Honorable Robert P. Griffin
United States Senate
Washington, D.C. 20510

JUL 13 1972

Dear Senator Griffin:

This is in further response to your February 14 inquiry transmitting a February 7 letter from Norman E. Clarke, M.D., Oak Park, Illinois, concerning chelation therapy using ethylenediamine tetraacetate (EDTA or disodium edetate) in the treatment of arteriosclerosis. We are sorry for the delay. Dr. Clarke enclosed a January 7 letter addressed to Representative John E. Moss from G. F. Gordon, M.D., Sacramento, California, we did not receive the attachments listed in Dr. Gordon's letter.

Under the Federal Food, Drug, and Cosmetic Act, enacted in 1938, the factor of safety was the only consideration for approval by the Food and Drug Administration (FDA) to permit commercial marketing of a new drug. Claims as to the effectiveness of a drug were not evaluated by the FDA and were the manufacturer's responsibility.

In 1962 the Act was amended to extend the requirements for approval to include substantial evidence of effectiveness. The criteria to be used in determining this was also prescribed in the amendments. As defined therein, "* * * the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof."

These amendments also conferred on the Food and Drug Administration the responsibility to review the decisions made for drugs introduced to the market from 1938 to 1962, which had previously been approved only on the basis of the evidence of safety, and to determine whether there existed substantial evidence of effectiveness for the purposes for which they are labeled. The Food and Drug Administration contracted with the National Academy of Sciences - National Research Council to assist in this review.

EDTA combines with certain metal ions to form cyclic complexes which are water soluble, virtually undissociated, and readily excreted by the kidneys. The uses of the drug were considered by the National Academy of Science-National Research Council (NAS/NRC) and our initial evaluation was published in the Federal Register on January 13, 1970 (35 FR 437; DESI 8922, copy enclosed); this notice also set forth detailed labeling.

Although in the above notice the drug was considered possibly effective in treatment of occlusive vascular disorders, the labeling specifically noted that it was "not indicated for the treatment of generalized arteriosclerosis associated with advancing age." No manufacturer objected to this limitation of use and it now appears in the labeling of these products. In the Federal Register of July 16, 1974, (copy enclosed), the Food and Drug Administration (FDA) noted that no evidence had been received in support of the less than effective indications, and that they had already been deleted from the labeling.

The notice of July 16, 1974, did not extend the opportunity for hearing to any persons other than holders of the specified new drug applications and persons who manufacture or distribute similar identical or related drugs because the Federal Food, Drug, and Cosmetic Act explicitly limits the persons who may request a hearing. We will, however, accept and consider information from other sources if it is provided in a reviewable form and appears to represent well-controlled clinical studies. In August of 1974, Dr. Harold Harper attempted to provide comments on our July 16, 1974, notice, but his comments were not accepted as reviewable. A copy of our letter to Dr. Harper, then President of the American Academy of Medical Preventics (AAMP) dated January 9, 1975, (is enclosed). It points out that the unindexed, unanalyzed, and unsummarized material submitted by AAMP did not comply with regulatory requirements governing submission of data and would not be considered. AAMP was invited to assemble the data in the proper format and, if the data represented adequate, and well-controlled clinical studies, they would be considered by the Bureau of Drugs. We have had no response to date. We also, in that letter, explained to Dr. Harper that investigational drugs, could be legally studied under a Notice of Claimed Investigational Exemption for a New Drug (IND). No IND has been received for this use of disodium edetate, however.

Disodium edetate is not a benign drug. Its principal harmful effect in ordinary use is renal injury, which tends to occur when the daily dose exceeds 50 mg/kg, and can be fatal. It can also provoke serious hypocalcemia. It is contraindicated in patients with severe renal disease and/or anuria. It is, despite its risks, a useful drug in patients with severe hypercalcemia, a life-threatening condition, and in some patients with ventricular arrhythmias associated with digitalis toxicity.

As far back as 1969, a number of physicians have urged FDA to approve use of disodium edetate in the treatment of arteriosclerosis. The treatment, which is apparently popular among some physicians, cannot at present be paid for under Medicare because disodium edetate is not approved for this use. The treatment programs generally require hospitalization for one or two weeks and are quite expensive. Before FDA could permit this indication in labeling, however, we must have substantial evidence in the form of well-controlled clinical studies, to show that chelation treatment is of benefit in the treatment of arteriosclerosis and is safe. Without such evidence it is not legal for labeling to recommend the drug for this purpose. In the absence of evidence of safety and effectiveness, the use of disodium edetate in the treatment of arteriosclerosis is investigational and should be carried out under an IND. To date, however, no physician or sponsor has filed a plan or protocol to study the use of disodium edetate in such treatment. It is incorrect for Dr. Clarke to characterize our enforcement of legally mandated standards as unfair or dishonest "resistance".

Evidence presented in the U.S. District Court for the Eastern District of Louisiana in a recent action against a physician promoting chelation therapy and misbranding disodium edetate is pertinent to this discussion. On September 28, 1976, the U.S. District Court for the Eastern District of Lousiana granted a preliminary injunction (CA NO. 75-1790) enjoining H. Ray Evers, M.D., and Meadowbrook Hospital from administering disodium edetate, calcuim disodium edetate and other chelating agents to persons referred to Meadowbrook Hospital for purposes of receiving the treatment.

Testimony at the injunction hearing established that Dr. Evers was misbranding disodium edetate by promoting its use for purposes not listed in current labeling. He had held a press conference and distributed promotional literature advocating disodium edetate therapy for cardiovascular therapy; promotional literature of a same sort was distributed at a convention of the National Health Federation. It was shown that Dr. Evers continued to distribute chelation therapy advertising to prospective patients and that both he and Meadowbrook Hospital enjoy a national reputation as employing this drug in the treatment of arteriosclerosis.

More important, as described in the Court's memorandum and order (copy enclosed), evidence was presented that chelation therapy, as practiced by Dr. Evers, was extremely hazardous:

> At the outset, the Court notes that the evidence presented as to the existence; vel non, of irreparable injury caused by the misbranding of EDTA was mixed. Nevertheless, the Court is convinced that unless the continued misbranding of EDTA at Meadowbrook Hospital is enjoined, serious and irreparable harm will occur to the individual patients at the hospital

and the public generally. See, Morgan v. Fletcher, 518 F.2d 236 (5th Cir. 1975).

Dr. Kenneth C. Schneider, who is a medical consultant at the Dallas Regional Office of the Public Health Service, testified in detail about three deaths he concluded were directly caused by the administration of EDTA at Meadowbrook Hospital. Dr. Schneider, who was qualified as an expert in preventive and public health medicine, further testified that five other patients died either from renal failure or congestive heart failure following administration of the drug.

Dr. John David Spence, a qualified expert in internal medicine, clinical pharmacology and neurology, testified concerning his review of the medical histories of twenty-one Meadowbrook Hospital patients, fourteen of which he concluded died from EDTA therapy. Causes of death ranged from insulin shock, congestive heart failure caused by administration of a high saline solution carrying EDTA, and renal failure.

Finally, Dr. George L. Bailey, Clinical Professor of Medicine at Tulane University Medical School, and an expert in toxicology and nephrology, testified that EDTA should be employed solely for the treatment of lead poisoning (and even then at great risk). One woman patient retained nearly forty pounds of edematous fluid because Meadowbrook Hospital maintained her on a highly saline solution containing EDTA, which fluid Dr. Bailey removed by means of dialysis.

Admittedly, several doctors and a number of individuals testified on Dr. Evers' behalf as to the beneficial effects of EDTA chelation therapy. The Court in balancing the value of this testimony is satisfied that the possible benefits of the EDTA therapy employed at Meadowbrook is far outweighed by the serious actual and potential damage caused by the drug in such therapy. Unrebutted evidence has established that EDTA chelation therapy has been indiscriminately applied to patients at Meadowbrook Hospital and that a number of them have died as a result. This Court is not in a position to condone the haphazard application of a drug for treatment of conditions which its use is contraindicated. To do so would be to authorize the deaths of many in the faint hope of saving a few.

In addition to the review by the National Academy of Sciences-National Research Council (copy of their review is enclosed), there has been a more recent review of the literature pertaining to chelation

therapy in arteriosclerosis. In a recent issue of the Western Journal of Medicine (enclosed), Drs. Craven and Morrelli, of the Department of Medicine at the University of California, reviewed this literature. They found no study that was well-designed or controlled and used objective measurements to determine improvement. They concluded this treatment was investigational and should be conducted under carefully controlled conditions in an academic institution by experienced investigators.

Dr. Alfred Soffer, editor of the Archives of Internal Medicine, has also commented recently on chelation therapy (enclosed), comparing it with certain other therapies that generate great enthusiasm but little useful data. He specifically cites a recent statement by the California Medical Association which concluded that the usefulness of chelation therapy is unproven and that use of the drug for this purpose is investigational and should be conducted under the usual investigational procedures, including the informed consent of patients.

As noted above, no one has attempted to study chelation therapy under an IND or submitted evaluatable material in response to a Federal Register notice. We have, on occasion, been handed examples of X-rays or EKGs said to show improvement, but never in the form of a full report of a study of any kind. We therefore can conclude only that chelation therapy is plainly not supported by satisfactory evidence and we have seen that there are reports suggesting it may be extremely hazardous.

One patient mentioned by Craven and Morrelli is particularly disturbing, viz., a patient who appeared to have died when "a calcium embolus freed from a large arterial plaque" lodged in his brain. It must be recognized that arteriosclerosis involves predominantly the larger blood vessels; if any agent could "dissolve" arteriosclerotic plaques abruptly, it would be anticipated that chunks of the calcium and lipid-filled plaques would break off and head "downstream" where they would inevitably, unless they broke up further, lodge in a smaller blood vessel, occluding it. This, of course, can happen spontaneously in people with arteriosclerosis and is a common cause of strokes and transient ischemic attacks. The possibility that chelation therapy, even if successful in dissolving arteriosclerotic plaques, might provoke such embolization is yet another reason to consider the therapy investigational and its safety and effectiveness unestablished.

In summary, the use of disodium edetate in the treatment of arteriosclerosis is of unproven value and thus investigational, but no one has as yet been interested in carrying out well-controlled studies under an IND to see if the technique is useful. We are also aware of no studies in animal models of arteriosclerosis, which ordinarily should precede experimental studies in humans, to see whether there is benefit. No party has ever provided us with an organized submission attempting to show that disodium edetate is

effective therapy in arteriosclerosis; instead we have been handed unorganized data from patients without any attempt to describe a formal study. Under the circumstances, we have had no choice but to attempt to prevent improper promotion of the drug and to point out its unproven status.

We believe the above describes the current status of disodium edetate and responds to most of the factual points in the letters of Drs. Clarke and Gordon. You will note that Dr. Gordon is incorrect in stating (top of page three) that no correspondence to Dr. Harper followed his meeting with FDA. It is also worth noting the misleading suggestion by Dr. Gordon that the use of calcium disodium edetate in children (page five of his letter) implies recognition of safety, as that substance is not the same as the disodium edetate used in treatment of arteriosclerosis and is less capable of decreasing the serum calcium (it contains calcium already). Moreover, it is effective for the removal of lead and so its hazards can be considered acceptable because of its beneficial effect.

Dr. Gordon's discussion on page five indicates a failure to appreciate the importance of controlled trials in evaluating such subjective symptoms as angina, leg cramps, and memory, which often respond to placebo. His apparent indifference to whether or not the improvements are real or are placebo effects seems inappropriate in view of the great cost of chelation therapy and its possible hazards. There is no persuasive reason for avoiding the kind of well-controlled trials that would permit objective evaluation of chelation therapy. Whether there is sufficient rationale behind this treatment to feel that studies should be publicly funded is for the National Heart and Lung Institute and the Veterans Administration to decide. A negative response on their part would not, however, prevent such studies from being carried out by proponants of this therapy, after appropriate animal studies are conducted to serve as a basis for human trials.

We hope this information is helpful to you. If we can be of further assistance, please let us know.

Sincerely yours,

cc: Congressional Liaison Office

Robert C. Wetherell, Jr., Director
Office of Legislative Services

8 Enclosures
FR Vol. 35, No. 8, 1/13/70, p. 437-439
FR Vol. 39, No. 137, 7/16/74, p. 26056-26057
1/9/75 letter to Harold Harper, M.D., President AAMP
Memo and Order, 9/28/76 U.S. District Court,
Eastern District of Louisiana.
NAS/NRC report on Endrate Disodium IV (NDA 11-355).
Craven and Morrelli: Chelation Therapy. Western J. Med. 122:277-278, 1975.
Soffer: Chihuahuas and Laetrile, chelation therapy and honey from Boulder, Colorado. Arch. Int. Med. 136:685-866, 1976.

cc: HFL-10(2)
HFD-1
HFD-30(2) PSavino
HFD-110
HFD-110:Congressional File
R/D: HFD-110(2) AEAuer:cto:3/16/77:4/5/77:4/6/77
Init: AEAuer:4/5/77
RTemple:4/6/77
JAHalperin:4/6/77
PJSavino:4/7/77
MJFromer:4/22/77
F/T:MAG:crw:7/6/77