The Treatment of Cancer with Arginase

A Report by the Cancer Commission of the California Medical Association

In the summer of 1951, inquiries were made of various members of the Cancer Commission of the California Medical Association concerning the usefulness of arginase in the treatment of human cancer. These inquiries were stimulated by the publication of a "Symposium on Arginase in Cancer Research" in a bulletin issued by a medical foundation in California, and by reports emanating from a physician connected with the Hollywood Presbyterian Hospital. The commission conducted an investigation into the nature of the treatment and the results attributed to it.

1. Nature of Treatment Method

Arginase is an enzyme which occurs in the liver and other mammalian tissues. It is said to split arginine into urea and ornithine. It is apparently of relatively low concentration in malignant tissue. Attempts have been made for some years to treat cancer with arginase, the drug having been given by various parenteral routes, notably by vein. The question arises from time to time as to the purity of the arginase being used, and as to the possibility of contaminants being the "beneficial" factor, if such exists. The name of the agent was changed by one group to hepesa in 1953.

2. Proponents

The persons prominent in the current arginase discussion are essentially as follows:

Wesley G. Irons, D.D.S., formerly connected with the University of California College of Dentistry.

Ved Vrat, a Hindu biology student, formerly associated with Dr. Irons and subsequently connected temporarily with the Permanente (Kaiser) Foundation.

E. Forrest Boyd, M.D., a Los Angeles physician and surgeon, formerly Chief of Staff at the Hollywood Presbyterian Hospital.

Leo W. Hosford of San Francisco, a drugless practitioner (graduate of the San Francisco College of Drugless Physicians, 1934) and operator of a mortuary college.

Dr. Irons was graduated as a dentist in 1922 and practiced for some years in San Jose. From 1922 to 1943 he worked variously as a student at the University of Southern California, as an anatomist in the Walt Disney Studios, as a director of "research" in the Kern County General Hospital, and reportedly as a shipping clerk and a high school teacher. From 1945 until 1950 he was an instructor in the U. C. College of Dentistry. His interest in cancer reportedly began in 1939 when a relative died of the disease. He apparently became convinced that arginase could control or cure cancer, and proceeded to experiment with it. In 1949, Irons and Vrat were associated briefly. Then Vrat left to join Permanente.

In February 1950, application for a research grant was filed with the Committee on Growth of the National Research Council, from the American Institute of Radiation, in which Dr. W. G. Irons was listed as principal investigator and "Ved Vrat, Histologist" as chief assistant. In August 1950, a letter that requested withdrawal of the application stated: (1) that Dr. Irons was no longer with the American Institute of Radiation, and (2) that "the Institute is now under the sponsorship of the Permanente Medical Foundation, and has severed all connections with the Electronic Medical Foundation of San Francisco."

Mr. Vrat came to the United States from India in 1946. He entered Stanford but failed to complete the requirements for Ph.D. in the biological sciences. He was disqualified by the University after eight quarters. In 1949 he was a laboratory technician at the Richmond (Calif.) Hospital and in 1950 was listed as Director of Cancer Research at the Permanente Foundation.

In July 1951 Mr. Vrat published three articles indicating control of mouse cancer by arginase in the Permanente Foundation Medical Bulletin. Subsequently, Dr. Sidney Garfield, then director of that foundation, asked the Cancer Commission for a list of the names and addresses of physicians in the United States interested in cancer control, in order to send them the Bulletin. By October 1951 the rumors concerning a new cancer "cure" reached such proportions that the following letter was released by the Permanente Hospital to the secretary of the Cancer Commission and others:

THE PERMANENTE HOSPITALS
Broadway and MacArthur Blvd.
Oakland 11, California
October 9, 1951

Dear Doctor:

It has come to our attention that there are rumors regarding a claim for cancer cure by the use of arginase and it has been attached to the Permanente Foundation.

We have been working with arginase in the treatment of some mouse transplants of cancer with encouraging results. These results have been published, a copy of which is enclosed. We have used arginase on two patients: one a primary carcinoma of the breast, inoperative, with metastasis to the brain and lung. This patient died during the course of treatment. A second patient with a synovia of the knee joint, treated by amputation of the leg, but with present widespread metastasis to the lung was treated. To date, this patient has shown no encouraging...
response to the arginase treatment. These are the only patients that have been treated by any member of the Permanente Hospital or by arginase prepared by our Research Department.

We understand there are other groups, particularly in Southern California, who are using some form of arginase therapy on patients, but we have absolutely no connection either personnel or material-wise with these groups.

I assure you that we have made no claims to cure cancer, as the results of the two patients that we have treated would indicate. Our work is being carefully controlled and we have no intention of publicizing the use of arginase on humans until proper scientific results are obtained. Very truly yours,

THE PERMANENTE HOSPITALS

(signed) C. C. Cutting, M.D., Chief of Staff
In 1953 Vrat treated some leukemic mice supplied by Dr. A. C. Griffin of Stanford and claimed beneficial results. Mimeographed copies of a manuscript bearing his and Dr. Griffin's name were released in the East and caused a flurry of excited speculation. The manuscript was withdrawn at Dr. Griffin's insistence.

In August 1952 Vrat's connection with the Permanente (Kaiser) Foundation was terminated. Dr. Eaton M. MacKay reportedly continued but did not publish further arginase studies.

Dr. Boyd is a Los Angeles physician and surgeon who was graduated from Stanford School of Medicine in 1919.

Mr. Hosford is a drugless practitioner who operates the San Francisco College of Mortuary Science. In 1950, along with Drs. Irons, Boyd and others, he founded the Charles E. Irons Memorial Cancer Foundation. This was incorporated on June 4, 1951, and steps were reportedly taken to raise some $135,000.

Mr. Hosford aided Mr. Vrat and Dr. Irons in their arginase work. He notified the dean of one of the medical schools in California that excellent results were being obtained in cancer, using arginase.

On April 21, 1953, Mr. Hosford addressed to the American medical associations the following letter:

S.AN FRANCISCO COLLEGE OF MORTUARY SCIENCE
America's Premier College
1450 Post Street, San Francisco 9, California

April 21, 1953

Office of the President
DR. L. W. HOSFORD
American Medical Association
535 North Dearborn
Chicago, Illinois

Gentlemen:

We are sponsoring, in collaboration with the Charles E. Irons Memorial Cancer Foundation, a project in basic research with relation to malignancy.

Hereafter, clinical work on humans has been carried on in Los Angeles under the supervision of E. Forrest Boyd, M.D.

We are now setting up an institutional research project at our college at 1450 Post Street, San Francisco, California. We earnestly urge your full and complete cooperation. Should you be interested in this project and in cooperating with us, would you be good enough to advise us, and we will then endeavor to work out arrangements with you as to the nature and extent of your cooperation.

Very truly yours,

SAN FRANCISCO COLLEGE OF MORTUARY SCIENCE
Dr. L. W. Hosford, President

This was acknowledged by the Cancer Commission on April 23, 1953, with a request for information concerning the "institutonal research project." No reply was received.

Since the Commission was receiving inquiries about the cancer treatment project, the secretary of the Commission visited the college on April 30, 1953. He found a small treatment unit, with a few outpatients waiting to be seen by Dr. M. P. Ream of San Leandro. He was informed that Dr. Boyd visited the unit only on Tuesdays or Wednesdays. There were no bed patients. In one room was a gynecological table, without any visible examining instruments or linen. No nurses were visible. A full report of the visit is available in the files of the Commission.

While Dr. Hosford wrote to the medical associations on College of Mortuary Science letterhead, he addressed a prospective patient on Memorial Foundation paper as follows:

President-Research Director
WESLEY G. IRONS, D.D.S., A.B., M.A., M.S.
W. Hosford, President

Secretary-General Manager
LEO W. HOSFORD, D.P.M.

Vice-President-Medical Director
E. FORREST BOYD, A.B., M.D., F.I.C.S.

WESLEY G. IRONS, D.D.S., A.B., M.D., F.I.C.S., Treasurer-General Counsel
LEO W. HOSFORD, D.P.M.

CHARLES E. IRONS MEMORIAL CANCER FOUNDATION
April 14, 1953

DIRECTORS
Wesley G. Irons, D.D.S., A.B., M.A., M.S.
E. Forrest Boyd, A.B., M.D., F.I.C.S.
Leor W. Hosford, D.P.M.
George E. Chapman, M.B., A.B., M.D.
Leo W. Hosford, D.P.M.
Edward M. Elliott
Miss C.
Jordan 7-0674 and 7-0675

Dear Miss C.:

At last we are able to announce the opening date of our new cancer research treating center in San Francisco, which will be the central point of research of our organization.

The date will be Monday, April 27th, at 1450 Post Street, which is the college building of the San Francisco College of Mortuary Science, the institution under whose auspices this project has been made possible.

Doctor Irons, Doctor Boyd and myself will all be in New York the latter part of this week for a few days and will return to get the treatment started as above stated, on April 27th.

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Would you please write me by return mail letting us know if you are still interested in taking these treatments. Would you also see that all of your records together with their biopsies, x-ray reports, etc., etc., are referred to E. Forrest Boyd, M.D., Supervisor, Research Center, 1450 Post Street, San Francisco 9, California. Please do this immediately so we can know how many will arrive and have all applications for treatment in well in advance so there can be no delay in carrying out the program. Doctor Boyd, as stated, will be the Medical Supervisor, and is a man with whom you are all acquainted.

Looking forward to seeing you and your mother on the above date, and hearing from you at the earliest date possible, I am, 

Sincerely yours, 

Dr. L. W. Hosford 
General Manager

3. Experimental Evidence Offered

No formal experimental evidence was offered to the Cancer Commission by the proponents of arginase in 1951. However, a paper reporting some experimental work was subsequently published by Drs. Irons and Boyd in Arizona Medicine. This paper quoted a 1946 publication of Irons (Journal of Dental Research, 25:497) dealing with subcutaneous and intraperitoneal injection of arginase prepared from fresh beef liver and the reactions thereto in twenty Hamilton-strain white mice. It also quoted a 1947 paper by Irons and Wiswell (Science, 106: 2756) reporting some tests on C3H cancer-strain mice. A number of mice with "spontaneous mammary carcinomata" were injected with arginase: "The tumors shrank; differential staining methods showed the distal portion of the tumor. After three days histo-decalcification was necessary before this mass could be sectioned for microscopic examination."

One animal was given arginase daily for three days. "Five days later when the tumor was removed, decalcification was necessary before this mass could be sectioned for microscopic examination."

One animal was given arginase directly into the mesial half of the tumor. After three days "histological examination showed the distal portion to be typically malignant, while the proximal half presented a picture of innocence."

The authors concluded that direct intratumoral injection of arginase produced effects identical with intraperitoneal administration—namely, a 28 per cent reduction in general tumor growth, and a 26 per cent decrease in the ratio of tumor length to weight.

4. Clinical Evidence Offered

At the request of the Cancer Commission, and by invitation of Dr. E. F. Boyd, Dr. Ian Macdonald was present at a demonstration of clinical results presented to the Cancer Committee of the Hollywood Presbyterian Hospital on February 20, 1952. Two groups of patients were discussed. The first ten had been examined by a subcommittee of the cancer committee of the hospital; the second ten were cases chosen by Dr. Boyd as being perhaps more representative of results.

Case histories were presented as follows:

(1) Mrs. G., an 88-year-old woman with a breast tumor since 1949. When first seen by the Tumor Board the left breast was completely infiltrated, with ulceration of the skin; there were bilateral axillary and left supraventricular nodes. Treatment with arginase began on Aug. 6, 1951. Fifty-nine treatments were given. The patient died on Oct. 6, 1951. The pathologist, Dr. Andrews, stated that the original biopsy showed a well-differentiated carcinoma, and that the same neoplasm was seen in sections from the autopsy, with areas of necrosis and fibrosis. The was no difference in the pre- and post-treatment microscopic sections.

(2) Mr. H., a 62-year-old male with bronchogenic carcinoma proven by biopsy on July 19, 1951. He had dyspnea, weakness and cough; pleural fluid was aspirated but showed no cancer cells on smear. Treatment began on July 13, 1951, a total of 50 treatments with arginase was given and the patient died on September 5, 1951. Dr. Benz (radiologist) reported that the major portion of the left side of the chest was opaque, that there was a posteriorly placed mass and there was an osteolytic metastasis to the left scapula. Dr. Hilliard (laboratory technician) reported that the anti-enzyme values indicated a rapid process and that the antichymotrypsin rose steadily under treatment.*

(3) Mr. M., a 37-year-old male with a history of two to three years of diarrhea. On Aug. 24, 1950, a colon resection was done for carcinoma of the sigmoid, at which time metastases to the liver were present. In January 1951 he had pain along the left costal margin and in the left shoulder and by May 1951 had lost 40 pounds in weight. On July 20, 1951, there was a large lower abdominal mass and treatment with arginase was begun. By Aug. 3, 1951, there were no changes in physical findings but the patient was undergoing progressive deterioration and died on Aug. 21, 1951. Dr. Andrews reported that the surgical specimen showed a fairly well differentiated adenocarcinoma and that a biopsy of the liver showed the same neoplasm. At autopsy the carcinoma was still well differentiated, there was fibrosis and degenerative change. Dr. Benz stated that a gastrointestinal series showed gastrocolic and enterocolic fistulae. Mrs. Hilliard reported that 33 determinations of antienzymes in blood serum were done and 23 determinations of urinary uropepsins with no evidence of improvement in the pattern at any time. The later findings indicated good adrenal function at first which became worse after treatment began.

(4) Mr. M., a 46-year-old male. In January 1949 developed a lump in the right knee which became larger and was biopsied in June 1949 and showed a fibrosarcoma. On July 25, 1953, the primary lesion measured 9 x 9 x 5 cm. Sixty-seven treatments with arginase were given and the mass was thought to be possibly smaller and softer. The patient had metastases to regional nodes and lungs. Amputation was done. Dr. Andrews stated that the original biopsy showed an active fibrosarcoma with many mitotic figures. The amputation specimen showed necrosis of the tumor with no mitotic figures. There was a collagen increase. Dr. Boyd reports that the patient now has considerable weakness and a cough. He has had no treatment since December 1951. Dr. Benz demonstrated bilateral pulmonary metastases and six weeks after treatment began all of the metastases were increased in size. Mrs. Hilliard reported that the anti-enzyme pattern showed no improvement.

*Dr. Philip West and Mrs. Hilliard reported on the response of patients by means of the antichymotrypsin and antienzyme values of blood serum.
(5) Mrs. V., a woman with age not given. Developed swelling and retraction of the nipple in January 1950 and an increasing mass in the breast. In December 1950 there were multiple involved nodes in the left axilla. The patient had weakness and pain in the back. Ninety-six treatments with arginase have been given since July 19, 1951, at which time the left breast contained a 6 x 8 cm. central tumor, and there were multiple enlarged hard fixed nodes in the left axilla. Biopsy on Aug. 29, 1951, showed metastatic adenocarcinoma. Last examination on Feb. 19, 1952: The primary lesion of the breast measured 8 cm. in diameter, there was a left axillary mass 3 x 3 cm., the liver edge was hard and irregular and there was a hard mass occupying the umbilicus. This patient stated that she "feels no better." Dr. Andrews stated that the lesion was a well-differentiated adenocarcinoma with fibrosis and no mitoses. Dr. Benz reported that the chest showed pulmonary fibrosis with no evidence of metastases. Mrs. Hilliard reported that the antichymotrypsin fell from 4.5 before treatment to 5.0 in October but by November had risen unfavorably to 8.5.

(6) Mrs. E., a 40-year-old woman. In May 1950, noted a tumor in the breast which subsequently was treated with Koch serum, testosterone and Premarin® with gradual increase in size of the breast tumor. On November 14, 1951, the breast was small, hard and fixed to the chest wall; there was involvement of the axillary nodes on the right side and bilateral supraclavicular node involvement. A biopsy showed scirrhous carcinoma. This patient had 121 treatments with arginase and last examination on Feb. 18, 1952, showed that the mass in the breast was larger, with more skin involvement, and moderate increase in involvement in the axillary nodes which were now fixed to the scapula. She had gained weight. Dr. Andrews stated that he had no microscopic section to review. Dr. Benz said that radiographic examination showed no evidence of metastases. Mrs. Hilliard reported that six determinations had been done. The last one on Dec. 18, 1951, showed unfavorable progress.

(7) Mr. X., a male, aged 56, name not available. In December 1950, nephrectomy was done for carcinoma of the renal cortex. In June 1951, fractured the right forearm and complained of pain in the back with demonstration of metastases and x-ray treatment to both areas. This patient had had 68 treatments with arginase although the date of beginning such treatment was not stated. At last examination, Feb. 19, 1952, the patient said he felt better but he had severe anemia, was more enfeebled, weaker and dyspneic. There was a mass in the right side of the abdomen with induration of the entire abdominal wall. Dr. Andrews reported that slides made elsewhere were typical of a clear cell carcinoma with areas of degeneration and hemorrhage. Dr. Benz demonstrated pyleographic studies done elsewhere with a mass at the lower pole of one kidney. In October there was radiographic evidence of metastases to the ribs and lungs and the last examination in February 1952 showed a mass of pleural effusion filling the entire right side of the chest, extensive destruction of ribs, new pulmonary lesions and a pathological fracture of one radius. Mrs. Hilliard reported that ten tests had been done from November through December showing a moderately progressive pattern, and no essential change.

(8) Mrs. B., a 50-year-old woman. From 1929 to 1930 she had x-ray treatment to her leg for removal of hair. In 1942 she injured her patella and an ulcer developed in this area which became larger and then improved but did not heal. In 1947 a "cyst" of the patella was removed which on microscopic examination showed epidermoid carcinoma. A graft was used for closure. From 1947 to 1951 the patient was well until she suffered another injury to the leg with new ulceration and pain for which a sympathectomy was done. When seen on Nov. 26, 1951, the right leg showed an indurated granular ulcer at the site of the previous operation and on Dec. 18, 1951, biopsy showed epidermoid carcinoma Grade I to II. Since the above time she had been on treatment with arginase, number of treatments not stated. The patient was presented to the group on Feb. 20, 1952, and on questioning said that she felt better. There were three areas of ulceration 2½ x 1¼ inches and 1 inch and ½ inch respectively in size and the base of these ulcers was reported as being "thicker." Dr. Andrews reported the original biopsy and said that there had been no additional biopsies. Dr. Benz reported that radiographic studies showed no change.

(9) A 32-year-old male, name not obtained. In March of 1950 a tumor in the right axilla was biopsied and showed metastatic carcinoma, primary site undetermined. Eight x-ray treatments were given at the Los Angeles Tumor Institute. In February 1951 there was recurrence of the axillary lesion with pain in the shoulder. In May 1951, further x-ray treatment was given. In November 1951 pain recurred with diffuse rales in the lungs and winging of the right scapula. Three treatments with arginase were given and the patient died one month after beginning treatments. Dr. Andrews reported that autopsy showed a primary carcinoma of the ileum with metastases to the brain and death from cerebral hemorrhage. The microscopic section showed no evidence of change from the treatment given. Dr. Benz reported radiographic findings of hilar adenopathy and military pulmonary metastases, which grew progressively.

(10) Mrs. W., a woman, aged 57. In November 1950 a lump in the breast was found and in January 1951, biopsy showed cancer. The lesion, however, was in the underlying chest wall and she went to the Mayo Clinic where some surgical procedure was done and ten x-ray treatments were given and some months later four x-ray treatments were given. The excised material showed chondrosarcoma. Treatment with arginase began on Aug. 12, 1951, and 198 treatments were given. Examination on Feb. 19, 1952, showed around the infraclavicular area several soft small nodules; the fourth rib was thickened and stony hard. There was a chondrocostal mass in the area of the seventh rib. At this point it was learned that on Feb. 1, 1952, the patient had a resection of the chest wall by Dr. Bert Cotton but the disease was so extensive that residual tumor was left attached to the pericardium. Dr. Andrews reported that comparison of the original sections from the Mayo Clinic with the surgical specimen of Feb. 1, 1952, showed definite changes following treatment with arginase, consisting of increase in fibrous tissue with degeneration of cartilage and encapsulation of the tumor.

Dr. Boyd then announced that the present review of his project was being done over his protest, and the reasons for protest were: (1) inadequate time had elapsed to permit proper evaluation; (2) the dose of arginase had not been established as he now gives 20 times greater dosage than at the beginning of the project; (3) an attempt at evaluation on the basis of inadequate evidence is unscientific. He said on the other hand if present review was for a guide as to future conduct of the project, that was satisfactory. He stated that, for the benefit of the representative of the Cancer Commission, the choice of the ten cases supervised by the committee at the Hollywood Hospital was their own and not his. Three of these cases he said fell short of one of the criteria, that they failed to survive for six months after the beginning of treatment. A fourth case he stated was an
Dr. Boyd stated that in all over 8,000 doses of arginase given intravenously there had been no death due to the use of the drug in a total of 125 cases. He said that arginase reduces the amount of narcotic the patients require, that they are happier, that some of them gain weight, and that 20 of the patients he has treated have returned to their full-time occupations. He stated that Case No. 10 above was pronounced by the Mayo Clinic to be inoperable, and that arginase made the lesion operable. He said that live patients are all that count and one should see the patients to be convinced of the value of the treatment. Patient No. 10 listed above then was brought in. She embraced Dr. Boyd affectionately and stated that she felt wonderful.

Dr. Boyd then showed a Mrs. N. who had metastases to the left lung from a carcinoma of the breast as demonstrated on Jan. 5, 1950. On April 28, 1950, there was radiographic evidence of lymphogenous involvement of the lung and by June 6, 1951 the left lung was completely obscured. The patient had x-ray treatment in February, March and June 1951 and also had testosterone during these months. Dr. Boyd did not say how much arginase this patient had had or when the treatment began. On Oct. 13, 1951, Dr. Benz showed films with extensive changes in the left lung which he interpreted as being postradiation, as x-ray treatment had been given to the entire left side of the chest.

The radiographic appearance in January 1952 was static. Dr. Boyd claimed credit for arginase that this patient was well and had been back at work for ten months.

(11) A child was then shown who at 18 months of age in May 1950 developed epileptic seizures, and was admitted to Children's Hospital in January 1951. Exploration showed a gliosarcoma of the third ventricle, a biopsy being done at that time. The child had been under treatment with arginase since May 14, 1951, still had seizures and when shown to the group had severe strabismus, was unable to walk a straight line; and it was stated that at home the child was to the head because of her constantly walking into walls and objects in the room. Dr. Boyd stated that since treatment with arginase the child's "word power" had improved. It was then learned that following the exploration the child received x-ray therapy given by Dr. Robert Freeman in Pasadena.

(12) A child about age three (J.R.) on Sept. 7, 1951, showed a lump on the back of the head which was biopsied and showed fibrosarcoma. Films in Sept. 1951 showed an osseous defect in the occipital bone from without, a sharply demarcated area. The soft tissue tumor was surgically resected, after which treatment with arginase was given. Films taken in January and February showed progressive healing of the former bone defect so that now it is completely bridged by callus. Dr. Benz interpreted these radiographic findings in the skull as being most likely due to pressure erosion of the overlying tumor with an acute osteomyelitis. Dr. Boyd maintained that the bone was destroyed and that healing was due to arginase.

(13) A 59-year-old male (Mr. R.) had an adenocarcinoma of the lung proven by bronchoscopic biopsy in October 1951. He was dyspneic and it was difficult for him to talk when treatment was begun with arginase in October, since which time 112 treatments had been given. The patient was shown to the group. He said he still had some cough and had nausea from the medicine which he received but no longer had bloody sputum. Radiographic findings on June 12, 1950, and Nov. 2, 1950, showed a slowly growing lesion at the right hilum, on Jan. 2, 1951, atelectasis of the right upper lobe, on Oct. 25, 1951, extensive involvement of the right lower half of the lung. Further x-ray examination on Jan. 15, 1952, showed a right pneumothorax following an exploratory operation at Sawtelle, while on Feb. 18, 1952, the entire right side of the chest was completely dense.

(15) A woman, Mrs. S., age not given, developed abnormal uterine bleeding in 1948, and was treated by surgery and irradiation at intervals up to 1951 for metastases involving the pelvis from a primary adenocarcinoma of the uterine cervix. Gastrointestinal x-ray examination on Feb. 5, 1952, showed a partial small bowel obstruction and the presence of a lower abdominal mass. Prior to this time the patient had had 100 treatments with arginase and Dr. Boyd stated that the perineal floor which was tight had now become relaxed. At surgery on Feb. 12, 1952, the right half of the colon and some of the ileum was resected. Pathological examination showed the specimen to consist of a mass of loops of bowel bound together by dense fibrosis with a few small foci of cancer cells stated by Dr. Andrews to be present. Mrs. Hilliard reported that this patient was always in poor nitrogen balance.

(16) A Mrs. S., who had an adenocarcinoma of the right breast and radiographic examination Nov. 29, 1951, showed bilateral pleural effusion with nodular densities in the left pulmonary field. On Feb. 18, 1952, effusion was less and there were areas of patchy atelectasis. This woman's original treatment was on Feb. 20, 1951, when she had a right radical mastectomy and this was followed by postoperative x-ray therapy. On five occasions pleural fluid had been aspirated but no smears were obtained. She had severe dyspnea at the time the abnormal radiographic findings were demonstrated and Dr. Brown (radiologist) indicated his belief that the findings at that time were more consistent with cardiac failure than with metastatic disease.

(17) A 33-year-old woman (Mrs. S.J.) had a squamous cell carcinoma of the uterine cervix for which irradiation was given in February 1949, at the Hollywood Hospital. Following this she was stated to have an abdominal mass. On Feb. 6, 1951, treatment with arginase was begun and Dr. Boyd stated that the patient was now perfectly normal, and it was possible now to do a pelvic examination whereas this was not possible before arginase was given. Dr. Brown stated that the lesion was treated with 7,000 milligram-hours of radium and that x-ray treatment was given from Aug. 29 to Oct. 25, 1949, and from December to January 1950, there was a depth dose of 8,000 r in the midpelvis and 4,000 r in the perimetria. On Jan. 13, 1950, examination by Dr. George Sharp showed no evidence of disease.

(18) A male, age and name not obtained, on March 10, 1951, had a pneumonectomy at Sawtelle for a squamous cell bronchogenic carcinoma in the left lower lobe with infiltration of the pulmonary vein. On May 14, 1951, he began arginase treatment and he was stated to have gained 40 pounds in weight and to be working regularly although he had a chronic cough. Serial radiographic examinations were reported from Sawtelle as showing no change since the operative procedure.

(19) A women with carcinoma of the cervix, name and age not obtained, with spread to retroperitoneal nodes, had exploratory operation elsewhere and was brought to Hollywood Hospital by ambulance. The onset of her disease was in February 1950 with uterine hemorrhage, and on July 6, 1951, she was explored and said to be inoperable. Then Dr. Boyd stated that the microscopic diagnosis was leiomyo-
sarcoma of the uterus with abdominal spread. Before begin­
ing treatment with arginase she had had two abdominal
masses; she now had three and she would soon be eligible
for surgical treatment.

Dr. Boyd then summarized his ideas by saying that argi­
na se had prolonged the lives of 40 patients long beyond
their natural expectancy, that 21 of them are back at work,
that there has been no damage in any instance, and that
some inoperable cancers have been converted to operable.
He said that if his premise is correct new vistas are being
pioneered. Radiographic findings must be interpreted in an
entirely new light (as in cancer of the lung which may
seem to be growing denser under treatment, due to fibrosis
and deposit of calcium in the tumor with arginase).

He also stated that this treatment opens a new field in
microscopy and that new methods of staining and study of
tissue are necessary to interpret properly the changes in
cancer produced by arginase.

Surgery has an entirely new future in the treatment of
cancer, he said, as more than 50 to 75 per cent of cancers
can be made operable, he said, by treatment with arginase.
Dr. Boyd stated he had a number of patients then waiting
for operation who have been made operable by treatment
with arginase.

The internist also has a new vista in the field of cancer,
Dr. Boyd said, with different symptoms to be interpreted in
the light of this new treatment with the necessity of support­
ing adrenal function along with the use of arginase. He
mentioned that insulin does not cure all diabetics.

Dr. Boyd stated that four years of work and a vast amount
of money are required. The patients so far treated have
spent more than $150,000 at the Hollywood Hospital. Cutter
Laboratories, he said, had signed to pursue the investigation
of arginase and had assigned a full-time research man to
begin work at the Hollywood Hospital in the week of Feb.
25, 1952. [Cutter Laboratories later withdrew. See later
paragraph: 9. Consultant and Other Reports.]

(20) Dr. Rusche was then asked by Dr. Boyd to describe
a case of his, and Dr. Rusche stated that the man had carci­
noma of the bladder which after treatment was less vascu­
lar, but that there was now extensive spread of tumor pos­
terior to the bladder.

This concluded the session.

5. Autopsy Data Offered

The proponents offered no autopsy data to sub­
stantiate statements that arginase had verifiable ef­
fects on cancer in terms of convincing tissue
changes or tumor arrest.

6. Experimental Evidence Developed by the Cancer
Commission and Independent Investigators

Immediately after the publication of the “Sym­
posium on Arginase in Cancer Research” referred
to in the introduction, the Cancer Commission
made extended efforts to secure some arginase for
research purposes. Some of the drug was promised
but none was forthcoming for several weeks. Fi­
nally, through the kind services of Dr. Cecil Cut­
ingen, Mr. Vrat made available sufficient arginase
for Dr. Winsor Cutting to treat two mice that had
cancer. The mice died of cancer. Subsequently Dr.
Cutting checked the findings on 30 animals, with
similar results.

Dr. A. C. Griffin, associate professor of bio­
chemistry, Stanford University, informed the sec­
retary of the Commission on September 24, 1952,
that he had completed three series of studies of the
effect of arginase on leukemic mice. He wrote:
“Right now, I am of the opinion that this drug has
little effect on the course of the leukemia with which
we are working.”

Dr. M. B. Shimkin reported in 1951 that Dr.
David Greenberg, professor of biochemistry at the
University of California and one of the world’s
outstanding authorities on arginase, could not con­
firm shrinkage of tumors in experimental animals
with cancer. The animals died of cancer in the
usual manner.

Dr. C. C. Stock, chief, Division of Experimental
Chemotherapy, Sloan-Kettering Institute for Can­
er Research (Memorial Center for Cancer, New
York City) conducted a series of tests in conjunc­
tion with Dr. Irons in 1953, injecting groups of
cancer-bearing animals (C57Bl/ma mammary adenocarcinoma in C3H mice) with arginase supplied by
Dr. Irons. No significant inhibition in growth and
no tumor regression was observed. (Letter to Can­
cer Commission, June 15, 1953.)

7. Clinical Evidence Developed by the Cancer
Commission

On January 17, 1952, a subcommittee of the
Commission (chairman, Dr. Ian Macdonald) ad­
dressed a formal request to Dr. E. F. Boyd to re­
view his work with arginase in the treatment of
patients with cancer. This request resulted in the
meeting above referred to.

Since that time the Commission has attempted
to maintain a follow-up of the cases, with little
collaboration from the proponents. Of the original
20 patients discussed at the Hollywood Hospital
meeting, three were already dead of cancer at the
time of the meeting; three are known to have sub­
sequently died of cancer (cases 4, 9, and 16). Two,
apparently well (cases 8 and 13), had surgical re­
mov­al of the lesion. One had no evidence of disease
when arginase was given (case 17). In the re­
mainder there was no objective evidence of im­
provement.

Members of the Commission have reviewed the
following cases or case histories:

(21) Male, child with “sarcoma of the pleura.”
Treated by Dr. Boyd in Los Angeles in 1952 and
x-ray films interpreted as showing calcification of
the tumor after three weeks’ treatment. Died, within
some weeks’ time with disease uncontrolled.

(22) Female, with carcinoma of the breast treated
by Dr. Ream in Alameda County. Died with exten­
se metastasis (autopsy).
On April 3, 1952, Mr. F. A. Cutter wrote to the Cancer Commission, “... we found insufficient objective evidence of therapeutic value to cause us to divert our current research from other channels. We therefore terminated what has amounted to an option on a license agreement.”

In the 1952 annual report of Cutter Laboratories to stockholders this was referred to as follows:

“Some of the company’s stockholders have asked what made Cutter’s stock go up so fast early in the year and what made it fall the same way later in the year.

“An unfortunate rumor got started that we were on the verge of coming out with a cancer cure. Like most rumors, there was a grain—but only a grain—of truth in it.

“We were investigating a so-called cancer cure which turned out disappointingly, as have dozens of other similar products we have investigated in the past. When this became known, quite a few sold stock and toward the end of the year, when the stock was down, there was further selling, presumably to establish capital losses.”

The Cancer Committee of the Hollywood Presbyterian Hospital after reviewing the cases treated by Dr. Boyd, recommended in March 1952 that no further patients be treated with arginase; this was approved by the medical advisory board of the hospital and accepted by its administration. The latter decided that, until the original animal experiments could be confirmed by competent authorities, no further patients were to be treated.

The cases presented and the case histories discussed by Dr. Boyd at the February 1952 meeting of the Hollywood Presbyterian Hospital Cancer Committee were reported to and reviewed by the Cancer Commission of the California Medical Association at its regular meeting in Los Angeles, April 26, 1952. Dr. Robert Scarborough, then chairman of the Commission, was authorized to state that: “All available evidence to us indicates that arginase has no beneficial effects in the control of cancer in experimental animals or in patients. To date, it must be concluded that arginase is valueless.” This statement was released to the press, and was published in California newspapers in April 1952.

10. Conclusions of the Commission

Arginase (also termed hepasynt) has been advocated for the treatment of cancer. The current proponents have claimed “miraculous results.”

The Cancer Commission has collected information on more than 26 patients treated with arginase, at least six of whom are now dead with the disease. Of those alive, no patient has been found with ob-

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jective evidence of control of cancer under treatment with arginase or hepasyn alone.

The hospital in which the treatments were given in 1951 and 1952 lists 120 patients as having received arginase; by May of 1953, 70 of these patients were known to be dead with cancer.

Autopsy studies disclosed no evidence of specific chemotherapeutic effect.

There is no evidence to date that arginase (or hepasyn) has a beneficial effect on patients with cancer.

REFERENCES