nt1u:1.•r inl°itl'r.
Chickl.'n livl•rs	Ar-;1_•nic, t growch-pro11101 ing suh..,,a,u·l.' uLd in puul11,· h4d	Accumulative and toxic.
Co111ntL·r1_ial whitt· hn•ad	Calciu111 or sodiu1n propio11a11.•	Alll.'rgi<.· n·aninns.
l\1JrgarinL'	UL•111o:1tt· of oda, a prL'..,l'rvativl.'	All<:rgic reactions including al'11l\· hiv<.:S.
Ycgc·t.oble oil	Bl 1H· (bu1yla1L·d hydrox_vtolu<·nt,) and UIIA (butylatcd hvc.lrox_'anisole)	J\lll.'rgiL rl·actions, acute hivc,, '"clling of lip,, ey< he1nor1 haging.
Crl.'t"ll pl'ppers	\Vax coating, usl.'d as a prl'"il'f\'.ltiVl'	l1npuritit•s in wax 111ay be \:lllH, 'l.'I i1u:iti11g.

Dr. Steinemann 5/14
thought this might
interest you. Liane

Dr's Liane Best & Silver,

MAY 14 1976

Sirs:

Read your recent article in Prevention regarding M.S.G.
I discovered by process of illimination what she was allergic to. Her reaction starts with itching palms & feet her mouth begins to swell and she eventually passes out. We have to give her Benydrid either 6 minutes to keep her from choaking to death. When its over her stomach is upset for a week. We read labels; everyone. This should be banned from the market.
I don't know how this effected her as a baby. Could she be the cause of Crib death? Sure hope your research will serve to help this problem.
Campbells soup Co would be a good place to start.

Sincerely
Mrs Norene Obermeyer

; t

May 26,, 1976

Liane Heit-Lehrer, Ph.D.
20 Stanitol'd StNet
Boston, Mass. 02114

Dear Dr. Heit-Lehrer:

Enclosed is a copy or an article the local paper here wrote about Dx-. Stemmermann. I thought you would like to see it with all the coDrectiona ahe baa added.

I plan to come to Boston in ugust with a stopover there on my way to Ossippe,, New Hampshire tor vacation. It you happen to be in Boston on Saturday, August 7th or 8th, I would really like to meet you.

Dr. Stemmerma.nn had hoped to BBlue Penciled" the article in the paper before it was printed but the paper didn't give her the opportunity to do it.

Regarding the Beatrice Trum Hunter letter--the article in MEDIC"AL WOHLD NEWS which she re.terred to was onethhat featured Dr. Olney•s work in which he incidentally mentioned the Dailey patient about whom Dr. Stemmemann had written to him. We do not have a copy of this. Dr. Finegold' a work -as also .featured.

Thank you for all the vonderO l work you have done on th!s project and we will let you know if anything new develop•.

Sincerely yours,

Betsy

LIANE REIF-LEHRER PhD
Assistant Professor
Department of Ophthalmology
Harvard Medical School
and
Associate Scientist
Department of Retina Research
Eye Research Institute of Retina Foundation

Mailing Address:

20 *Staniford Street*
Boston, Massachusetts 02114

Telephone: 617 742-3140} *x*326
617 742-6580

May 28, 1976

Dr. M.G. Stemmermann
Owen Clinic Institute Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Stemmie:

Enclosed is a check to cover the expense for the sausages and mailing.

I have a very exciting potential case. I received a letter from a school teacher who had seen my work somewhere, and who has a child who has been on dilantin on and off for about 10 years and is beginning to have calcification problems. Other than this, everything is alright. I will keep you posted.

Sincerely,

Liane

LRL:a

LIANE REIF-LEHRER PhD
Assistant Professor
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and
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June 1, 1976

Betsy Matthews
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Ms. Matthews and Dr. Stemmermann:

Thank you for the article from the newspaper about Dr. Stemmermann:

We usually take some vacation time in August ourselves and don't know yet when it will be, so it is hard to say whether I will be here on August 7 or 8. However, there is a good chance I will be around, in which case, I will be happy to meet with you.

Thanks for the information on Beatrice Truro Hunter. I have had some correspondence with her in the last week and she also filled me in on the details.

I am off to Washington tonight and to San Francisco for the Biochemistry meetings on Thursday, and then I have a grant due July 1st. I will try to call after that if I have gotten any interesting news on the latest "case".

Sincerely,

Lr

LRL:a

Dr. Liane Reif-Lehrer

LIANE REIF-LEHRER PhD
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Department of Ophthalmology
Harvard Medical School
and
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July 6, 1976

Dr. M.G. Sternmermann
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Sternmie:

Thank you for your letter of July 3 and the enclosed article from the Huntington Herald Dispatch. The most interesting thing perhaps about the article is how poorly written it is. It starts somewhere down the road and kind of meanders ending with that long quote from Ebert. I certainly agree about the word "allergy" always coming into the MSG story, which is very misleading. I:11 try to do my best on getting some hard data as soon as I can. Meanwhile, I hardly think it's worth the effort or the time on either your part or mine to answer this particular article.

Please keep me posted on anything interesting that happens.

Sincerely,

L1

LRL:a

P.S. I am enclosing some notes that I took from a strange phone call I got today. Can you make any heads or tails of this?

LIANE REIF-LEHRER PhD
Assistant Professor
Department of Ophthalmology
Harvard Medical School
and
Associate Scientist
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July 22, 1976

Dr. M.G. Stemrnermann
1319 - 6th Ave.
Huntington, West Virgina 25701

Dear Stemrnie:

Thanks for your notions on that phone call. I do believe that woman told me she had an electric stove so the gas leak is probably not pertinent. I've written to ask if there is any family history of benign essential tremor.

What can you tell me about amyl nitrite which is apparently used for angina. I had an interesting phone call a short time ago from someone from the Lipton soup Co. who wanted to know what I knew about glutamate, and he mentioned that apparently that apparently the symptoms of amyl nitrite inhalation are similar to those of Chinese Restaurant Syndrome.

I have been "bugged" lately by some letters from a man named Giacometti from COFAG. I believe he is probably the Italian equivalent of Dr. Ebert. Do you happen to know him or anything about him. Best regards.

Sincerely,

Liane

LRL:a

October 14, 1976

Liane Ie11'-Lehl'er, Ph.D.
20 stani1"ord Stree•t
Boaton, Mass. 02114

Dear Liane,

fte•••o•·rgiv• m• tor neglecting to anever your letter or July 22, 1976. During vacation• it apparantly vaa "lost" and baa recently come to light.

Probably by this time you already learned that anyl nitl"ite can produce &JJDPtoma aot unlike thoae 01' Chinese Restaurant SJndrome. Of particular interest to me is metaboliam 01' nitrites in 1'ooda producing nitroaam1nes which are oarcinogena.

On October 22, 1976 I have agreed to an interview with a Canadian Broadcast Company fJor a program described as be1ng like "60 Minutes" on . I told them that having alread7 given 999 MSG intel"Yiews dul"ing the past year that th• 1000th would probably not hurt me. It you have any pet notiona that you believe I ahould stress let me know. As you may N member I can almoat alva7a be reached betveen 12:00 and 1:00. Incidentally this int•rview vaa apparently stimulated by tlie Nev !egland Jou,mal ot Medicine article.

Sineere17,

Some thought• rl relationahip *ot* "shiver" and seizures•

"Shivering" nom a11y ia one manitestation *ot* h7Pothalamio control *ot* bod7 temperature. Theretore, as a epileptoc maniteatation it has been olaaaitied with "diencephalic seizuns," commonly aaaociated with tumora (colloid cyata) *ot* the ventriculea with intermittent spinal tluid block. Obviously it is important to ditterantiate between "normal" ahivering and abnorma1 but non-epilept6c shivering.

Other than "tumo:r-aigns", the EEG *ot* patients with shivers shows no conaistent abnormalitiea. Int he Gibbs• atlas, (1952 "' edition) "shiver1ng" is listed aa an aUI'a in 0.,5 and 1otal manitesitation in 1. (4.27 caaes) associated w1th 6/14 per second positive spikes. Thia EEG sign is believed by many encephalo• graphe:s to be normal in ahild:ren. Certain11 it is much more oommon than shivering attacks and the relationahip is questionable.

The cbier ditterenee between ep1lept1c "shivers" and MSG shivera, is the absence *ot* an7 sign *ot* disturoed consciousness in the latter. The child doeannot stop whatever he is doi , nor does he otten dl'Op whatever he m7 be holding.

Ot the three ohildren I have studied to date, none share an:y other C.N.s. oharacte:ristio. DaileJ is normal; abodes retal'ded; Hager typica1 minimal brain d7a!"unotion with mild aigns of neurological impairment on the right side of the body.

* * * * *

The Rhodes &1'9 on vacation.

* * * * *

Hager has a sister, tive years older than he normal without "shiV01"s"•

* * * * *

Do whatever you like about publiehing• Have you talked with Vivian Shih at Mass• Genera1? Sho will probably know about increase in the "central cluster" or glutamate arter meala in a variety 0r chiltlren.

M. G. Stemmermann, M.D.

EYE RESEARCH INSTITUTE
OF RETINA FOUNDATION
20 Staniford Street
Boston, Massachusetts 02114
(617) 742-3140

November 5, 1976

Dr. Stemmerman
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington West Va. 25701

Dear Stemmie:

Please excuse me for not answering your letter of Oct. 14 sooner. I have recently accepted an appointment to be on an NIH Study Section and for the last many weeks, I have been doing nothing but reading grants which finally ended in a trip to Washington last week and I am only now trying to get back to my normal activities.

My curiosity about amyl nitrite was about whether it is still used clinically, what is it in fact supposed to do, and is anything known about the mechanism - - - I too am interested in the metabolism of nitrites in foods producing nitrosamines, but, really more in terms of how it effects my eating habits and those of my children than as a research project.

I was interviewed by the Canadian Broadcast Company on October 13. It was actually I who suggested, after they insisted on knowing who else they should talk to, that they contact you (I hope you don't mind). The contact was actually stimulated not by the NEJ Med. article but rather by my article (copy enclosed) which came out and was picked up by a Professor of Nutrition who has just finished writing a book with the woman(Ruth Frame , who I suspect interviewed you. I was quite insistent that I would only agree to do this if I could screen the final airing, and they originally agreed, but I'm not at all sure now that they will do it. I hope this wasn't too much of an imposition Ythey were at one point quite insistent on interviewing some of the families of the children and I finally allowed them to contact one of the families in New Hampshire that I got viO...Lombroso, after first checking with the family. I would be most curious to know how it all went and what you thought of the whole thing.

Sincerely,

Lrāne

LRL:a

Special Article

Possible significance of adverse reactions to glutamate in humans[1]

November 8, 1976

Liane Re11"•Leh:rer, Ph.D.
20 Stanitord Street
Boston, Maaa. 02114

Deal' Liane,

Many thanks *tor* the "Special Arti:cle" :reprint. I thought that I knew all that vaa known about MSG but apparantl7 I miaaed aome •Ot the animal woric. There ia ope objective observation t:ai.tmentioned e1ther in your review *ot* experimental wo k or 1n Table 1,, namee17, normal or low body tem ttature. Poa,aibl7 I haven't mentioned this but 11 is important in *ditte*rentiaticm in children. I:f a child "shivers" and ia also teveriah, I would doubt that MSG la reaponaible evenit he has recently oonaumed a bowl *ot* wonton with a side order of West Virginia sausage. Do 7ou know it anyone else has made a similar observation? Unfortunate1y negative findings azte too often i ored.

How 1ε you uppl'Y' *ot* rep:rinta for this artlole1t If 7ou can spaN them I would kike to havo two. one for the pediatrician who tirst treated the Daily chilo. The other is for :Or. Ruth Harris, formerely of Columbia now chist or Pediatrics Or Marshall University Medical School. This school i• in th& process of de•elopment, it owns departmenth eads, a rev l'eaidenta, but no etudents un il the autumn of 1977. Dr. Harris and I are tyying to get something going with inborn metabolic errors (gllactosemia is b3r bag). Perhaps we can inteNat hr in MSG.

Did you ave a good time with the T.V. people from Canada? I won't be able to viev the show here, but perhaps you can getilt in Boston.

Sincerely yours,

Special Article

Possible significance of adverse reactions to glutamate in humans[1]

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ABSTRACT

Of those exposed to Chinese restaurant food, our studies indicate that 25% report adverse reactions (Chinese restaurant syndrome (CRS)), presumably to the monosodium glutamate (MSG) content. The possible significance of the symptoms is discussed in the light of the known neuroexcitatory activity of MSG. It is suggested that CRS may result from a "benign" inborn "error" or metabolism that is deserving of further study, particularly in individuals with certain other metabolic abnormalities or who are on certain types or drug therapy.-Reif-Lehrer, L. Possible significance of adverse reactions to glutamate in humans. *Federation Proc.* 35: 2205-2211, 1976.

Monosodium glutamate (MSG) is widely used as a flavor enhancer. In the last decade, a sizable literature has appeared concerning the effects of glutamate in vivo. These experiments have been confined almost entirely to rats, mice, chickens, and, in much smaller numbers, monkeys (1, 6, 42, 56-59, 62, 71, 72, 79, 80). Implicit in many of these studies was the question of whether or not MSG is safe for human consumption. Although this question is of obvious interest, the more pertinent question to which the studies should have been addressed (but concerning which, almost nothing has been published) is not whether the population at large is at risk, but rather whether particular groups of individuals may be adversely affected by consumption of unregulated amounts of this material.

Glutamic acid is a natural component of proteins. It has been known for some time that this amino acid possesses somewhat unique flavor-enhancing properties (78) perhaps related to its known neuroexcitatory properties (14, 18, 38). Since 1910 (44), monosodium glutamate (MSG) has been increasingly used as a food additive. Current world production is 262,000 metric tons per year (77). It is one of the active ingredients (along with salt) in soy sauce (16), is a common ingredient in packaged foods, and is sold as a condiment for home use. Monosodium glutamate is also found in the free form in a number of natural foods. Appreciable quantities of MSG are sometimes used in restaurants, especially Chinese restaurants. MSG is on the FDA listing of GRAS (Generally Recognized As Safe) substances.

In 1957 Lucas and Newhouse (42) reported that neonatal mice injected with MSG developed severe retinal damage and became blind within several weeks. Subsequently other workers reported similar findings in rats and chicks (56, 62). Isolated embryonic chick retinas are severely damaged when exposed to glutamate (69). In addition, a number of workers have reported damage to the arcuate nucleus of the hypothalamus of rodents treated with MSG (6, 56, 57). Reports of similar damage in monkeys have been very controversial (1, 6, 28, 55, 58; 59, 71, 72). Susceptibility to MSG appears to be dependent on both age and species.

In 1968, a discrete group of symptoms experienced by some people after eating in Chinese restaurants and thus often referred to as "Chinese restaurant syndrome" (CRS), was reported to be due to the MSG in the food (5, 74). Shortly thereafter, Schaumburg et al. (75) tested a group of individuals with increasing dosages of MSG dissolved in clear broth and found that those who "complain" of Chinese restaurant syndrome are sensitive to less than 3 g; however, all but one subject in the study exhibited symptoms given a sufficiently high dose of MSG. Shortly after the appearance of some of the above studies, it was recommended in 1970 that MSG be removed from packaged baby foods (31).

Recently Reif-Lehrer has reported (67) that 25% of a population sample who have been exposed to Chinese restaurant food exhibit at least some adverse symptoms; children are apparently also susceptible.

WHAT IS THE NATURE OF THE CRS SYMPTOMS?

What in fact is the so-called Chinese restaurant syndrome? The condition has been recognized for many years

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Abbreviations: MSG, monosodium glutamate; CRS. Chinese restaurant syndrome.

by those "afflicted" with it but even many of its "victims" were not cognizant of its etiology until the late sixties when it was reported as being caused by MSG (5, 74, 75). In some of the early reports concerning adverse reactions to MSG, the symptoms appeared to be allergic reactions to contaminants of the glutamate from the source of isolation; e.g., individuals who reacted to MSG extracted from beets did not react to this material obtained from wheat gluten and vice versa (64). There may be a few individuals who are allergic to MSG; but Chinese restaurant syndrome does not appear to be an allergic reaction (74, 75).

In 1968, a Chinese physician reported that since his arrival in this country he had exhibited strange symptoms whenever he ate in a Chinese restaurant; he suggested that it might be of interest to find out more about this "rather peculiar syndrome" (39). Later that year, Schaumburg and Byck (74), as well as a group of students from New York University School of Medicine (5), reported that so-called Chinese restaurant syndrome was, in fact, caused by the MSG in the food.

The following year Schaumburg et al. (75) reported a somewhat more definitive injection and ingestion study on 56 individuals in which they pointed out that when MSG is given orally, symptoms appear only if a meal is eaten by a susceptible individual on an empty stomach. Given a high enough oral dose of MSG in a low-protein low-fat medium, all but one subject exhibited some or all of the characteristic symptoms, i.e., tightness-burning-headache sensations. They reported that 7 g of monosodium o-glutamate, 5 g of sodium chloride or 5 g of glycine did not provoke symptoms in two subjects who did respond adversely to 3 g of monosodium L-glutamate. These authors determined that the intensity and duration of the symptoms appeared to be related to the dose of MSG. The highest dose used was 21 g (oral). Only one of 36 subjects did not respond, and this individual did get symptoms after 50 mg (intravenous). Thirteen subjects were injected intravenously, 25-125 mg giving minimal symptoms. The first symptom appeared in 17-20 sec and was a burning sensation in the upper torso; chest pressure symptoms came about 5 sec later; the last symptom to appear was facial pressure which lasted about 2 to 3 min (compared to 30 min after oral administration). Schaumburg et al. reported (75) that the chest pressure sensation can be very alarming and that one of their subjects, a physician, had requested an electrocardiogram after a Chinese meal; however, subjects "infused" with 500 mg MSG showed no electrocardiographic changes despite the presence of severe chest pains. In two subjects, 50 mg (oral) of diphenhydramine (an antihistamine) did not affect the response to oral MSG. This would suggest that CRS is not an allergic reaction to MSG. Aspirin (600 mg) also had no effect. These authors suggested that the burning sensation is a peripheral phenomenon rather than being due to nervous system stimulation. They reported that the headache pattern, when present, is that of a combined vascular-muscular contraction headache. They concluded that those subjects with CRS had oral thresholds for MSG of 3.0 g or less. Eight out of 36 subjects (22%) in their study fell into this category. This is in good agreement with the data obtained in our study (67).

In 1971, Ghadimi, Kumar and Abaci (26, 27) reported that Chinese restaurant syndrome symptoms were remarkably similar to "the diffuse and evanescent action of acetylcholine in humans" and suggested that Chinese restaurant syndrome is a "transient acetylcholinosis".[2] In their study, 14 subjects were given 150 mg MSG per kilogram body weight (approximately 8-12 g per person) orally after an overnight fast. All volunteers developed at least some symptoms and were categorized according to severity into four groups. The symptoms described by their subjects are listed in Table I, and are very similar to those reported by Reif-Lehrer (67). Ghadimi et al. (26, 27) reported that larger doses of MSG resulted in only mild symptoms when the same subjects were "primed" with parenteral atropine (an anticholinergic drug). On the other hand, in one subject with questionable response to the initial dose of MSG, severe symptoms developed when the MSG was given together with a subclinical amount of prostigmine (a cholinergic drug). These authors also reported a 30 decrease in cholinesterase activity in plasma 60 min after MSG ingestion; however, it is not clear that the data shown are really statistically significant. It is interesting that in one dog injected with acetylcholine by Ghadimi et al. profuse salivation and lacrimation resulted; these symptoms were also reported by subjects in our study. However, unlike the effect reported in humans by Ghadimi et al. after MSG ingestion, the dog injected with acetylcholine had a greatly reduced heart rate. Cholinesterase levels were measured in the plasma of this dog and did appear to exhibit a transient decrease. Ghadimi and coworkers reported no symptoms in subjects treated with histidine. Likewise, in an earlier report by Levey in 1949 (40) several amino acids were administered parenterally; of these, only glutamic and aspartic acids gave rise to undesirable side effects, e.g., nausea and vomiting.

In 1972, Kenney and Tidball (37) suggested that the CRS phenomenon might involve the "cutaneous free nerve endings or chemical sense" and also pointed out that subjects experiencing headache often compare "the pain with that of migraine with similar prodromata." These authors concluded that MSG was the initiator but not the ultimately effective agent in this syndrome (37).

It should be pointed out that a number of papers have reported that MSG is not the cause of the Chinese restaurant syndrome (48, 73). In some of these studies subjects were mostly males, who, according to other reports (5, 37, 67), are less susceptible to MSG effects. For this and other reasons these conclusions are questionable and have been refuted by others (32, 55). From all the studies that have been reported, the balance of the evidence seems to indicate that MSG is, in fact, the causative agent of Chinese restaurant

[2] It is of interest in this regard that a small percentage of the acetyl moiety of acetylcholine in rat and guinea pig brain slices can apparently be synthesized from [^{14}C]glutamate (51).

TABLE 1. Reactions to MSG

Symptoms reported by 14 volunteers given oral doses of MSG[a]
Complaints definite but mild (duration: 30 min)
numbness of the neck
heaviness of the eyelids
drowsiness
headache
sensation of pressure in the chest
numbness of the legs
Symptoms more pronounced (duration: 20-45 min)
substernal pressure
abdominal discomfort
nausea
urgency of urination[b]
Symptoms persisted for 1-12 hours
headache[c]
thi1·st'
burning or pressure"
Rushing"
palpitation"
abdominal discomfort"
urgency of bowel evacuation"
retro-orbital pain
Symptoms strikingly severe
vomiting
prolonged headache
other above sympLOms
Symptoms in 01·der of frequency of appearance
sensation of tightness in the back of the neck
feeling of pressure behind the eyes
frontal or temporal headache
sleepiness
facial Rushing
sweating
nausea
feeling of pressure on the side of the face
thirst
pressure and a burning sensation in the chest
abdominal pain
Symptoms not reported by volunteers, but obvious to observers
mood change from lively and talkative to quiet and subdued (b)
Other observations
electrocardiogram tracings were normal
no changes in blood p1·essure
no changes in pulse rate

"Taken from 14. Ghadimi et al. (26). [b] Only I subject. [c] These symptoms contir,ued for hours. "These symptoms tended to be limited to a few minutes.

syndrome. Admittedly, one troublesome aspect of the accumulated literature in this field concerns two reports (9, 33) in which volunteers were fed high doses of MSG but were not reported to have any adverse reactions. Again in both of these studies all but one of the subjects were apparently males. (The significance of the apparent sex difference in sensitivity to Chinese food has yet to be firmly established.) One study by Bazzano, D'Elia and Olson involved only 14 subjects, all college students (R. E. Olson, personal communication). A study by Himwich and Peterson concerned serum glutamate levels and involved primarily psychotic patients (the four controls were staff members) who were not specifically observed for overt symptoms (W. Himwich, personal communication).

WHAT IS UNIQUE ABOUT MSG THAT MAY EXPLAIN THESE SYMPTOMS?

Glutamic acid is known to be a neuroexcitatory substance (14, 18, 38) and, along with GABA, aspartic acid, glycine and taurine, has been much examined as a neurotransmitter candidate (36, 90). Logan and Snyder (41) have isolated synaptosomes rich in glutamate from rat brain; in crayfish and locusts, it has been reported that glutamate may be the principal neurotransmitter substance (17, 84, 86). Moreover, glutamate is used in the food industry as a Aavor enhancer. Since taste is dependent on sensory neuron action, one may conjecture that the flavor-enchancing property of glutamate could result from its ability to "excite," or increase the sensitivity of, such neurons. It is interesting to note that the process is somehow selective, since MSG apparently only enhances meat-like Aavors and has no effect on fruit-like Aavors (16).

In the last 30 years, interest in glutamate has ranged from its use in treatment for psychiatric disorders (34), epilepsy (29) and mental retardation (3) to more recent concerns that large doses may, under certain circumstances, be harmful. In all these cases, however, there has been an underlying implication that this amino acid is neuroactive.

WHAT MIGHT BE DIFFERENT ABOUT THOSE WHO GET CRS?

Many individuals probably have "benign" inborn errors of metabolism which normally go unnoticed. Examples of such entities might be the appearance of thio compounds in the urine of some individuals after eating asparagus (4, 89) (the so-called asparagus effect), a red coloration in the urine of some people after eating beets (4), or the headaches that result in some individuals after consumption of cheeses and other foods rich in tyramine (12, 30). Perhaps CRS is another benign lesion[3] which happens to be challenged in our society due to widespread use of MSG as a Aavor-enhancing food additive.

According to the instructions on a popular commercial brand, MSG is recommended for use on "meat, poultry, fish (½ tsp. (=2.85 gm) per lb.); casseroles, gravies, soups, stews, sauces, vegetables and salads, (½ tsp. per 4-6 servings)." Using these suggested amounts, it is possible to envision a meal (seafood cocktail with sauce, soup, 8 oz. steak, mashed potatoes with gravy, vegetable and salad) in which an individual could consume 4-6 g of MSG. Quantities of MSG used in some Chinese restaurants are apparently higher. Schaumburg et al. (75) reported that a sample of wonton soup analyzed by them contained 3 g MSG/200 ml soup.

It is interesting to note th::it Orientals had previously cooked with a seaweed called *Laminaria japonica.* It was not until 1910 that a Japanese chemist, Ikeda, determined that it was glutamate in this seaweed that was probably responsible for the flavor-enhancing properties (44). The amount of glutamate resulting from cooking with the seaweed was probably appreciably smaller than the amounts being used currently.

Kenney and Tidball reported that elevation of plasma glutamate levels after glutamate ingestion (33, 37) was not significantly different in MSG-sensitive and nonsensitive individuals (37). We plan to repeat these experiments. In addition we will analyze pre- and postingestion serum from both types of individuals for possible differences in *a)* levels of enzymes and cofactors involved in glutamate metabolism and *b)* glutamate transport proteins.

[3] For example, a deficiency of an enzyme or cofactor concerned with glutamate metabolism, or possibly an alteration in a glutamate transport protein, or the like.

IS MSG HARMFUL?

MSG does not appear to have any gross, overt effects in normal humans on either adults or children or in fact, fetuses (82). Moreover,' pe ple with severe reactions to MSG have been known to survive multiple attacks with presumably no permanent ill effects (37, 74).

At least two questions must be asked apropos of MSG ingestion: 1) how much gets through the gut and into the bloodstream as glutamate, and 2) how much of that which gets into the blood gets through the blood-brain and blood-retinal barriers (or into the hypothalamus)? Much of the glutamate released into the intestine is apparently rapidly converted to alanine under normal load conditions. At elevated glutamate concentrations, most of the glutamic acid is absorbed as such and the alanine production is relatively low (52). The appearance of glutamate on the FDA listing of GRAS ubstances indicates that glutamate 1sa natural and abundant component of proteins and is considered as "safe" when used in accordance with good manufacturing practice as a food ingredient. However, the intestine might cope quite diferently with glutamate residues released at a finite rate of proteolysis from protein material, compared to ingestion of a large close of the amino acid in free form (52). Moreover, as Schaumburg et al. (75) and others (9, 24) have pointed out, effects of glutamate (and presumably absorption of this and other amino acids) differ, when ingested in different media.

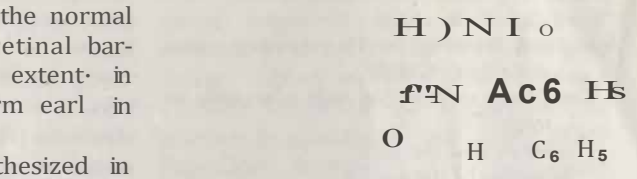
Ghaclimi et al. (26, 27) apparently analyzed blood samples from their test people for glutamine and glutamic acid, but did not present the results. Levey et al. (40) showed increase in blood glutamate in patients infused intravenously with amino acid mixtures, and Himwich et al. and Kenney and Tidball found elevated plasma glutamate levels after glutamate ingestion (33, 37), but the latter workers found no difference in plasma glutamate levels between "reactors" and "nonreactors" given equal doses of oral glutamate (this would indicate that there is no difference in absorption of glutamate in the gut[4] between sensitive and nonsensitive individuals). Even elevated levels of glutamate in the bloodstream are unlikely to penetrate the normal blood-brain and blood-retinal barriers to any appreciable extent· in higher animals, these form earl in development.

Glutamate can be synthesized in the brain and the retina, and does not need to be brought in from external sources (76). On the other l_1and, this ami o acid may be brought into ne1:vou tissue by an active process whICh mvolves saturable sites. his again would help to protect the llssue from an overload of the amino acid in the serum. On the other hand a certain amount of glutamate in ali probability also gets into these tissues by diffusion. Moreover, certain areas of the h_ypothalamus are apparently not subject to blood-brain barrier restrictions.

In any event, subtle, long range, and perhaps cumulative effects of MSG would be difficult to trace, but may become apparent at some future time, especially since appreciable amounts of glutamate are being added to human diets. If we assume that people with normal physiology are unaffected by even large doses of MS, it is nevertheless interesting to conJecture that there are perhaps individuals who, for reasons of altered states of metabolism, might be adversely affected by MSG. An interesting group to study might, for example, be diabetics who are known to have leaky retinal blood vessels. Perhaps in such individuals, small but cumulative amounts of MSG can get into the retina. Another group of interest may be epileptics. In 1972 Upton and Barrows (85) suggested that the central effects of diphenylhydantoin (dilantin, etc.) and the folate deficiency which it may cause[5], might complicate the response to MSG by sensitive individuals who are also on this drug, which is used in the control of epilepsy. It is interesting in this regard that glutamate can cyclize to pyrrolidone carboxylic acid (pyroglutamic acid), which has a structure not dissimilar to that of the drug:

pyrrolidone carboxylic acid

diphenylhydantoin



Recently, a case of a child with shudders apparently induced by MSG was brought to my attention by a pediatric neurologist (M. G. Stemmermann, personal communication) (Table 2). This child did not respond to diphenylhydantoin treatment (70), but symptoms were completely alleviated by a diet that excluded exogenously added glutamate[6].

The case of the child with shudders, (see Table 2) as well as some of the symptoms reported in a questionnaire study in our laboratory (67) indicates a very wide spectrum of sensitivity toward MSG and suggests that perhaps some individuals should avoid exogenously added MSG. In some individuals, glutamate (or some other chemical that results from glutamate ingestion) may be getting through the blood-brain barrier, or, e.g., to certain areas of the hypothalamus, and may result in undesirable effects.

ANIMAL STUDIES CONCERNING EFFECTS OF MSG

There appears to be little question that MSG injected into young rodents and chickens causes retinal damage (42, 62, 79, 80). Experiments in our laboratory have shown that the concentrations of exogenous MSG that

[4] In Hannup disease, e. g., there is inherited defective intestinal absorption of neutral amino acids. Bacterial conversion of accumulated tryptophan 1·eaching the colon leads to indoluria which is apparently responsible for the symptoms in this condition.

[5] Oral contraceptives have also been reported lO inhibit the same enzyme (i.e., same as diphenylhydantoin) concerned with folate metabolism (83).

[6] We think we have found four additional cases of MSG intolerance in children (70). In one of these children, treatment with vitamin B_6. for an unrelated problem, appeared lo obviate the adverse effect of MSG (M. S. Stemmerman, personal communication). We wonder whether other reports of shudders in children (46) may not also, at least in some cases, be a result of MSG intolerance. In a fifth case I have recently found, both the severity and frequency of the shudder attacks were apparently increased by dilantin. See also Reif-Lehrer, L. *Pediatrics.* In press.

TABLE 2. Infantile "Chinese restaurant syndrome""

Child with innumerable seiwres f'om ages 6 month, to approximately 12 months, at which time all MSG-containing foods were eliminated from the diet. Concomitantly seiwres ceased. Attacks usually occurred in clusters, afternoon and evening, and ceased during sleep. Three observed in a 10-min period consisted of momentary "shudder·" of the head, neck and shoulders, and trunk. Three EEGs in th,·ee different laboratories were normal. The child's development has been normal with a Vineland Social Quotient of 92 at 9 months. The first woth appeared at 2.5 months and adult foods begun at age 6 months.

Me·dical bibliography

4/ 2/71		Born
10/14/71	(6 mo)	First sei1.ures. Phenoba,·bital started.
11/ 6/71	(7 mo)	Sei1.ures continue. Dilantin added.
12/30/71	(8 mo)	Sei1.ures continue. Mysoline and pyridoxinc added.
1/27/72	(9 mo)	Seizures continue, 100 or more per day, complete neurosurgical workup negative.
2/15/72	(10 mo)	All MSG-containing foods eliminated from the diet.
2/20/72	(10.5 mo)	No seizures for past 3 days, first free period since onset. Reduction of anticonvulsants begun.
3/20/72	(11.5 mo)	Off all antico,wulsants. No seiwres.
5/10/72	(13 mo)	Few attacks 2-3 hr after sutTeptitious ingestion of pizza("Snitched" from the refrigerator with the help of an older brother).
8/72	(17 mo)	Several attacks after ingestion of family hog, locally prepa,·ed sausage later found to contain MSG.
2/73		No attacks for 7 months.
8/73		Deliberate trial of a spaghetti dinner with commercially prepared sauce containing MSG. Seizures within 3 hours, the first one in 1 year.
2/74		Diet-watch continues. No attacks since spaghetti trial in August 1973.

Perhaps this child merely "outgrew" her attacks, but her story has unusual features. Among these are: /) Type of attack, unlike any of the usual "minor" seizures of infancy. 2) normal EEGs in three laboratories.3) No retardation of developmental landmarks.4) Lack of ameliorating effect by anticonvulsants. *5)* Ingestion or adult foods at an earlier age than usual.

Note added September, 1975-No auacks except after annual trials with '·MSG meal."

"Above data courtesy of: Dr. M. G. Stemmermann, M.D., Medical Di,·ector Owen Clinic Institute, Inc.. 1319 Sixth Avenue, Humington, West Virginia 25701.

cause damage to isolated embryonic retinas (69) are lower than the reported intraretinal concentration of this amino acid (60). This is consistent with data that indicate that glutamate is compartmentalized in neural tissue (10, 81). It has been reported that there are at least two separate pools of glutamate in the retina: that involved in general metabolic pathways such as the citric acid cycle, and that involved in neuronal activity (10, 81).

Glutamate damage to the brain appears to be a matter of some disagreement. The data seem fairly convincing that such damage does occur in young rodents (6, 56, 57). Reports of brain damage in monkeys by Olney et al. (58, 59) were challenged by other workers (1, 71, 72) but rebutted by Olney (28, 55).

In all the animal studies in which brain damage has been reported as a result of MSG treatment, the lesions have been hypothalamic. It may be pertinent that in the case of the child with "infantile Chinese restaurant syndrome," Stemmermann (personal communication) reported that "the attacks observed were not the usual, minor motor epileptogenic manifestations, but rather probably of hypothalamic origin ... clarity of the sensorium (was) the outstanding difference."

Another question of interest has been whether MSG could cross the placenta to affect fetal animals. Murakami and Inouye (35, 49) have reported brain lesions in mouse fetuses after maternal injection with MSG or monosodium L-aspartate. Cross placental glutamate effects in primates are difficult to assess according to reports in the litarature (53, 82).

Bhagavan et al. (11) have reported that MSG in a dose smaller than that used by Olney in adult mice and by Adamo and Ratner (2) in infant rats caused somnolence in 99% of weanling rats within 5 to 20 min after intraperitoneal injection, and induced tonic-clonic seizures in some of the animals. Hypersalivation was also seen in many (52%) of the animals, and 31% displayed spastic tremors. These authors noticed that excess pyridoxine (the vitamin that is involved in the metabolism of glutamate and GABA) could significantly increase the occurrence of the spastic tremors. They concluded that 3.4 mg ISG/g body weight injected intraperitoneally to weanling rats may cross the blood-brain barrier. Fencl, Koski and Pappenheimer (23) reported that rats infused into the lateral ventricle with a total of 0.25 *μ,mole* glutamate over a period of 30 min exhibited significant depression in locomotor activity in the next 18- to 24-hour period. Over a range of concentrations used, they noted variability in responses with periods of depression and hyperactivity; they also reported salivation and occasional convulsions. Lynch, Adkins and West (43) reported that weanling and young adult rats (normal and alloxan-diabetic) given "free" (nonbound) MSG orally had, not only elevated plasma alanine, aspartate and glutamate, but also significantly elevated glucose levels. Glutamate has also been reported to alleviate hypoglycemic comas in humans (45). (This may also indicate the desirability for further studies concerning the possibility that diabetics might wish to control their MSG consumption.)

In experiments with dogs, Elwyn et al. (21) showed that the composition of essential amino acids in the gut was similar to that of an ingested meal except that aspartate and glutamate were largely converted to alanine, ammonia, glutamine, and glutathione. Other workers have reported (61) increased levels of glutamate in serum of rodents after the animals were fed diets high in glutamate. Boaz et al. (13) have reported that oral MSG loading (1 to 4 g/kg body weight) results in "rapid and extreme" elevation of plasma glutamate levels, proportional to load, in neonatal monkeys. Levels of plasma aspartate but not other amino acids were also elevated. Several workers have reported increased plasma glutamate in humans after MSG ingestion (33, 37). Mushahwar and Koeppe (50) also found an increase in serum glutamate in infant rats, after intragastric injection of MSG (4 mg/g); they found no increase in brain glutamate, but did find in-

creased brain glutamine, in agreement with findings of other workers (76). Again, the data are quite variable. However, since a variety of physiological reactions attributable to glutamate have been seen in various animals including the CRS in man, it seems fairly clear that some of this amino acid (or a resultant metabolite) must be reaching places beyond the gut to cause these reactions. Fifkova and Van Harreveld (25) studied glutamate effects in the developing chicken. They reported that effects on, for example, the electroencephalogram (EEG) were absent in chickens 5 days after hatching, which suggested that the permeability of the blood-brain barrier for glutamate decreases markedly 5 days after hatching; they do point out, however, that others have observed changes such as weight drop and a change from an alert EEG to a sleep pattern, after glutamate administration in chickens somewhat later than this. These authors point out that these less severe effects of glutamate must indicate that a residual permeability for this amino acid must persist for some time after the blood-brain barrier has lost the much greater permeability for glutamate of the prehatching ages.

Pradhan and Lynch (63) have reported that when neonatal rats were treated with 5 g MSG/kg body weight (by stomach tube) daily from the 5th to the 10th day after birth, the surviving animals showed growth suppression, significantly reduced spontaneous motor activity, and impaired discrimination (maze) learning.

Injection of MSG has also been reported to affect certain endocrine functions (e.g., reduction in body size and weight, hypophagia, and the like) in neonatal rats (66) but another laboratory reported no such changes when animals were fed MSG along with other food (2, 88)[7].

Some of the CRS symptoms that are observable (as opposed to necessarily reported by the subject) have also been noted in animal studies. It is important to remember in trying to extrapolate from the studies in animals to humans that *1)* many of the animal studies have been done by parenteral injection of glutamate in relatively high doses, and by gastric intubation, which is very different from ingestion of this chemical as part of a meal, and *2)* many experiments concerned with the effects of substances on various physiological parameters have been done in rodents for reasons of economy and ease of handling the animals. Dosages are often translated in terms of glutamate dosage per kilogram body weight, but different species have different metabolic rates and may have widely varying sensitivities to particular substances.

One wonders, particularly in countries where the per capita consumption of MSG is high, if there is any possibility that any subtle nervous disorders or unexplained retinal pathology could be due to cumulative effects of MSG in individuals with preexisting abnormalities that may make them more susceptible.

FOOD ADDITIVES RELATED TO MSG

A new artificial sweetener recently developed by G. D. Searle & Co. (Chicago, Ill.) was provisionally approved by the FDA in July, 1974 (22).[8] This material, called Aspartame, is L-aspartyl-L-phenylalanine methyl ester.

Preliminary experiments in my laboratory (unpublished results) have shown that 2.4 mM Aspartame inhibits glutamine synthetase induction in cultured embryonic chick retinas (as measured by its glutamyl transferase activity) (68), to the same extent as does 2.4 mM MSG (69). Experiments to determine the effects of this material on retinal morphology are in progress. Olney (47) (personal communication) has evidence that Aspartame causes brain damage in animals similar to that reported to result from MSG. We are currently trying to determine whether retinal tissue hydrolyzes Aspartame to its corresponding amino acids or whether the observed effects are due to the dipeptide per se. In most types of experiments concerning effects of MSG, aspartate appears to act in a manner analogous to glutamate. It would seem desirable to determine definitely whether aspartate causes CRS symptoms in MSG-sensitive individuals. Likewise, it would be of interest to determine whether individuals sensitive to MSG would also get similar symptoms from Aspartame. Searle estimates (personal communication) that the average daily consumption of Aspartame would not exceed 1.2 g per person. Only about two-fifths of this represents aspartic acid. This would, therefore, not appear to be a problem. However, phenylalanine itself has also been reported to cause brain damage in animals (15). In addition, if MSG-sensitive diabetics were more at risk from ingestion of glutamate (and aspartate (?)), it would be important to consider that it may specifically be diabetics who are most likely to use this artificial sweetener[8].

OTHER CONSIDERATIONS

With the increasing concern about food additives, MSG has been of interest for reasons of its sodium content as well as the glutamate effect. An appreciable number of people are not aware that salt does not necessarily mean sodium chloride. People who are told to adhere to low salt diets occasionally go to great lengths to eliminate sodium chloride but do not consider other sources of sodium, including MSG. In addition, consumers are not always aware (despite labeling regulations) that "Accent"[9] is pure MSG. Furthermore, Bartoshuk et al. (7) point out that even those who realize that MSG is a source of sodium are unaware that use of MSG as a salt substitute may actually increase sodium intake since it takes three times as much MSG as sodium chloride to achieve a comparable "saltiness." Ebert (20)

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[7] There is an appreciable literature about the fact that absorption of amino acids is very dependent on other substances present in the gut. This is evident in the work of Bazzano et al. with MSG (9) and in the studies of Fernstrom and Wurtman (24) with tryptophan. In the latter case, starving for two amino acids which share receptors for tryptophan causes increased uptake of tryptophan (24). It is also apparent from the observation that individuals who are only borderline sensitive to MSG will get symptoms from clear soup but not from foods rich in protein or lipid (67, 75).

[8] General Foods Company had already announced plans to use Aspartame in some of their packaged foods (54); however, a recent report that a decomposition product of Aspartame may cause uterine polyps in mice has put a temporary halt on the use of this material (87).

[9] Registered trademark of International Accent Co., Watertown, Mass.

and Reaume (65) have criticized Bartoshuk on the ground that MSG is a flavor enhancer, not a salt substitute. This is a valid criticism; however, the misconception that MSG can be used in place of table salt might not be uncommon, as Bartoshuk herself and others have suggested (8).

Despite regulations making it mandatory to label foods with the ingredients they contain [10] even the educated consumer may not know the chemical nature of the ingredients printed on the label; moreover, most individuals are not in a position to assess the safety of these substances.

CONCLUSIONS

Adverse reactions, presumably resulting from monosodium glutamate (MSG) ingestion, appear to be fairly common in humans (37, 67). It is possible that the symptoms, commonly called Chinese restaurant syndrome, result from an inborn "error" of metabolism that is benign under normal circumstances, but elicits symptoms under high MSG load. The threshold dose of MSG in sensitive individuals varies appreciably (75, and Reif-Lehrer, unpublished observations). It seems unlikely that MSG even in large doses is harmful to normal individuals. However, the fact that some people apparently respond rather severely to commonly used quantities of this material would seem to indicate that further study of this matter, by both the medical and biochemical communities, is warran d.

[10] MSG may be used without label declaration (19) in mayonnaise, French dressing and salad dressing.

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November 15, 1976

Dr. Stemmerman
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Stemmie:

Thanks very much for your letter of November 8. You did once mention to me that you had a suspicion that MSG reaction might be accompanied by hypothermia, but all you said was that it was only an impression gathered from the fact that Denise had a thermometer stuck in her mouth at every conceivable opportunity. I do not know of anything in the literature on this particular topic. If you do, I would very much appreciate some references. Also, I am not absolutely clear on just what you mean by your first paragraph and would very much appreciate it if you could elaborate and explain to me what it is that you feel was left out.

Enclosed please find two more copies of the reprint. We have a goodly supply and I'd be happy to send to anyone who is interested. I did have an interesting time with the Canadian program people but I am quite concerned about the fact that I really would like to screen the thing before it is aired and I have not heard a word from them since they were here.

I would be most interested in speaking to Dr. Ruth Harris if she is interested in talking to me about MSG. My problem right now is that I am getting complimented and blasted at the same time and I'm wondering which will win out. Friday, for example, I got an unbelievably nasty letter from Dr. Wurtman from MIT along with a very nice letter from John Olney. In addition, there came a telephone call from a physician at the Cape who had some rather interesting things to tell me about what may be MSG related phenomena in himself as well as possibly in two of his children. I have to write to him to clarify some of these things and would be interested in talking to you about it some time. I really would love to make contact with the Daily child. Do you think her mother would allow her to be tested in some very simple fashions? Could you provide me with her current address? If I don't get some hard data in this field soon, things will get increasingly rougher. It's about time that one fi 11,Plly clinched whether or not this.is a rea1.phenomenon. Enclosed is a paper sent me by Olney which I received on Friday, I thought this might be of particular interest to you.

Sincerely,

Liane

LRL:a

Brain Research, IJ2 (1976) 420–424

Acute glutamate-induced elevations in serum testosterone and luteinizing hormone

Adult ♂ rats

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(Accepted May 10th, 1976)

Glutamate (GLU) and certain structurally related amino acids excite mammalian central neurons when applied by microelectrophoresis to their dendritic and soma! surfaces[3]. Olney and co-workers[16] suggested the term 'excitotoxic amino acids' for these compounds after finding[15] that GLU itself and its exitatory analogues, when administered subcutaneously to experimental animals, destroy neurons in the arcuatc nucleus of the hypothalamus **(AH).** They postulated that the toxic action of GLU on central neurons is essentially an extension of its excitatory activity[12]. Perez and Olney[17] have demonstrated in mice that subcutaneously administered GLU is selectively accumulated by AH, but not by the immediately adjacent ventromedial nucleus or more remote brain regions, and that the time course of GLU accumulation by AH g arallels the time course of lesion formation in that nucleus.

Several lines of research, including GLU neurotoxicity studies, suggest that AH is an important neuroendocrine regulatory center. Selective lesioning of AH by GLU treatment of infant rodents gives rise to sequelae such as obesity, skeletal stunting, reduced weights of the adenohypophysis, gonads and accessory sex organs[8,10,18,19,21] and reduced pituitary content of growth, luteinizing and prolactin hormones[8,18].

Various efforts have been made recently to influence neuroendocrine function by the administration of putative neurotransmitters to experimental animals[6]. Such experiments often have involved administration of the test compound intraventricularly since a direct interaction with central neurons is sought and neurotransmitters typically have poor access to brain from blood. GLU is regarded as a possible excitatory transmitter in the mammalian CNS and has traditionally been considered an amino acid which is blocked by blood-brain barriers from entering the brain. However, recent evidence[17] indicates that subcutaneously administered GLU does readily penetrate AH. The purpose of the present study was to determine whether systemically administered GLU influences serum levels of testosterone and luteinizing hormone (LH) in the male r t. Ou as that a dose of GLU below that required to kill AH neurons might nevertheless stimulate them to fire at increased rates and thereby disturb e d rine systems regulated by these neurons, one of which is thought to be the p1tu1tary-gonadal axis.

Althou2h adult as well as infant rodents are susceptible to GLU-induced brain d a m ; ; , the dose required to damage adult brain (1.5-2 mg/g) is substantially higher than that required to damage infant brain (0.3-0.5 mg/g)a,[13]. In the present study we administered GLU to adult male.rats at a dose of l mg/g, this being a dose we estimated would lead to high e ough GLU levels in AH to excite but not kill arcuate neurons. Seventy-eight Holtzman male rats (55 days of age), weighing approximately 300 g, were employed. Rats were injected subcutaneously either with GLU, 1 mg/g or NaCl, 0.35 mg/g (the molar dose-equivalent of 1 mg/g GLU). Six rats from each group "";ere then killed at 0.25, 0.50, 1, 2, 4 and 6 h following injection. An additional group of 6 uninjected rats designated as 0 h treatment group was included to control for possible effects of the NaCl injection itself. The injections were staggered so that the time of sacrifice always occurred at the same time of day to avoid possible circadian influences on hormone levels. The rats were decapitated and blood, collected from the trunk, was allowed to clot at 0-4 °C for 3-4 h, then centrifuged at 2500 rev./min for 20 min. The sera were removed and stored a t - 2 0 °C until assayed. Serum testosterone levels were measured by a highly sensitive and specific radioimmunoassay which has been described elsewhere[1]. Reagents for the LH radioimmunoassay were provided by the Rat Pituitary Hormone Distribution Program of the NJAMDD. The anti-ovine LH antiserum was generously provided by Dr. Gordon Niswender. The double-antibody radioimmunoassay has been described elsewhere[9].

NaCl control

Control rats treated with hypertonic N a g had serum levels of testosterone and LH which did not vary significantly, at any posttreatment interval, from the baseline values of2.25 ng/ml and 16.0 ng/ml respectively, obtained in the untreated (0 h) controls (Fig. l). In experimental animals, however, testosterone and LH rose to 3.8 ng/ml and 34.0 ng/ml respectively l5 min following GLU treatment, dropped precipitously into the baseline range by 30 min, then gradually rose again in the 2-4 h interval. After an elevation at 4 h, LH returned to near baseline levels by 6 h, whereas testosterone continued to rise between 4 and 6 h to reach a peak value of 4.75 ng/ml at 6 h.

Perhaps the most striking feature of these data is the brief time span between treatment and the occurrence of the first serum hormone elevations. Possibly, even earlier and higher peaks might have been revealed if measurements had been taken earlier, perhaps at 5 or 10 min following treatment. It may be relevant that uptake and accumulation of GLU in AH following subcutaneous administration also occurs very rapidly. Substantial elevations of GLU concentrations in AH have been measured within 7.5 min after a subcutaneous injection[17]. It is not clear why testosterone continued to rise 6 h after GLU treatment whereas LH returned to baseline in the 4-6 h interval. However, since no assay was performed between 4 and 6 h, it is possible that LH actually continued to rise to reach an unknown peak between 5 and 6 h, then fell quickly to its 6 h level and that an equally rapid drop in testosterone would have been found if values had been recorded slightly beyond 6 h. Moreover, had earlier points on the curve been established it might have been found that LH changes were antecedent to the testosterone changes. These speculations, if correct, would make the LH and testosterone curves essentially parallel to one another with LH changes preceding the testosterone changes slightly in time.

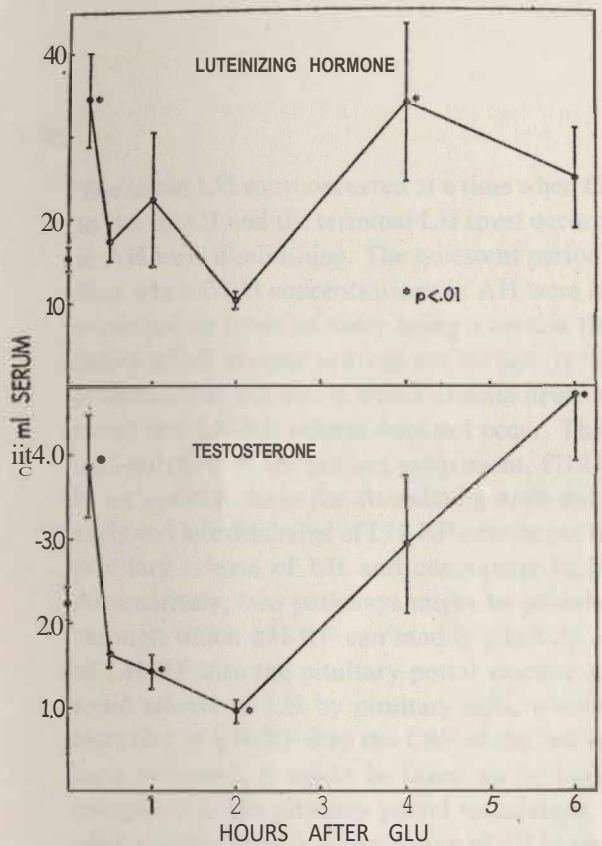

Fig. 1. Luteinizing hormone and testosterone concentrations (mean ± S.E.M.) in serum at sequentia 1 intervals following GLU injection. Controls, both uninjected (0 h) and NaCl-injected are given as a single pooled value on the ordinate.

Several lines of evide_nce suggest that LH releasing factor (LH-RF) is concentrate in the arcuate-median eminence region of the hypothalamus[6], although the intracellular localization of LH-RF within this region is not well established. Presumably, even if LH-RF is synthesized in the perikarya of AH neurons, the stores which are held ready for discharge into the portal vasculature are contained in axons which terminate in the nearby external mantle region of the median eminence. It seems unlikely that GLU acts directly on these axon terminals to effect release of LH-RF in view of evidence from both electrophysiological[2] and electron microscopic[11,15] studies that GLU exerts its excitotoxic effects against dendritic and soma! membranes but not against axons. It is quite consistent with available evidence, however, to postulate that GLU causes accelerated firing of arcuate neurons by a direct action on the dendritic or soma! surfaces of these neurons and that the action potentials transmitted down their axons either trigger the release of LH-RF from the terminals of these axons or from other nerve endings with which they form axo-axonic synapses.

The observed elevation of serum LH was biphasic with a sustained quiescent period between peaks. It is of interest to compare this curve with that reported elsewhere for GLU accumulation in AH over a 6 h period following GLU administration[11].

The initial LH spurt occurred at a time when GLU concentrations were just beginning to dse in AH and the terminal LH spurt occurred at a time when GLU concentrations in AH were diminishing. The quiescent period, on the other hand, corresponds to the time when GLU concentrations in AH were highest. Thus, both LH peaks might be explained in terms of there being a certain threshold concentration of GLU in AH below which arcuate neurons are excited (reversibly depolarized) and LH-RF release is stimulated, but above which arcuate neurons become silent (sustained depolarized state) and LH-RF release does not occur. That is, during the early and late, but not mid-portions of the present experiment, GLU concentrations in AH may have been in an optimal range for stimulating nl!uronal firing and this may have triggered an early and late discharge ofLH-RF into the portal vasculature to give rise to the biphasic pituitary release of LH and consequent biphasic testicular output of testosterone. Alternatively, two pathways might be postulated, one rapid and the other delayed, through which LH-RF can modify pituitary output of LH. GLD-induced discharge of LH-RF into the pituitary portal vascular system could conceivably result in very rapid release of LH by pituitary cells, whereas delayed release might occur by the secretion of LH-RF into the CSF of the 3rd ventricle from whence, as Knigge et al.[4] have proposed, it might be taken up by tanycytes and transported slowly in their cytoplasm to the pituitary portal vasculature. Finally, it is possible that the first LH peak resulted from a direct action of GLU on the pituitary and the second LH peak from an LH-RF mediated mechanism activated slowly by a build-up of GLU in AH.

Since the pituitary-gonadal axis may not be the only endocrine axis affected by GLU, the present experiments should be extended to include a broad spectrum evaluation of endocrine parameters following acute GLU administration. It is known from several GLU studies that the oral route of administration is nearly as effi.cient as the subcutaneous route in producing either plasma GLU elevations[7,20] or hypothalamic damage[13,14]. In recent feeding studies, Van Gelder[22] demonstrated that mice reared on a diet supplemented with low concentrations (0.5 %) of added GLU exhibited stunted skeletal development. That this might reflect a GLD-mediated disturbance in the hypothalamic regulation of growth hormone output remains to be explored. Whether the current practice of adding GLU in concentrations up to 0.5 %or more to foods ingested by immature humans entails risk of inducing subtle disturbances in somato-sexual development through repetitive stimulation or suppression of neuroendocrine regulatory functions during the formative years also warrants consideration.

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Deoember 3, 1976

Liane Bsit-Lebrer, Ph.D.
20 Staniford Street
Boston, Maaa. 02114

Dea.r Laine,

'1'h ext.ra rep.rinta a.r.rived and have been dispatohed where I hope tne7 will do aome good. My reterenoe to an omiaaion in Table I, "othe.r abae.rve.tiona", refers to hypo-the.rmia. Aooarantly in the past, I have not made this clear, *tor* it has occurred not onl7 in the Daile7 ohild but alao the tew other• I have.

Usually tha family bring• Denise Daile7 to see me eaoh eummer to report on the •arner trial *ot* "sausage" but not thia year. Perhaps they a-e in Cal11'omia. P.ankly I aee no point in i'ul'ther clinical trials *ot* HOO. I personall7 am satisfied that it ia poor atut't tor some people ard I couldn't oaN leas what BI17one else thinks MIT, Harvard or Timbuctoo. I am a pragmatiet. It abstention works, abstain, irreapective *ot* the absence *ot* quadruple blind studiea.

I would be in favor of cl!nleal trials in known or poaaible aensitives, provided the7 were aceompanied by biochemical evaluation of blood and urine (I don't aak *tor* spinal fluid). Can't you devise an enzyme protooat that ould touch all baaea even NJDotely involved? Oan you uae RIA or aometbing? My ignoranoe ia this field ia abyssimall O.r had you guessed? Incidentally, I would like oonatant monitoriq *or* temperatu:i-e betore, during, and atter.

Your long list *ot* subjective aymptoma tollowins MSG ingestion in my, opinion. is one *0r* the **reasons** why the syndrome is auapect. '!'hatis the beaut7 *ot* working with oh1ldren. The7 are not primed to complain, but one can observe behavioral and ph7sical changes.

Then 1• a ready made clinioal t:rial in the school hot lunoh p NJB--1t aaneon• would like to takcle 1t. Almoat certainly acae *ot* the tooda ael"t'ed oontain MSG on acne da7a. Have the teaohera •••• all paper work o Ill atudenta and Ncol'd all diacipllnary incidents, eta. tor 1-2 hours atter lunch.

When this data ha been collected, go back and oheok the lunoh menus. Ir there are clusters ot poor performance among aome of the children, on MSG d&Js, it would be interesting. Oal"'l"J out the same oba•i-vationa on average, leaming disability and special eduoation studenta, perterable 9 7ea s old and 7ounge .

Pleaae don't be diacouraged. 'Twas eve thua.

Sincerely yours,

M. G. Staae rmann, M.D.

YEAR BOOK OF PEDLiTRICS

EDITOR: SYDNEY S GELLIS, ?,LD.
171 HARRISON AVE.
BOSTON, IIIASS. 02111

December 21, 1976

Dr. L. Reif-Lehrer
20 Staniford Street
Boston, MA 02114

Dear Dr. Reif-Lehrer:

I am planning to include in the Year Book of Pediatrics the article by Michel Vanasse et al, "Shuddering attacks in children: An early clinical manifestation of essential tremor" which appeared in Neurology 26:1021-1030, 1976 (Nov.) and wonder if you'd like to write a brief editorial commen t which would follow the abstract of the article. In the comment you could expand on your experience with glutamate and shuddering attacks in children. If you can write a comment, I'd need it by July 1.

With kindest regards,

Since\ely,

Sydney S. Gellis, M.D.

EYE RESEARCH INSTITUTE
OF RETINA FOUNDATION
20 Staniford Street
Boston, Massachusetts 02114
(617) 742-3140

December 22, 1976

Dr. M.G.Stemmermann
Owen Clinic Institute Inc.
1319 Sixth Avenue
Huntington, West Va. 25701

Dear Stemmie:

Thanks very much for your letter of December 3. I'm sorry its taken me so long to answer but things have been very hectic here. We have had a new interesting case again last week. This is a 14 year old boy who began getting severe migraine headaches with vomiting at age five. The child has been suffering with this for many years. About a year ago, in fact, December n Y5, his mother was told by someone (quite coincidently) that she had heard that MSG might have something to do with headaches. The mother went home and cl rrd her cupboard of all''MSG containing[1] foods, i.e., via ingredient lab(l\ g,s,and the child has had n.a headache in the intervening 12 months except once this summer when,v1siting in London and ate in a Chinese Restaurant! This is quite reminiscent of the 14 year old boy in Connecticut.

We do have lots of things planned. The problem is that I can only do these things under the supervision of a physician, and that has been somewhat of a problem. Moreover, it's difficult getting children to be tested. This latest case --- the mother seems interested in having the child tested and said that she would speak to the child and the father and get back to me --- we shall see. I have lots of things planned for the testing including the temperature monitoring as per your suggestion. Also, as of a few days ago, I have finally made contact with a neurologist here in the area, who says that if I can convince him that this is all interesting enough, that he would have the time and would be willing to help me with the clinical testing --- of course, that's a big if. I have sent him a load of reprints and am waiting to see if he will invite me out to talk further about this topic. He had an interesting cautionary remark: he said that one of the problems with the seizure-migraine business is that it's a very peculiar business and sometimes you can feed somebody "turnips and they'll stop having symptoms for two years", and you never know why.

Your idea about the school hot lunch program is an interesting one but my last go-around with school superintendents was not terribly successful, at least not in our town of Lexington. However, we have a new, hopefully more reasonable superintendent, perhaps I should try again. However, I'm not sure that that's the best place to go at the moment. I'm considering doing a personal letter mailing to Pediatricians around the country asking them to check their files for possible cases. After all, the initial testing for this is so simple

and benign that it's awfully difficult to imagine that anyone might be reluctant to try this --- the only exception to this is that in the Dailey child and more pertinently, in the New Hampshire child, and the Westchester child, it would appear that Dilantin was doing no good and in fact, and this is most clear in the New Hampshire child, Dilantin seemed to be making the shudder attacks worse --- so that an essential part of testing in those children who may be on anti-convulsant therapy is that one must cut out dilantin along with limiting glutamate --- of course, that will have to be sorted out as well. Anyway, that's all for now. Please keep in touch.

Sincerely,

11

LRL:a

LIANE REIF-LEHRER PhD
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Harvard Medical School
and
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December 27, 1976

Dr. M. G. Stemmermann
Owen Clinic Institute Inc.
1319 Sixth Avenue
Huntington West Va. 25701

Dear Stemmie:

Have you seen this article by Vanasse, Bedard and Andermann you first called my attention to when there was a write up in Medical World News. Note especially the last page.

Sincerely,

L,

LRL:a
enc: Neurology 26

LIANE REIF-LEHRER PhD
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and
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March 22, 1977

Dr. M.G. Stemmerman
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Stemmie:

Thank you very much for the copy of the letter from Mrs. Dailey. Since you have carefully fixed up the address for me, I presume it's okay to write to her and I may try to do this soon. Meanwhile, things are very slow. My glutamate grant did not get funded and I'm reapplying once again. If you had time, a letter from you supporting the whole idea of the research concerning the effects of glutamate in humans, might help. I would need to have it within the next week and a half or so. If you don't have time, don't worry about it.

Meanwhile, the item concerning the"glutamate children pp ared in the March 1 issue of Dr. Gellis' new PEDIATRIC NOTES. So far, on March 18, I received a letter from one parent and upon calling the pediatrican found that he may have two cases of possible interest. I've written to the pediatrican to try to get more information and will let you know what happens as things develop. I'm getting more and more frustrated at how slow moving all this is turning out to be, but I spoke to someone at NIH the other day who is very encouraging and felt that the grant had gone to the wrong institute. He has offered to guide it along the next time, but once again, it will take time. He wants me to send him the grant by mid April and he will help me process it and get it in for the July 1 deadline which means, however, that I won't hear until just about a year from now.

Is there any additional information on any of the other children that we were interested in, e.g., I never did hear from Mrs. Rhodes; and I'm curious to know how things are going with the 12 year old that you treated with Vitamin B6. Please keep me posted and I'll do the same for you.

Of the 12,000 questionnaires we sent out to Twins last summer, we've only gotten about 200 back so we can't do much with them, but a rough hand-tabulation would seem to indicate that sensitivity to MSG is probably hereditary. The Twins are having an international convention this Ay gust and we're hoping to have a representative there to try to "extrac\ additional questionnaires so that we can firm up those data. Thats all for now.

sincerely,

Lr

LRL:a

LIANE REIF-LEHRER PhD
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and
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April 5, 1977

Dr. M.G. Stemmerman
Owen Clinic Institute Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Dr. Stemmerman:

In looking over my notes on the Dailey child, I'm a little confused by one thing and am hoping that you can clarify it for me. According to the notes that I have on several of our telephone conversations, I believe you mentioned to me that Mrs. Dailey had told you at her last "appearance" in 1976 that she had been testing Denise once each summer with some MSG containing food and that "the child still cannot tolerate food with added MSG" --- in the more recent letter it sounds as though Mrs. Dailey is unwilling to test Denise with MSG. Is this a recent development? - or did I misunderstand the original message? - or did you ask her whether she would be willing to have Denise tested (as per our discusssion some time ago) and is this a response to that request? Also, I am wondering whether the paragraph about the bottles that you gave her to send to the Doctor in Missouri might not be a misunderstanding and whether she might have meant Massachusetts. --- I seem to recall that we had talked about asking her to send some urine at one point. Is that what she was referring to? I'm trying to write something about this into my grant and would really appreciate an early response to these various questions. I know you're very busy so please feel free to jot some answers on this sheet & return. I'm enclosing a stamped self-addressed envelope just to make things easier for you.

How are things going?

Sincerely yours,

LRL:a

April 8. 1977

Liane Reif-Lehrei-, Ph.D.
20 Staniford Street
Boston, Mass• 02114

Dear Liane•

Herewith the answers to your questions. If you would like Mrs. Dailey to cooperate with anything I am sure shw would be willing to do so as she is an ardent anti-MSG missionary.

1. Is Mrs. Dailey unwilling to test Denise with MSG? On a trial basis I am sure she would be willing to cooperate but she gave up the annual testing when Denise continued to react. However I have not recently (within 8 months) brought up the subject.

The doctor in Missouri to whom Mrs. Dailey referrs to ii DJ-. Olney whom I Contacted when I first diagnosed Denise's problema. I have not discussed your project as far as collection of urine for Denise as she had moved and I did not knoW her addredd•

I trust the above clarifies our p ior discussion• I alwa7s have found Mrs. Dailey to coopert e and I am sure she will be glad to hear £rom you•

I have lost track of the 12 year old whom I treated with Vitamin B-6. However, I have had many other children w1th delayed bone age whom I have started treatment with this v1tamin (25 mg.). I have not yet heddlong enough time to 11ve firm answers but those treated seem to have responded. On the other hand, bone age might have improved during the Dormal course of developmental growth. A few of these aN also MSG sensitive•

The Rhodea tami.17 ha• moved• Glenn Brown still 1s uudez-atu.47.

I tNat th1a clariti•s e7erything• I still have on17 Deni•••• the only othe:rwisen ormal ch11d

Let me know it' 7ou haYe any more questions.

Sino• youi-s,

M. G. Stemmermann,M.D.

KlS/blm

June 24, 1977

Liane Reif-Lehrezt, Ph.D.
20 Stanifol'd Street
Boston, Massachusetts 02114

Dear Liane,

Many thanks for your MSG questionaire study. In the samo mail carae the May/June issue of THE SCIENCES, New York Academy of Sciences publication. Please note tho artiole by Patrick L. McGeer, nThe Unbnlaneed Br in." On Ps.ge '!7 b repozwts an anitmal model of Huntiggton•s Chor9a through injeotion of glutamate into the straitum. 'ihile the "shudders" I have oba6'rved &I'e not chorei!'orm, age may make the ditterenoe• Huntington'3 chorGo is an inherited disease .first appearing in the middle bears of life.

Perhap to you this i 11 old stuff, but to mo it was of greatinterest.

Sincerely yours,

U. G. Sternmermann, M.D.

LIANE REIF-LEHRER PhD
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June 30, 1977

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Stemmie:

Just thought you might like to see the enclosed.

What's new?

Sincerely,

a

LRL:a
enc.

Dr. Liane Reif-Lehrer

Just sent in a new NSG grant yesterday – Hope this one makes it. ——

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and
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March 1$, 1978

November 25, 1977

Liane Reif-Lehrer, PhD.
20 Staniford Street
Boaton, Mass. 02114

Dear Lianet

Many thanks for the oop1•• of your lateat MSG excursiona into print. I am delighted that you are not letting th1a problem "die" and continue to 1'98pond to the literatuN.

I am at111 looking *tor* a "normal" child who is sensitive but with no 1uok to date. Perhaps the pediatricians in my area have been 11atening and are atopping MSG ingestion, then b1 depriving me ot, clinioal mater1al.

My most recent oaae, a *ta• 1••r* old, with both tremors and "shudders" alao haa cranioateno•ia. EEG showed no epileptiform actiYity. Withholding MSG atopp•d the "shivers" but not the tremors• But now th1a little girl v1ll probably need surgery.

Inaidenta117, my brother (the patholog1st in Hawai1) has reoentlJ begun 1n•estigating MSG as a poasible amine preoursor or nitros-... a possib1e gastro-intest1nal carcinogen. MSG ia suspect beoause of it• high sodium, a oharaotenetio of the diet ot people at risk for stomach cancer and uloer.
Ot course this 1s all very "iffy" at the moment.

Again many thanks jnd keep in touoh.

S1noerely youra,

M• G• Stemmermann, M.D.

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November 25, 1977

Dr. M.G. Stemmermann
Owen Clinic Institute, Inc.
1319 Sixth Ave.
Huntington, West Va. 25701

Dear Stemmie:

It's been some time since we corresponded. Anything new and interesting?

Sincerely,

Liane

LRL:a