Assembly Concurrent Resolution No. 20.

Senator Gibson moved the adoption of the resolution.

Resolution adopted unanimously.

By the Committee on Legislative Functions:

Senate Resolution No. 10—Amending Senate Standing Rule 40 to change the names of certain standing committees.

Resolved by the Senate of the State of Nevada, That Senate Standing Rule 40 is amended to read as follows:

40

Standing Committees.

The standing committees of the Senate and their respective jurisdiction for the reference of bills and resolutions are as follows:

1. Commerce and Labor, seven members, with jurisdiction over measures affecting primarily Titles 52–57, and chapters 489, 703–704A and 707–712 of NRS.

2. [Education, Health, Welfare and State Institutions,] *Human Resources and Facilities,* six members, with jurisdiction over measures primarily affecting Titles 33, 34, 37–40 and 42 and chapters 583–585 of NRS.

3. [Environment, Public Resources and Agriculture,] *Natural Resources,* six members, with jurisdiction over measures primarily affecting Titles 26 and 45–50 and chapters 488, 581, 582 and 586–590 of NRS, the Tahoe Regional Planning Compact and the Nevada Tahoe regional planning agency.

4. Finance, seven members, with jurisdiction over measures primarily affecting chapter 286 of NRS and over appropriations, operating and capital budgets, bonding and any measures carrying or requiring appropriations and favorably reported by any other committee unless such reference is dispensed with by a two-thirds vote of the Senate.

5. Government Affairs, seven members, with jurisdiction over measures affecting primarily Titles 18–22, 24, 25, 27–31 and 36 and chapters 281–285, 287, 288 and 407 of NRS, except measures affecting primarily the Tahoe Regional Planning Compact and the Nevada Tahoe regional planning agency.

6. Judiciary, seven members, with jurisdiction over measures affecting primarily Titles 1–16 and 41 of NRS.

7. Legislative Functions, seven members, with jurisdiction over measures affecting primarily Title 17 of NRS and the operation of the legislative session.

8. Taxation, with jurisdiction over measures affecting primarily Title 32 of NRS.

9. Transportation, with jurisdiction over measures affecting primarily Title 44 and chapters 403–406, 408–410, 481–487, 705 and 706 of NRS.

Senator Echols moved that the resolution be referred to the Committee on Legislative Functions.

Motion carried.

By the Committee on Legislative Functions:

Senate Resolution No. 11—Providing for the appointment of an additional Senate attaché.

Resolved by the Senate of the State of Nevada, That John Kenneth Creighton is elected as an additional attaché of the senate for the 59th session of the legislature of the State of Nevada.

Senator Echols moved the adoption of the resolution.

Remarks by Senator Echols.

Resolution adopted unanimously.

By the Committee on Commerce and Labor:

Senate Concurrent Resolution No. 18—Ordering a study by the Legislative Commission of the feasibility of providing health insurance to retired public employees.

WHEREAS, Senator Gallagher reentered politics in 1953 and represented White Pine County in the Senate for the next 12 years, serving as president pro tempore of that body during the 1959, 1960 and 1961 sessions; and

WHEREAS, Charles D. Gallagher's devotion to community service is illustrated by his membership in the White Pine County Chamber of Commerce and Mines, the Rotary Club, the White Pine Museum and the Masonic Order; now, therefore, be it

Resolved by the Senate of the State of Nevada, the Assembly concurring, That the members of this body mourn the loss of a respected Nevada citizen and extend their condolences to the surviving family of former State Senator Charles D. Gallagher; and be it further

Resolved, That a copy of this resolution be transmitted forthwith by the legislative counsel to the surviving family of the late respected Charles D. Gallagher.

Senator Blakemore moved the adoption of the resolution.

Remarks by Senator Blakemore.

Resolution adopted unanimously.

Senator Sheerin moved that Amendment No. 249A to Assembly Bill No. 7 be withdrawn.

Remarks by Senator Sheerin.

Motion carried.

Senator Neal moved that Senate Bill No. 328 be re-referred to the Committee on Environment, Public Resources and Agriculture.

Motion carried.

Senate Resolution No. 10.

Senator Echols moved the adoption of the resolution.

Remarks by Senator Echols.

Resolution adopted unanimously.

Senator Wilson moved that Senate Bill No. 109 be taken from the General File and be placed on the Secretary's desk.

Remarks by Senator Wilson.

Motion carried.

Senator Ashworth moved that Senate Bill No. 137 be taken from the General File and be placed on the Secretary's desk.

Remarks by Senators Ashworth, Bryan, Neal and Wilson.

Motion carried.

Senator Gibson moved that Lester Wisbrod and Donald LaPlante be accepted as accredited news media representatives and that they be assigned space at the press table and be allowed the use of appropriate facilities.

Motion carried.

GENERAL FILE AND THIRD READING

Senate Bill No. 141.

Bill read third time.

Roll call on Senate Bill No. 141:

YEAS—17.

NAYS—None.

Absent—Glaser, Hernstadt, Schofield—3.

Assembly Bill No. 141 having received a constitutional majority, Mr. President declared it passed, as amended.

Bill ordered transmitted to the Assembly.

SENATE COMMITTEE ON HUMAN RESOURCES
AND FACILITIES

The meeting was called to order at 8:10 a.m. on Saturday, March 19, 1977 in the Las Vegas City Hall Commission Chambers with Senator Jack Schofield in the Chair.

PRESENT: Chairman Jack Schofield
Vice-Chairman Joe Neal
Senator Wilbur Faiss
Senator William Hernstadt

GUESTS: Assemblyman Danny Demers
Thorne J. Butler, M.D. - OPPONENT
Marvin Kratter - PROPONENT
Stuart L. Nightingale, M.D. - OPPONENT
Jacob Hack - OPPONENT
Harvey Howard - PROPONENT
Connie Edwards - OPPONENT
Mario Soto, M.D. - PROPONENT
Alfred T. Sapse, M.D. - PROPONENT
Max Hayman, M.D. - PROPONENT
Mary Ellen Dykstra - PROPONENT
Louis L. Friedman, M.D. - OPPONENT
Omar Fareed, M.D. - PROPONENT
Daniel Wilkes, M.D. - OPPONENT
Joseph Quagliana, M.D. - OPPONENT
N.B. Drew - PROPONENT
Theodore Jacobs, M.D. - PROPONENT
Alan W. Feld, M.D. - OPPONENT
G.L. Rutherford - PROPONENT
John Shipp - OPPONENT
Buck Monari - PROPONENT
Mike Culbert - PROPONENT
Maurice Pearlman, M.D. - OPPONENT
Don Murray - PROPONENT
Harold Miller, M.D. - OPPONENT
Jack C. Cherry - PROPONENT
Grace E. Benson - OPPONENT
A.R.L. McNaughton - PROPONENT
Mary Lou Haynes - PROPONENT
Ronald Harris - OPPONENT
Louis Popp - PROPONENT
Roland C. Bartlett - PROPONENT
Harold E. Feikes,M.D. - PROPONENT
Marion Keaton - PROPONENT
L.L. Elliott - PROPONENT
June Brainerd - PROPONENT
Russell G. Stephans - PROPONENT
Grace Levendis - PROPONENT
Frend Befree - PROPONENT

A.B. 121:
Chairman Schofield opened the hearing by stressing that this meeting will stress courtesy to all speakers and he emphasized that the members of the Committee had not

Committee name was changed pursuant to Senate Resolution 10, which was passed on March 16, 1977.

made up their minds and this second hearing was held because the Senate Committee felt that during the initial hearing on A.B. 121, they had not had the opportunity to question the individuals who testified.

Assemblyman Danny Demers: Mr. Demers began by saying that he introduced the bill as a request of Mr. Thomas Patton.

Mr. Demers said that he has heard many people that they are afraid that patients will go to Laetrile first, and bypass the orthodox cancer treatments. In response to this concern, Mr. Demers read several pertinent sections from the "Rorvick Report", (Exhibit "A"). The sections read covered statements from many professionals and physicians who question the information being passed on to the American public. Mr. Demers also felt that the amendment including Gerovital (GH3) is a worthwhile addition.

Thorne J. Butler: Mr. Butler was the beginning opposition speaker, and is a physician in Las Vegas, representing the Nevada State Board of Health as Chairman. Dr. Butler said that the opponents are interested in individual care, and are also concerned that the process proving this therapy is a legislative mandate. Dr. Butler said that the opponents are also concerned about the image of Nevada as a state where people come for hopeful treatment with a drug whose therapy has been touted to do many different things with no proof.

Mr. Marvin Kratter: Mr. Kratter, President of the Rom-Amer Pharmaceutical Ltd, was the beginning proponent speaker. Mr. Kratter said that he would like to endorse the statements of Dr. Butler as it is important that good research be done for the safety and efficacy of the drug. Gerovital and Laetrile are not banned or prohibited substances under the Nevada laws. Mr. Kratter said that he is the controlling stockholder of the Rom-Amer Corporation which researches Gerovital (GH3). The Food and Drug Administration has approved two IND's (Investigation of New Drug), and these are only granted after animal studies have been completed. Mr. Kratter said that the actual ingrediants of GH3 have been known for approximately seventy years, and every one of the components are neither banned or controlled substances. He said the first clinical work on GH3 was done in Romania in 1956, and the drug is now used in four different countries. Mr. Kratter stated that there have never been any reported cases within the scope of the clinical investigations of this drug by recognized investigators within the United States and Canada that has revealed any serious debilitating side affects or serious toxicity. Mr. Kratter said that he thought that the basic issue was one of a freedom of choice. He also read into the record the names of many physicians who give support to GH3,: Dr. Sidney Cohen (Professor of Psychiatry at the Neuropsychiatric Institute, University of California); Dr. Thomas Bann (Professor of Psychiatry at the universities in Nashville, Tennessee and Montreal,

Canada); Dr. Leonard Kamer (Associate professor at the New York Medical College in Fifth Avenue Hospital); and Dr. Max Hayman (Professor of Research-Psychiatry at U.C.L.A.).

Dr. Stuart Nightengale: Dr. Nightengale represented the Federal Food and Drug Administration in opposition to A.B. 121. In discussing GH3, Dr. Nightengale said that cocaine does interfere with the activity of certain other drugs. Dr. Nightengale read sections from the American Geriatrics Society publication (Exhibit "B") which is a review of the use of procaine in the treatment of the elderly. He reviewed problems that occured during the investigative studies of GH3. He said that the F.D.A. has not yet had the opportunity to discuss these issues with Mr. Kratter of Rom-Amer, however, basically the phase two of the studies were generally felt to be invalid because they were not sufficiently randomized, controlled or 'double-blinded', and in some cases there were problems with the appropriate dosage. Another issue has been that longer-term studies in Phase Two (more than three months testing on humans) cannot proceed at the present time because no prior animal testing has been done. Rom-Amer in the past has been alleged by the F.D.A. to be violating the IND regulations, which forbid the commercialization of an IND product, specifically Rom-Amer has reprints suggesting that GH3 was already safe and effective, for its investigational purposes. Rom-Amer was instructed not to use the tradename 'Gerovital' for its product since it implied an indication for which it was not being tested, i.e., its affect on the aged. Dr. Nightengale said these problems were ones that the F.D.A. had with the previous owner of Rom-Amer and they expect to discuss these Mr. Kratter in the near future. Dr. Nightengale said that he had received a telephone call from the Security and Exchange Commission who requested a review of the proposed press release to be issued by Rom-Amer, as follows: "Rom-Amer Pharmeceuticals LTD stated today that a bill pending before the Nevada State Legislature which the Company is actively supporting, authorizing the prescription and sale of the Company's anit-depressant drug, Gerovital H3, or GH3 in the State of Nevada may have caused the recent interest in the Company's stock. A Company spokesman pointed out that, although the bill had been passed the State Assembly, it was still in the legislative process and that no ensurance could be given that the bill would be passed by the State Senate or if passed, would then be approved by the Governor. If the bill presently pending before Nevada legislative body becomes law, the Company believes that it will be able to legally market Geritoval in Nevada without further approval from the United States Food and Drug Administration." Dr. Nightengale said that the F.D.A. requested a change in the following sentence of the press release, and he read what was finally written,"However, the F.D.A. has stated that it will assert authority over and prohibit the sale of Gerovital H3 within the boundries of the State of Nevada. The Company further indicated that even if the bill were to become law

in Nevada, sales of GH3 would be limited to the State of Nevada, which is a thinly populated area from which only limited sales can be anticipated. The spokesman further noted that the drug will only be available on a prescription basis to patients who request it. The Company noted that since its prior exclusive activities have been limited to IND's, it has no operating income since its promotion. No assurances can be given that any such income will be earned in the future. The Company indicated that it still is conducting research with the view to attempt to have GH3 approved for sale in interstate commerce by the F.D.A. Until such F.D.A. approval is obtained, the Company cannot make sales of GH3 in interstate commerce. The Company noted that up to three years or more of additional testing of GH3 could conceivably be required before the F.D.A. would be in a position to consider granting approval to GH3. However, the Company stated that no assurances could be given that such approval would ever be attained. The Company stated to its knowledge, no bill was presently pending in any other State Legislature permitting the sale of GH3 in anyother state. The spokesman also noted that the Company is currently negotiating terms with the Romanian authorities for the manufacture of GH3 in the State of Nevada. Although the Company anticipates a favorable outcome of such negotiations, no depended assurances can be given that such negotiations will ultimately be successful."

Dr. Nightengale said that it has been alleged that the procaine hydrochloride or Laetrile for that matter, is a safe or harmless drug. By the definition of the Federal Food, Drug and Cosmetic Act, no drug is considered safe for marketing or general use until it has passed through full animal and human testing. The data from such use is compiled and then reviewed in relationship to the indications for use of that drug as they were viewed by the initial testing of that drug. Dr. Nightengale said who will be responsible for the safe use of these drugs on different populations? No reproductive study of this drug in animals has been carried out to his knowledge. Who will remove the drug from the market in Nevada, should a problem arise?

He said that different type of threat is imposed by Laetrile than that of Gerovital. There had not been appropriate safety studies for humans to allow an IND to be granted for Laetrile. Laetrile has gone through multiple and pre-clinic testing with animals and has not shown any effectiveness in any animal screening tumor systems.

Senator Hernstadt: Doctor, you mentioned that Gerovital or procaine had some allergic reaction in the central nervous system. This is sort of a technical question, and please correct me if I have the wrong handle on this, but it is my understanding that Gerovital is not only procaine, but is two or three other stablizing drugs because procaine by itself, from my understanding, disintegrates fairly quickly

when injected into the system, and it is the stablizing medium that helps the function over a period of several hours.

Dr. Nightengale: There has been a lot of discussion over a period of time about just what Gerovital is, and the final conclusion is that it is 2% procaine hydrochloride. Rom-Amer may have a patented combination of other proportions used, but in terms of toxicity, I do not think we have data to say that it should be left optional necessarily.

Senator Hernstadt: Does the F.D.A. have any evidence of this drug or substance when it is prescribed the way it is currently where it is available, having any adverse toxic reaction?

Dr. Nightengale: As a general statement, Dr. Ostfeld from Yale reviewed about 285 different reports and some were to have bad reactions reported, but I do not recall any specific details. The problem with the world literature on Gerovital is that the studies have been generally 'miserable', in termed of well controlled, double-blind, random studies.

Senator Hernstadt: Do you know of anyone that has died, or has become severely impaired from the taking of GH3?

Dr. Nightengale: I myself do not, but if you look at Goodman-Guildman which refers to the fatal prophyläxis they must have gotten their information from something. No one is sure that what is called GH3 is the same thing in all these studies that occur in world literature.

Senator Neal: Does the F.D.A. accept studies done in the medical field of other nations without testing the drugs in this country?

Dr. Nightengale: As a general rule the answer to that is no, we would require at least some reports and studies to be done in this country.

Senator Neal: You made reference to the press release -- am I to understand you took your position of involvment due to a proceding of the stock exchange?

Dr. Nightengale: Yes. I first got the release from a person who works in the Office of Compliance in the Bureau which I am in, who said our advice was requested by the S.E.C.

Senator Faiss: Could you at this time, approve GH3 as an anti-depressant only for the aged?

Dr. Nightengale: Well, no. The IND process is in early Phase II. We would not get to the end of the investigational process until Phase II were completed, we have good evidence of efficacy in the elderly, but then you would have to have a Phase III

extensive study, and the Company would submit a new drug application, which is a culmination of all the studies that have been done on the IND, then the FDA reviews this for either approval or disapproval.

Senator Faiss: I am not an expert in the field of medicine, therefore I am going to have to rely on the people's testimony today, and on my own limited research, I do not understand this, how can this be an unproven new drug since it has been in use over twenty years and is now in general use throughout the world?

Dr. Nightengale: A drug can be approved for marketing in any country in the world, but can not be marketed in this country unless it meets our standards. We require safety and efficacy, which many countries do not require.

Senator Faiss: I have been told that we manufacture several drugs in this country that although they are not legal here, they are distributed and sold elsewhere in the world, is this correct?

Dr. Nightengale: Theoretically, it is not supposed to occur.

Mr. Marvin Kratter: I was asked to limit my remarks to five minutes, I spoke for five minutes, this gentleman has spoken for one hour (Dr. Nightengale). I ask to be recognized at this time because if I have to wait until seven o'clock tonight, to refute these things, I doubt if anyone will remember all of the things that have been said.

Senator Schofield: This hearing is not for a confrontation between the F.D.A. and Mr. Kratter or anyone else. If manufactured in Alaska, would they be able to distribute Laetrile anywhere in the United States?

Dr. Nightengale: It would be a violation of interstate commerce, to receive the products to manufacture the drug, and it would also be a violation to transport the product out again.

Senator Hernstadt: Why hasn't anyone from F.D.A. or any other major cancer research institute visited the Tijuana Clinic?

Dr. Nightengale: I am sure that there are many American scientists who are qualified who have visited the clinic. The F.D.A. likes to review data and records. We wrote to Dr. Cantraras in Mexico and asked him to give us the data that he had available on patients that he had treated there, and we would make an attempt to follow-up on them in this country. Dr. Cantraras gave us twelve cases, these individuals were tracked down and no evidence was found that Laetrile had any affect on the general course of what happens in cancer.

Senator Hernstadt: If we were to legalize Laetrile or GH3 in Nevada, what recommended safety criteria at the State level would you recommend, and what kind of removal provisions would you recommend?

Dr. Nightengale: I cannot speak to you at the State level on how you would do this.

Senator Hernstadt: With respect to having intra-state use, is the F.D.A. concerned with the substances themselves or the principle of a state establishing intra-state use of a substance?

Dr. Nightengale: Laetrile is being considered in 25 state legislatures and we are concerned because of the quackery involved, and the harm it could cause. Gerovital is a unique situation, where a sponsor with an IND with the F.D.A., already has a license to use the drug in an exempt fashion for investigation, and has gone to the state legislature for legalization.

Senator Hernstadt: How many new drugs has the F.D.A. cleared in the last five years?

Dr. Nightengale: They range from new therapeutic benefits to the truly new and useful drugs, and I think we average somewhere between 15 and 20 new chemical entities per year, for the last several years.

Senator Hernstadt: What is the cost and time factor for each of these?

Dr. Nightengale: I really cannot speak to that. It probably takes 6 to 7 years to get a drug approved going through the whole IND and NDA process. The expense would be quite variable based upon the drug itself.

Senator Faiss: After talking with my family doctor yesterday, I am disturbed, as he said that if aspirin were introduced as a new drug, it would take 15 years, if ever, for it to be approved because no one knows exactly how it works.

Dr. Nightengale: You do not have to know how a drug gets its final effect to be approved. The real issue is the risk/benefit ratio that we consider.

Chairman Schofield: Commented for the record that the Committee attended the hearing on a voluntary basis, and this is at no cost or added expense to the State of Nevada treasury. I would also like to thank all the volunteers who traveled here to help us deliberate this important issue for the State of Nevada. Also, none of our Committee members own any stock in any company involving these substances. I would also like to thank the City of Las Vegas for volunteering this building.

Mr. Kratter: As a result of Dr. Nightengale's presentation, we have had what feels like a 'smear tactic', and it is not anything new in terms of what has been happening between the pharmaceutical industry and the F.D.A. We are a public company, and as such we are regulated by the S.E.C., and we are required

to make certain announcements. While negotiating to acquire this company in October of this year, I was concerned with the effect that the injection of my name into the Company might have on the stock. We voluntarily went to the S.E.C. and said that the injection of my name may affect this stock, and we would like for you to order a trading fault. The S.E.C. said they saw no reason to put into effect a trading fault. When the stock started to run in the last couple of weeks, we again met with the S.E.C. and said the stock may be running on false hopes.

Chairman Schofield: Senator Hernstadt raised a point of order, we would like for you to keep your remarks to the statements that Dr. Nightengale made.

Mr. Kratter: I would like to ask if Dr. Nightengale is aware of the fact that the press release was initiated by the Company, in conjunction with the S.E.C. and whether he knows that the S.E.C. called the F.D.A. at the request of the Company in order to be sure that what the Company was saying in terms of a possible F.D.A. involvement, was accurate?

Dr. Nightengale: I have a memo of the telephone conversation which said that the F.D.A. received a call from the S.E.C. in Los Angeles with respect to the subject of recent legislation being considered in the State of Nevada which would permit availability of Laetrile and Gerovital H3 to the public. They indicated that because the bill had passed the lower house, the firm has prepared an issuance of a press release concerning Gerovital H3, and Mr. Tucker of S.E.C. requested a statement of F.D.A.'s position if the law passed. I didn't mean to imply that the S.E.C. said that 'you must do it'.

Mr. Kratter: I think there is some confusion in terms of the safety and efficacy of this drug with the F.D.A.'s position. He read from a statement of the Boston Herald American (4/27/75), and a letter from a former chief of the F.D.A, Commissioner Alexander M. Schmidt, M.D. (10/21/76), which he said he was reading as an endorsement from Senator Cannon. The letter quoted that "procaine hydrochloride is a rather safe drug when used in appropriate doses and in patients who are not allergic to it...". Mr. Kratter said that in 1975, 12 new N.D.A.'s were approved by the F.D.A. and the average cost ran $24.4 million, and the average time ran 8 years.

Dr. Nightengale: I have said everything that I have said in good faith and to the best of my knowledge. Safety is not known ultimately until the drug reaches the marketing stage.

Mr. Kratter: Does the F.D.A. take the position that twenty years of use in 42 countries has not demonstrated sufficiently that this drug is safe for continuing use?

Dr. Nightengale: Referring again to the Ostfeld paper, he commented that use of a drug in a country that does not have good food and drug laws is meaningless.

Mr. Kratter: Is Dr. Nightengale acquainted with Dr. Zung?

Dr. Nightengale: Yes, I had a meeting with Dr. William Zung last summer when he came to the F.D.A. to discuss Gerovital.

Mr. Kratter: Dr. Zung was hired by the F.D.A., and paid as a consultant. Dr. Zung did a double-blind study, and was accepted as an authority in this field. When Dr. Zung's study was received, which was favorable to this drug, the F.D.A.'s conclusion in a letter to the company was 'it was a lovely study, but all it is any good for, is to tell you how to do a new future study'.

Dr. Nightengale: No one is infallible and people who are excellent, may at certain times not produce what would be an ideal clinical search. In this particular case (he read from a letter--Exhibit "C") the consensus was that the Zung study was valuable in providing information on which to revise protocols for future studies.

Jacob Hack: A physical organic chemist asked Dr. Nightengale about the possibility of a chemical-chemical molecular level interaction between possibly one of the constituents of Gerovital and procaine?

Dr. Nightengale: I am not competent to respond to that question, but I suggest that that question be addressed to the sponsor of the drug to be looked into.

Sen. Neal: (To Mr. Hack) Your question seems to infer that once procaine is taken, and there is another drug present, can it combine and act as a single drug?

Mr. Hack: That is correct.

Dr. Harvey Howard: He asked Dr. Nightengale if he was aware of a court order in Oklahoma? Wherein the Judge gave the freedom to several Laetrile patients to acquire the Laetrile for their own use, under a physician's use.

Dr. Nightengale: The justice allowed that it was appropriate for the individual patient under the court order to continue to receive Laetrile pending the outcome of the administrative rule making procedure that the F.D.A. is currently pursuing.

Dr. Howard: You have directly or indirectly made a statement which I consider a threat to the Legislature of this State.

that the F.D.A. would actively attempt to stop inter-state commerce and interfere with the transport of ingrediants to this State for the manufacturer within this State, for use within this State of any substance which has not been tested?

Dr. Nightengale: There was no implied or direct threat to the State of Nevada, and the issue has to do with the drug itself and whether its transport is in violation of the Federal law.

Ms. Connie Edwards: Ms. Edwards representing the American Cancer Society asked Dr. Nightengale about a drug which was in use in Europe that was considered safe until taken by pregnant women.

Dr. Nightengale: I do not know what the exact laws were in Germany at that time, but it was a marketable drug by their standards.

Dr. Mario Soto: Why do some American laboratories make drugs that are not legal in the United States, but it is legal to bring them into the United States?

Dr. Nightengale: Theoretically one is not allowed to bring drugs into this country that are not approved for distribution of interstate commerce. One is discovery of the situation, and one is the magnitude of the situation.

Dr. Alfred Sapse: Dr. Sapse is a Rumanian who asked Dr. Nightengale how does the F.D.A. define Phase II in terms of number of patients?

Dr. Nightengale: It is an early Phase II meaning that it needs to have well controlled, randomized double-blind studies.

Dr. Sapse: The F.D.A. requires in Phase II, 100 to 200 patients in double-blind studies. I have submitted studies involving more than 300 patients carried out by the most refutable and famous scientists. The rules and regulations are not the same for everybody.

Dr. Nightengale: The rules and regulations are not the same in terms of the number of patients required because each drug and product has a different spectrum of safety and toxicity, and the F.D.A. is not restrained by the regulations that we must have a certain number. (Exhibit "D")

Dr. Max Hayman: We have made no claims for rejuvenation (GH3) our claims have been restricted solely to the anti-depressant effect. Dr. Hayman discussed the testing procedure used with Gerovital H3. He said they tested all age groups and every level of depressant.

Dr. Hayman said that his tests were conducted at weekly intervals for four (4) weeks. We gave 13 injections in all. With the sterile saline solution, there was a measurable degree of improvement, people react to placebos as they do to ordinary drugs sometimes because they expect to be helped. In regards to the Gerovital, the results of the Zung Study showed that cancer could be cured in five out of one hundred patients. Dr. Hayman said that 12% of the patients had side affects; like flushing, tingling in the mouth which lasted from five minutes to sixty minutes. The results were the same for the younger patients as well.

Senator Neal: Were these patients taking any other medication?

Dr. Hayman: No, that was part of the conditions of the test.

Senator Faiss: Dr. Nightengale testified that there were various instances of asthma and skin rash, what did you find in your tests?

Dr. Hayman: We did not have anything like that.

Senator Faiss: Was Dr. Nightengale's reference using the same formula you used?

Dr. Hayman: No, they used procaine hydrochloride by itself.

Senator Hernstadt: In the literature that you have studied, is there any indication that there is any permanent adverse affect from the use of Gerovital?

Dr. Hayman: No, I do not know of anything like that, in either the old preparation or the new. He submitted Exhibit "E".

Jacob Hack: I am in favor of the bill, however, I have one objection to using the tradename Laetrile. I would like to see Laetrile named generically,as Amygdalin is not Laetrile, per say, it is the synthetic process to develop it. Mr. Hack said that Laetrile should be, "l - mandelonitrite-beta-glucuronic acid".

Mary Ellen Dykstra: Ms. Dykstra ~~is~~ a 20 year resident of North Las Vegas,gave a personal testimony about her husband who had cancer. Her husband had had treatment in the Tijuana Clinic and she felt that if the cancer condition is considered terminal, then the patient should be given the choice of treatment.

Dr. Louis L. Friedman: Dr. Friedman, a physician from Nevada said that there is no scientific data on Gerovital which supports the claims made by the proponents of A.B. 121. Dr. Friedman said that procaine hydrochloride is a very dangerous drug, it can cause sudden death on injection, it can cause convulsions, it can cause respiratory arrest.

Senator Hernstadt: Do you know of anyone who has a permanent

disability on account of using GH3 in the way that it is designed to be used?

Dr. Friedman: I do not know of such, but I know of deaths as a result of procaine hydrochloride.

Senator Hernstadt: Yes, but we are talking about different dosages, so we are studying this from the point of view of an anti-depressant in accordance with a doctor's prescription.

Dr. Omar Fareed: Dr. Fareed of Los Angeles said that he has worked with Dr. Albert Schweitzer, Dr. Tom Dooley and continued as President of the Carr Foundation to work in International Communities to produce a health message in 40 countries. He conducted an open-end study with Gerovital, and concluded that it is a safe drug. He took 10cc's every day for a month himself and said it is a good anti-depressant.

Senator Faiss: Are there any withdrawal symptoms?

Dr. Fareed: None of the patients collapsed, some did miss it. We had one accidental death, which was a combination of sleeping pills and alcohol.

Senator Hernstadt: Were your tests and those of Dr. Hayman 'double-blind'?

Dr. Fareed: Mine were not, but those of Hayman and Zung were.

Senator Schofield: Do you think that passage of this legislation will interfere with the accreditation of Nevada's medical school?

Dr. Fareed: The community will have their medical school because there is a need for one.

Dr. Daniel Wilkes: Dr. Wilkes is a physician in Las Vegas, and said this issue is purely economic. He said that what the Legislature is doing is that the State of Nevada will approve the use of Laetrile as a therapeutic drug to treat a lethal disease, and yet there is no scientific proof.

Senator Hernstadt: The Senator asked if Dr. Wilkes was aware that the following was amended into the bill by the Assembly: "There will be a label or device affixed saying that Laetrile has not been approved as the treatment or cure of cancer by the Food and Drug Administration of the United States Dept. of Health, Education and Welfare"?

Dr. Wilkes: No, sir I was not aware of this.

Senator Faiss: Is cancer on the increase or decrease in the United States?

Dr. Wilkes: It is on the increase, sir.

Senator Faiss: What difference has surgery, chemo-therapy and radiation made on the death rate of cancer?

Dr. Wilkes: We are now curing Hodgkin's disease with intense radiation and chemo-therapy, and I haven't seen any of them cured by Laetrile.

Dr. Soto: I am a member of the International Society of the Therapy of Lung Cancer, headquartered in Washington D.C., and I am not using Laetrile, except in the cases where I know it will work. I did an open investigation through Phase 2 and Phase 3 at the General Hospital in Mexico City, in 1967 and 1968.

Senator Hernstadt: To make clear what your testimony is, you recommend the use of Laetrile in conjunction with other known treatments?

Dr. Soto: Yes.

Dr. Joseph Quagliana: Dr. Quagliana, a Oncologyst in Nevada, said that his major concern is that the physicians "worry" about the quality of care that is given to patients with cancer. The Doctor said that if Laetrile is made legal, he is concerned that citizens who were "on the fence" before in regards to this treatment, would feel that this is a legitimate way to treat and cure cancer, even if the label does not state this. Dr. Quagliana gave case histories where the patient took the Laetrile treatment against his advice, and the results were negative, sometimes resulting in death. Dr. Quagliana said that if Dr. Soto can publish in the medical literature that Laetrile reduces the toxicity of chemo-therapy drugs, then if he were convinced of this, he might prescribe it to his patients.

Senator Schofield: The Senator stated that when he and Senator Hernstadt visited the clinic in Tijuana, he never heard any of the patients make the claim that the Laetrile treatment was a cure. He also stated that they were told that they were the only U.S. officials to ever visit the clinic, and he understood that this included physicians. He suggested that if there was a "ray of hope" in this treatment, that perhaps the physicians should make the effort to visit the clinic.

Dr. Quagliana: He said that he hasn't visited several of the famous clinics in the United States, but their methods have been documented and he doesn't need to visit them to incorporate these proven methods into his practice.

Dr. Soto: The Doctor said that he had not stated that it was the amygdalin that was helping the patients, but rather a treatment involving amygdalin and a diet. He also said that all of his patients have had the benefit of the

conventional therapy. Dr. Soto discussed several of his cases for which he had brought documentation.

Senator Schofield: He asked Dr. Quagliana to go over the documents that Dr. Soto had brought with him during the 10 minute break and report back to the Committee.

Dr. Quagliana: The Doctor stated that in order for that to be done properly, he would have to review x-rays, biopsies and the entire case history.

Mr. N.B. Drew: Mr. Drew is a resident of Las Vegas, and he stated that he had taken GH3 for approximately 10 years, and is now 85 years old. Mr. Drew said that he feels that GH3 has helped him, as he is still active in business.

Dr. Theodore Jacobs: Dr. Jacobs said that he has practiced internal medicine in Las Vegas since 1963. He said that his testimony only represents his own views, and they do not represent the views of the A.M.A., the Nevada State Medical Association, or the Clark County Medical Society. Dr. Jacobs said that in early 1974, Dr. Sapse had asked him if he wanted to experiment with GH3 on several of his patients. He said that he was given official F.D.A. approval, and his name was amended to the I.N.D. #8681. During January and October of 1974, Dr. Jacobs said that he treated nine of his patients in an open-study, as all the participants knew they were receiving GH3. Dr. Jacobs said that they all had mild to moderate depression. He continued to state that one of the patients did not finish in the experiment; and of the remaining 8, six had significant improvement in their depressant behaviour. In seven of the eight, there were not any side affects, but one of the patients experienced slight light-headedness about five minutes after receiving the 100 milligram injection.

Dr. Alan W. Feld: Dr. Feld said that he has been practicing in Las Vegas since 1963. He said that he appears as a private citizen and not a representative of any organization. Dr. Feld said that there is no scientific evidence that Gerovital has any unique properties, that differ from plain procaine in the ataxic human being. Dr. Feld said that he still has yet to hear a physician connected with a University present published material in support of this drug. Dr. Feld said that the issue is not the availability of this drug, but an issue of 'promotion'.

Mr. Kratter: Mr. Kratter stated that he could not understand how Dr. Feld could make a statement that no publications, or University connected people, or no double-blind studies had been conducted in regards to GH3, when he had listened to Dr. Max Hayman's testimony where all of the above had been verified.

Dr. Feld: He stated that he had not seen such reports prior to this date.

Mr. Kratter and Dr. Feld questioned each other.

Senator Hernstadt: He asked if there is a discernable difference between procaine and GH3?

Mr. Kratter: He asked would the F.D.A. go to all this trouble to prove the efficacy of GH3 if it were not a new drug? And, he asked Dr. Feld if he knew of a single manufacturer of a procaine-hydochloride based drug that contained the four mentioned substances in the same relative proportions and assembled and manufactured in the same manner?

Dr. Feld: No sir, there is no none, he answered.

Mr. Glen Rutherford: He stated that he has a legal suit against the F.D.A. on Laetrile, and has won his opinion in the courts twice. He stated,"That all of these people who call themselves experts here this morning have never had cancer, I have had cancer!"

Senator Faiss: He asked if more than one doctor diagnosed Mr. Rutherford's case as cancer?

Mr. Rutherford: He answered yes, and he has had no other modalities except Laetrile.

Mr. John Shipp: He stated that the social consequences of passage of this legislation may be more than they estimate. He said that Nevada's welfare rolls are going to increase as people come to Nevada as a last hope in their treatment for Cancer, (opponent).

Mr. Buck Monari: He stated that he had had surgery and the Laetrile treatment. He also mentioned other friends he had that had taken the treatment of Laetrile and had lived.

Ms. Connie Edwards: She said that she was a volunteer for the American Cancer Society. She said that people who come to Nevada will expect state assistance for the medically indigent.

Mr. Mike Culbert: He said that he was representing the Committee for Freedom of Choice in Cancer Treatment. He said that in reading the bill he has not seen anything that states that physician's must abandon orthodox therapy. He said that the physicians using the metabolic treatment of which Laetrile is a part, report that 65% to 70% of the patients undergo some kind of positive response to this treatment. Mr. Culbert said that the proponents are put in a "Catch 22" situation where it is stated that Laetrile cannot be approved because it has not been adequately tested on humans, and it cannot be adequately

tested on humans because to do so would be illegal. He also said that Laetrile is or vitamin B-17 is a food factor, and not a drug and therefore should not come under the perimeter of the Food, Drug and Cosmetic Act as amended in 1962, which has been the "root of the problem". He asked how could Laetrile be considered just a placebo for desperate patients when it has also been give to animals as part of their regular diets and they have shown marked improvement, yet cannot understand the psychosis behind a "placebo"? Mr. Culbert said that raw amygdalin can be purchased in the United States now for $5.00/gram, and the smugglers sell it for about $3.00/gram. Also, this is being used either by itself or with a diet therapy in 28 countries, the most recent being Isreal.

Dr. Maurice Pearlman: He said that this legislation will set a precedent so that every Session there will be more and more requests regarding controversial drugs. How will this be handled in the future if the Federal system is bypassed in these matters? He also urged the Senators not to pass this bill because of the affect on adjoining states. He suggested that an agency be set up in the State that reviews drug matters, and licenses drugs. He said that this agency should be composed of professional people.

Mr. Donald Murray: A resident of Las Vegas, he said that he hasn't heard anyone talk against Laetrile that has cancer. He said that he has taken Laetrile every day for seven years, which he gets from Mexico and Germany. He said to Senator Hernstadt that it costs him over $1.00 per day.

Dr. Harold Miller: He stated that the has been practicing in Nevada since 1953, and is currently a resident of Henderson. He said that under no established criteria does Laetrile meet the qualifications of a vitamin. He said that Laetrile should not be impressed upon others as a vitamin. Dr. Miller said that about 15 years ago articles were written about the value of GH3 along with the prescribed course of treatment. He said that during one year, he conducted a double-blind study, giving one-half of the patients procaine and the other half, vitamin B-12. He stated that when this became controversial, he had trouble getting his patients to quit taking either one of the substances. He said that the people who administer these substances should be qualified; the patients should be registered and their diseases verified; and he said that any cancer patient should be allowed to have full access to all information regarding the disease; also, those patients in nursing homes should specifically be given these same rights.

Dr. Miller said that patients should come to Nevada for the treatment, and not be able to purchase the substances by mail.

Dr. Quagliana and Dr. Soto reported their discussion of five patient records. Dr. Quagliana went over each of the cases in detail, but he concluded that the study should have 100 patients treated with amygdalin, and 100 without it in order to have a complete statistical analysis.

Senator Hernstadt "thanked" Dr. Quagliana for his opinions and his time, and stated that he hoped that this hearing might stimulate the National Cancer Society, or other organizations into visiting the clinic in Mexico.

Dr. Jack Cherry: He said that he has been practicing medicine in Nevada since 1924. The doctor gave instances where he gave GH3 to his patients. He said that he did not know what the drug actually does, but in regards to his patients who had arthritis, "it worked wonders".

Ms. Grace E. Benson: She gave an instance of her aunt who did not begin her chemo-therapy, but went to the clinic in Mexico. Ms. Benson said that her aunt had layed in the clinic for four days, and the doctor hadn't even seen her yet, and she had trouble communicating because everyone spoke Spanish. She said that when she visited the clinic she was not that impressed.

Senator Hernstadt: He asked Ms. Benson which clinic she visited.

Ms. Benson: She stated that she believed it was the "Del Prado" clinic, and it costs her aunt $26,000.

Senator Schofield: He stated that he and Senator Hernstadt had visited the Clinic Cydel.

Mr. A.R.L. McNaughton: He said that the clinic that Ms. Benson is referring to is not one that is highly recognized, like the Clinic Cydel and the Contraras clinic.

Dr. Harvey E. Howard: He stated the scientific process that occurs when Laetrile is injected into the system. He spoke as a proponent of the bill.

Ms. Connie Edwards: She said that the bill does not have a mechanism to recall the substance Laetrile from the market if in two or three years it is found to be ineffective.

Senator Faiss: He asked how does the F.D.A. handle their "recalls"?

Ms. Edwards: She said that their withdrawal process is written

in the Federal law.

A.R.L. McNaughton: In the following respects, Mr. McNaughton spoke as an opponent to the bill. He said that the bill was deficient as far as controlling the quality and the knowledge of the physicians who may be using the substances.

Mary Lou Haynes: She stated that she was treated with Laetrile by Dr. Contraras in the Mexico clinic. She said that she was able to walk by herself again. She also said that she felt it was a fallacy that there had been testimony that Nevada would become a 'welfare state'.

Mr. Ronald Harris: Mr. Harris testified about his mother who took the Laetrile treatment at the Del Prado clinic, and it cost her $26,000. He said that she was taking Laetrile and the enzymes. Mr. Harris said that in her case she had completely negative results, and he felt that if this is to be legalized it should be controlled.

Mr. Louis Popp: He gave a testimony about his wife who had breast cancer. Her doctor wanted her to have a radical masectomy, she went on a Laetrile treatment, and is now feeling very well. Mr. Popp said that he researched the case of Mr. Harris' mother. He said that when he talked to the Del Prado clinic, the figure of $26,000 in costs was refuted by the doctor and the receptionist.

Dr. Thorne Butler: He said that the opponents feel that it is not a proper function of the Legislature to decide if a particular treatment in modality is correct. He asked if the State of Nevada was prepared to enter into the control and monitoring of a pharmaceutical industry whose products have at best minimum acceptance by recognized authorities? How will the State finance and staff the appointed agency necessary to carry out this function? What criteria will be established to assume the proper formulation for these two compounds? How, and who will establish this criteria? What type of labeling requirements will there be? He asked how will the State Division of Health finance this function?

Mr. Roland Bartlett: Mr. Bartlett said that Laetrile has been for sale in Australia, Brazil, Costa Rica, England, Germany, Greece, India, Isreal, Italy, Japan, Lebanon, Mexico, Peru, Philippines, Spain, Switzerland, U.S.S.R., Venezuela and Viet Nam. Mr. Bartlett said that he supported A.B. 121. Mr. Bartlett submitted a study on GH3 (Exhibit "G") and a letter from Senator Howard Cannon (Exhibit "H") for the Committee.

Dr. Harold E. Feikes: A practicing plastic surgeon in Las Vegas he stated that he has not seen significant reports showing the dangers of the drug. He also said that after about six months of treatment with GH3, his father eliminated a tremor he was experiencing. He said that he does not own any stock in the Rom-Amer Company, but he is on the Board of

Directors. Senator Faiss thanked Dr. Feikes for his frank testimony in regards to GH3.

Ms. Marion Keaton: Ms. Keaton spoke in behalf of GH3 and said that both she and her mother have been taking the substance for four years. Ms. Keaton said that her mother had severe arthritis in her hands, but after three weeks of being on GH3 was able to move her fingers, and know knits and crochets.

Mr. L.L. Elliott: Mr. Elliott said that he discovered that he had cancer on August 16, 1976, and two days later he went on the Laetrile treatment and his pain left. He said to Senator Schofield that he was operated on to remove the core of the prostate gland, and only returns to the oncologyst when he has a temporary infection.

Ms. June Brainerd: Ms. Brainerd stated that when she takes trips to Europe, she has friends that request that she bring back GH3 for their arthritis.

Mr. Russell G. Stephans: Mr. Stephans said that he has been a resident of Nevada since 1935. He stated that he has been taking GH3 since 1972, and is relieved of severe pains that he was having in his back and shoulders.

Ms. Grace Levendis: Ms. Levendis said that she has been taking GH3 for arthritis and is able to continue teaching because the pain has lessened.

Mr. Frend Befree: Mr. Befree stated that he is for the bill because no one can prove that Laetrile is harmful.

A.R.L. McNaughton: Mr. McNaughton said that he has been manager of the McNaughton Foundation since 1956. He said that for 21 years the Foundation has been working for the orderly development of Laetrile "around the world". Mr. McNaughton submitted "Exhibits I through Exhibit R". He said that in April, 1970, the Foundation filed with the F.D.A. a thousand, plus, pages of technical data in regards to the toxicity of Laetrile in animals and man. On April 20, 1970, the Foundation received the I.N.D. number for the Laetrile research, (#6734), but within a few days the F.D.A. sent a telegram cancelling the application, and it has never been reinstated. Mr. McNaughton said that he worked with Dr. Soto and the Mexican government to obtain clinical data on Laetrile in humans which they were not able to do in the United States. He said that in other countries the research is being concentrated on developing improved forms of Laetrile. He stated that no one has ever instigated a suit against a Mexican doctor, nor has anyone instigated a suit against one of the thousands of physicians who has "illegally" issued the substance. He stated that his foundation would be willing to operate in Nevada under rigid supervision as a non-profit clinic.

Mr. Marvin Kratter: Mr. Kratter summarized the position of the opposition. In reference to comments made earlier by Dr. Feld, Mr. Kratter read into the record, sections of studies that were done in the late 1960's on GH3 from universities and physicians in the United States.

Mr. Kratter also read from a letter that was sent to Assemblyman Robert Weise by the State Division of Health: "I have further information on Gerovital H3 which you might wish to add to your files. Two medical journal articles are attached which are pertinent to Gerovital H3, (1) Gerovital H3, a reveiw of the literature in 1976, gives historical information and notes, "no serious side affects or chronic have been reported in human clinical studies despite prolonged use..."; (2) Treatment of the Aged with Gerovital H3, Clinical Efficacy and Neuro-physiological Affects, 1975, "the aged patients treated with Gerovital H3 were helped more with the symtoms of anxiety and depression than the group treated with other drugs...(placebos and anti-depressants)".

Mr. Kratter discussed the difficulty of trying to conduct double-blind studies on depressed individuals who are in need of help, and he also commented how expensive the studies are to conduct.

Senator Faiss: The Senator asked if any legislators own any Rom-Amer stock?

Mr. Kratter: He said that he just bought a stock-transfer record of March 11, 1977, and he did not find the name of any Nevada legislators. Mr. Kratter said that stock can be purchased in the name of a brokerage firm, rather than an individual, however. He also said that he does not know of anyone who owns options.

Assemblyman Danny Demers stated that he felt it was commendable that since the introduction of A.B. 121, there has been almost 18 hours of hearings.

The meeting was adjourned at 5:45 p.m.

SEN. JACK SCHOFIELD, CHAIRMAN

SHEBA L. WOOLLEY, Transcribing Secretary

(Kristine Zohner Reber, Residing Secretary)

— Exhibit "A" —

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DMR-1

LOSING THE WAR ON CANCER: THE 'AWFUL NUMBERS' REVISITED

By David M. Rorvik

Inveighing ever more stridently against the cancer "quacks," whose menace in reality is no more than that of mere sitting ducks, the American Cancer Society cautions us to keep our sights firmly on "progress" and "proven cures" in the billion-dollar-a-year "War on Cancer." In its publication, "Unproven Methods of Cancer Management," the ACS states: "When one realizes that 1,500,000 Americans are alive today because they went to their doctor in time, and that the proven treatments of radiation and surgery are responsible for these cures, he is less likely to take a chance with a questionable practitioner or an unproven treatment." While health statisticians seek in vain to discover any substantive data that might even remotely authenticate this broad claim, other ACS spokesmen are not reluctant to make even more preposterous assertions. Helene Brown, president of ACS in California (front line in the guerrilla war with the cancer "quacks"),takes mighty strides against the most-feared disease of our generation each time she makes a public pronouncement, stating on one recent occasion that "there are now ten kinds of cancer which can be cured or controlled by chemotherapy" and, on another, astounding even the optimists with her conviction that "present medical knowledge makes it possible to cure 70 per cent of all cancers, if they are detected early."

Hope apparently springs eternal in Ms. Brown's unmastectomized bosom—and so does it at ACS headquarters where, if as one cancer researcher put it, "Brown is the Martha Mitchell of the cancer

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David M. Rorvik, a freelance writer, is an Alicia Patterson Foundation award winner. He is studying the politics of cancer research in the United States and elsewhere.

establishment," she is at least its unrepentant, pre-Watergate Martha Mitchell whose pronouncements still find favor in the inner sanctum of the cancer court. For Ms. Brown's optimism, however at variance it may be with the facts, is reflected in numerous ACS publications. In the ACS's "Hopeful Side of Cancer," for example, the first sentence boasts that "Cancer is one of the most curable of the major diseases in this country." Over at the National Cancer Institute, meanwhile, the situation has not been much different. NCI director Frank J. Rauscher Jr. has been fond of claiming that "the five-year-survival rate for cancer patients in the 1930s was about one in five. Today the figure is one in three." Both NCI and ACS persistently seek to convey the idea that progress, steady and sure, is being made, that there's light at the end of the tunnel if only Congress and the public will keep the funds flowing.

James Watson, the Nobel Prize winner whose discoveries in biology are fundamental to our further understanding of living matter, whether malignant or benign, asserts from a perch as nearly objective as one can attain in this imperfect society that our now vastly inflated national cancer program, the result of ex-President Nixon's declared "War on Cancer," the National Cancer Act of 1971 and the ensuing billions of tax dollars, is a complete "sham,"** A medical moonshot that misfired at its inception--except that the television cameras weren't there to make the disaster immediately evident, with the result that most Americans believe the "rocket" is still moving steadily toward its target.

Just a billion dollars a year for ten years, and we'll cure 90 per cent of all cancer, Dr. R. Lee Clark, president of the M.D. Anderson Hospital and Tumor Institute in Houston, promised in the 1960s. And Ralph Yarborough, then a Democratic Senator from Texas, bit. When it became evident that the Democrats might cop the next post-Apollo "spectacular," so did Nixon. The National Cancer Act of 1971 zoomed through Congress with only Gaylord Nelson, Democrat of Wisconsin, dissenting in the Senate, objecting to the Act as "a mischievious political compromise of a very important scientific matter." Today, the nearly autonomous National Cancer Institute has an annual budget of about $800 million, with which, its critics claim, it is merely perpetuating, albeit in greater comfort, the same vested medical interests which failed us with equal aplomb when they were funded at the still-generous, pre-1971 $200 million level.

By 1975, with funding at the half-billion-dollar level, Dr. Watson said that from his inside view, serving on the National Cancer Advisory Board, it was clear to him that the National Cancer Plan was having no impact and that the more than doubling of funds had merely doubled pre-existing programs. As for those claims of steady progress,

**In a less unguent mood, Dr. Watson described the Plan as "a bunch of shit, which characterization stimulated this writer, in a short piece for Harper's, to conjure an image of his own, likening the Plan, with its elaborate flow charts and golden budget to those Biblical whited sepulchres, "which indeed appear beautiful outward, but are within full of dead men's bones."

Dr. Watson charges that "the American public is being sold a nasty bill of goods. While they are being told about cancer cures, the cure rates have improved [since the 1950s] only about one per cent."

ACS/NCI propaganda to the contrary went largely unchallenged by the press until science writer Daniel S. Greenberg, author of The Politics of Pure Science, wrote an article for Columbia Journalism Review (January/February 1975) deploring both the misrepresentations of the cancer establishment and the press' unquestioning acceptance of its claims. The article loosed a storm of controversy and, finally, a flurry of "rebuttals" which were patently unsuccessful, managing only to point up more flaws in the official claims and to reveal an even greater capacity for distortion than had previously been exhibited.

When all was said and done, the "awful numbers" Greenberg marshalled with the assistance of an unnamed "government health economist who is well-versed in cancer statistics" remain dolefully intact, unscathed by the attempts of Dr. Rauscher, cancer researcher Emil Frei, NCI statistician Sidney Cutler, ACS science editor Alan Davis and others to undo them.** The facts, to which NCI statistics bear witness, are these: most of the "progress" ACS/NCI take credit for occurred before the early 1950s, in a period when cancer research funding was very small. The most compelling explanation for the pre-1955 improvement in survival rates is the post-war introduction of blood transfusions and antibiotics, both of which enabled more victims to survive not cancer per se but cancer surgery and attendant infections.

Since the 1950s, the five-year-survival rate for patients diagnosed as having forms of cancer which, together, constitute 66 per cent of the total incidence of the disease increased by five

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** Each of Greenberg's critics focuses heavily on those few categories of cancer in which noticeable progress has been made since the 1950s; each tries to give the impression that Greenberg ignored this positive data and that his analysis is therefore unreliable. In fact, however, Greenberg, at the very beginning of his piece, clearly describes all those areas in which progress, mercifully, has been recorded. Cutler's response to Greenberg appears in The New England Journal of Medicine (July 17, 1975); the same issue contains an editorial attack on Greenberg by Dr. Frei. Dr. Rauscher's rebuttal appears in the Journal of the International Academy of Preventive Medicine (Volume 2, No. 2, 1975) and is itself stunningly rebutted in the same issue by "Abraham M. Sarman," pseudonym of a government biostatistician whose superiors would not permit him to author the article under his own name. Lamest of the rebuttals is that of Davis at ACS. Among other things, he complained (Columbia Journalism Review, March/April 1975) that Greenberg's use of quotes from the 1971 ACS pamphlet, "The Hopeful Side of Cancer," was "not up-to-date reporting." Greenberg, in response, calls the ACS "unscrupulous," observing: "I went to the ACS and I said, 'Give me the literature you currently distribute to the public,' and that's how I got the damned thing." This is the pamphlet, by the way, which calls cancer "one of the most curable of the major diseases in this country." Apparently Davis is saying that statement was true, i.e, "up-to-date," in 1971 but no longer is. Curious turn of events.

percentage points or fewer. The three biggest killers fall into this disappointing category--lung cancer, with one percent increase in survival, breast cancer with a four percent increase and cancer of the colon with a one per cent increase. In another category, accounting for 12 per cent of the incidence, survival rates actually declined since the 1950s. Cancers of the vulva, penis, lip, bone and esophagus are among those that fall into this group. Survival rates for those stricken with cancers accounting for the remaining 22 per cent may be said, by some standards, to have improved more than five per cent, but this is scarcely enough to justify calling cancer "one of the most curable of the major diseases."

UCLA cancer researcher and epidemiologist Dr. James Enstrom cautions, moreover, that "the situation is really significantly worse than the official statistics [used by Greenberg and others] suggest." If one resists the convenient, arbitrary separation of cancers by body-organ affected (for there is still no proof that one cancer differs fundamentally from another) and examine all cancers together, then, Dr. Enstrom says, Dr. Watson is absolutely right: "survival rates have remained virtually constant since the 1950s." Furthermore, the data that is used to calculate the official statistics, he adds, "is heavily biased to begin with" because only the "best" hospitals, with better ancillary care, are allowed to contribute. Poorer hospitals with lower general standards of care and without the capacity to calculate "reliable" statistics are excluded. It is not unusual, Dr. Enstrom observes, to find twice as many patients dying of cancer in those poorer hospitals, yet these deaths are not represented in the final statistical sample. Dr. Enstrom and a colleague at the California Tumor Registry, a major contributor to the NCI's official compilation of statistics, are conducting a thorough analysis of the cancer statistics and are finding, they say, biometrical errors of sufficient magnitude to render "almost entirely unreliable" the five-year survival data that has been used to support claims of "progress" in the cancer war.

A government authority on cancer statistics, economist Morton Klein of the Department of Health, Education and Welfare, says his findings agree with those of Dr. Enstrom. Klein, who may now be identified as the statistician who assisted Greenberg, asserts that credit is often taken by the ACS/NCI where no credit is due. Much has been claimed for the efficacy of "early detection" in cutting cancer mortality, for example, but in fact, says Klein, there is no real evidence that the Pap smears, which are the leading edge of early detection today, have had any true impact. The "positive progress" that has been claimed in the battle against cervical cancer, he points out, is "not progress in terms of early detection or effective therapy; it just happens that the incidence, the number of women coming down with cervical cancer, has been declining dramatically for reasons no one understands. Those women who still get it, however, are not surviving any longer than they used to. The Pap smear, meanwhile, did not come into effect until the middle or later stages of the observed decline in incidence; in other words, the mortality was declining at the same slope [rate] that it is today well before Pap smears were used."

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Dr. Hardin B. Jones, a professor of physiology and medical physics at the University of California, Berkeley, has painstakingly

analyzed cancer statistics for decades. He finds today, as he found in the 1950s and 1960s, that "evidence for benefit from cancer therapy has depended on systematic biometric errors," that "in the matter of duration of malignant tumors before treatment, no studies have established the much-talked-about relationship between early detection and favorable survival after treatment," that "neither the timing nor the extent of treatment of the true malignancies has appreciably altered the average course of the disease," and that "the possibility exists that treatment makes the average situation worse."

A number of independent studies, reports, researchers tend to confirm this bleak outlook. Here is a sampling:

—Dr. Ian MacDonald, an internationally known cancer surgeon, now deceased, presented extensive data on breast cancer in the American Journal of Surgery (March 1966) and concluded that "the massive educational, diagnostic and therapeutic attack on mammary carcinoma of the past two decades has failed to alter rates of incidence and mortality of this most frequent malignant neoplasm in female patients. Reports on the therapy of mammary cancer in the surgical literature often lack significance through selected samples of small size and the lack of statistical validation." When the statistical errors are accounted for, he added, the corrected data "lend little if any support to the case for 'early' diagnosis."

—In 1968, speaking at the Sixth National Cancer Conference, Dr. Phillip Rubin, director of the Division of Radiation Therapy at Washington University School of Medicine, said: "The clinical evidence and statistical data in numerous reviews are cited to illustrate that no increase in survival has been achieved by the addition of irradiation." Sharing the same platform, Dr. Vera Peters of Princess Margaret Hospital in Toronto added: "In carcinoma of the breast the mortality rate still parallels the incidence rate, thus proving that there has been no true improvement in the successful treatment of the disease over the past 30 years, eventhough there has been technical improvement in both surgery and radiotherapy during this time."

—Seven researchers studied individuals afflicted with inoperable lung cancer, comparing survival times of those who received radiation therapy against those who received placebos (sugar pills). The results were published in the journal Radiology (April 1968). The authors conclude: "In several respects, the present study may be regarded as unique in character. It is prospective, large-scale, and multi-discipline. It involves strict randomization of concurrent, well-matched, inoperable male subjects between radiation, antitumor agents and placebo....Our results show that eventhough the difference in survival between the irradiated group and the control group was statistically real, the actual prolongation of life was discouragingly small. Of the patients given radiation, only four per cent more were alive at the end of one year, and their median survival time was only 30 days longer than that of those who received an inert compound (lactose)." Scrupulously honest in their presentation, the researchers, who had clearly hoped to find a significant positive effect from radiation, noted that "patients given radiation therapy generally

received better supportive care than control patients. Irradiated subjects had longer hospitalization and there was a general effort to maintain general health and to treat infections more vigorously during the course of radiation therapy. To what extent this affected the slightly better survival experience cannot be assessed."

--A group of researchers at Oxford University in England have published (a 1975 issue of the journal Lancet) a paper which confirms a previous study. Both studies reach the astonishing conclusion that the best treatment for inoperable lung cancer is no treatment. In the confirming study, patients were divided into three groups, those receiving no treatment, those receiving continuous single-agent chemotherapy and those receiving an intermittent combination of chemotherapies. The conclusion: no treatment "proved a significantly better policy for patients' survival and for quality of remaining life."

--Chemotherapies, in general, have been assessed by some to be largely ineffective--or worse. Dr. Dean Burk, while serving as head of the Cytochemistry Division of the NCI, addressed a letter to his boss, Dr. Rauscher, critical of the latter's 1972 White House statement that "the chemotherapy program is one of the best program components that the NCI ever had." Dr. Burk observed: "Frankly, I fail to follow you here. I submit that a program of FDA-approved compounds that yield only five-to-ten per cent 'effectiveness' can scarcely be described as 'excellent,' the more so since it represents the total production of a 30-year effort on the part of all of us in the cancer-therapy field." Even that five-to-ten "effectiveness," he adds, is suspect, possibly being more than offset (in the majority of patients who do not benefit from chemotherapy) by shorter survival and lower quality of remaining life occasioned by the (widely acknowledged) great toxicity of nearly all approved chemotherapies, most of which, Dr. Burk has observed, are capable of causing cancer in their own right.

--Dr. Matthew Block, professor of medicine at the University of Colorado Medical Center states (in a letter-to-the-editor, Medical World News, July 5, 1974) that by far the most valid way of assessing adequacy of cancer therapies is by comparing individuals treated with those therapies with individuals who receive no treatment at all. Therapies for Hodgkin's disease (where great progress is frequently claimed), he says, have not been evaluated in this fashion, with the result that those claims are not necessarily valid. "In the case of chronic lymphatic leukemia as we see it in adults," he continues, "if the survival time is no better than it was 30 years ago, then we must conclude that there is something we are doing to these people that is making their survival shorter." Why shorter? Because, he explains, we have now largely overcome those "incidental" infections, such as pneumonia, which, 20 and 30 years ago, killed so many chronic sufferers of leukemia. "Furthermore," he goes on, "the use of transfusions as well as other aspects of better ancillary care should have increased longevity in this disease, and if it is not any better we must then conclude that [despite] all the advantages now available, indeed longevity has been decreased by treatment [emphasis added]."

--Three researchers reporting on Hodgkin's disease in the Archives of Internal Medicine (December 1974) compare treated and

untreated individuals suffering from the disease (much as suggested by Dr. Block above). "The group that was given no therapy initially, yet survived long enough to be treated subsequently, is important in showing the extent of basic variation in the natural history of the disease and, indeed, that their eventual treatment may have had little effect on their survival. It should also be noted that, after one year from diagnosis, the survival of untreated patients is better than that of those who received subsequent therapy."

--Dr. John C. Bailar, writing in The Annals of Internal Medicine, says that the "promotion" of the latest effort at early detection, routine mammography (X-ray examination of the breast) is "premature." He documents the carcinogenic risks of such radiation and "regretfully" concludes "that there seems to be a possibility that the routine use of mammography in screening asymptomatic women may eventually take almost as many lives as it saves." Later he emphasizes that the "radiation hazards may be of the same order of magnitude as the benefits." Yet Dr. Rauscher and spokesmen of the ACS have been pointing with pride to programs encompassing mammography, citing these programs as evidence of new progress.

--Finally, there comes news that the cancer mortality rate, which has been going up by about one per cent per year for some time, rose by roughly three percent in 1975. NCI and officials at the National Center for Health Statistics have attempted to characterize the rise as illusory, the stuff of statistical artifacts. They have also sought to "explain away" the rise by attributing it, in part, to the influenza epidemic of 1975, the idea being that flu is sufficient to kill sufferers of chronic diseases, such as cancer. But this hypothesis, swallowed wholesale by much of the press, including The New York Times (which further embarrassed itself, in this writer's view, with an editorial called "Statistical Hypochondria," insisting that more "illuminating commentary" accompany the next batch of frightening statistics lest we again overlook something like the flu factor), has more holes in it than the Watergate tapes.

Dr. Enstrom points out that the mortality rate for cancer was, during the first ten months of the year "3.5 per cent higher for cancer but 3.7 per cent lower for heart disease, whereas both should have increased if flu was a major factor." Morevoer, in years when flu epidemics nearly paralleled the 1975 epidemic (1951, 1953, 1957 and 1960) there was, he says, "only a small increase in the cancer rate," as opposed to the whopping three-fold increase last year.

Meanwhile the National Cancer Rocket clunks along, blissfully far off course, which is exactly where the cancer generals, representing the varied vested interests of chemotherapy, radiotherapy, immunotherapy and virology, want to keep it, according to their critics. Despite overwhelming evidence that most cancers are caused by environmental factors, the obvious, preventive approach to cancer has been studiously ignored by those who control the cancer program. This fact was emphasized recently by a subcommittee of the National Cancer Program's highest level advisory board, which reported: "There was an obvious sense of general astonishment...that the National Cancer Program does not appear to have accorded an adequate

priority nor sense of urgency to the field of environmental chemical carcinogenesis....it would seem that the problem has been accorded a low priority...and, as far as could be judged, to absorb perhaps ten per cent of the budget...." The lion's share of the cancer "cause-and-prevention budget" is being siphoned off in pursuit of a human cancer virus, the existence of which remains wholly unproved after decades of study costing millions. Mindful of this, the subcommittee, which does not, however, have the power to set policy, recommended a sharp cutback in viral research, noting that "a viral etiology for most human cancers is an unlikely eventuality."

Another National Cancer Advisory Board subcommittee, chaired by one of the most distinguished names in cancer research, Dr. Norton Zinder, microbial genetics professor at Rockefeller University, investigated the viral research effort and observed: "It was only natural that when the SVCP [Special Virus Cancer Program] was formed, a small group of investigators was involved--an 'in group.' It now represents a somewhat larger 'in group' of investigators. Administratively, its procedures lack vigor, are apparently attuned to the benefit of staff personnel and are full of conflicts of interest.... the program seems to have become an end in itself, its existence justifying its further existence." In the wake of this scorching evaluation, which went on to specify several conflicts of interest, SVCP cleaned out some of the administrative cobwebs, but Dr. Zinder still doesn't believe anyone is going to come up with a viral anti-cancer vaccine. Ever. Dr. Rauscher, however, has indicated that he will resist a significant cutback in viral research--which is, incidentally, his own field of expertise and the centerpiece of the National Cancer Program.

Is the situation entirely hopeless? No. Most of those knowledgeable in the realm of cancer politics say that pressure from the public (through Congress) and from those segments of the scientific community which have not already been compromised by the cancer money can, in time, effect the shift from attempted cure (so far a dismal failure) to prevention, where a solid basis for defending against the disease clearly exists. When Congress insisted last year that NCI spend a couple million on nutritional aspects of cancer (a mandate NCI actually resisted) it was indulging in gross tokenism (given the total budget of nearly a billion dollars) but at least it was tokenism in the right direction. More recently President Ford's Council on Environmental Quality issued a 763-page report which concludes that up to 90 per cent of all cancers are caused by factors in the environment, most of them man-made. And this group of scientific experts, at least, didn't bother to try to justify past mistakes by juggling the statistics. They simply stated that the incidence of cancer in the United States has more than doubled since the start of the century and that there has been only barely discernible improvement in survival rates since the 1950s, the cancer establishment's self-serving protestations to the contrary notwithstanding.

SHORT TAKES/COMING ATTRACTIONS

Censored! Suppressed! Expurgated!

Here, at last, is the controversial lead paragraph which was chopped from my (probably) forthcoming defense of "Quackery" in Harper's Magazine:

> "Quack!" The word hisses, erupts, excites emotional shock waves; today, more even than "Communist!" does it excite to near-religious wrath the myrmidons of a monolithic establishment which, though medical and not military, has one-upped even the Pentagon in the recondite arena of tactical "enemy" overkill. Particularly when applied to cancer, the most-feared disease of our time, does the awful appellation become the shrill recheat that unleashes the hounds of hunt.

Actually, the paragraph was cut with the complete complicity of its author, who had secretly long since urrped over the graph's purple passions and so willingly bowed to what the editors politely referred to as "space problems." The remainder of the piece contends that the term "quack" is badly in need of neologism; that many of the real quacks hold cushy jobs in government and other "non-profit" places; that various controversial cancer treatments such as Krebiozen, Laetrile and the Gerson diet were never fairly appraised by those who condemned them.

In the 1950s, respected M.D. Max Gerson was hounded, maligned and nearly run out of business for daring to suggest that diet might have considerable to do with cancer. He was declared a fraud by all except his patients and those who bothered to investigate his work. Albert Schweitzer credited Gerson with saving his wife's life and hailed him as one of the world's greatest medical geniuses. John Gunther, the author, was similarly enthusiastic when Gerson treated his son. In the 1960s, Krebiozen was the cancer establishment's public enemy number one. Dr. Andrew Ivy, Krebiozen's principal champion in the United States was (how soon we forget) one of the country's leading medical men. He was director of the University of Illinois Clinical Sciences Department; he had been an American representative at the Nuremberg trials and a winner of numerous American Medical Association awards. He had authored more than a thousand scientific papers; the Food and Drug Administration often called upon him to give expert testimony in court. Dr. Ivy had everything to lose and nothing to gain by aligning himself with the Krebiozen forces—yet he did so because his own research with the substance thoroughly convinced him that it had a potent anti-cancer effect. Overnight the same interests that had previously acclaimed him condemned him. He was declared a fraud and a quack, his career ruined. And these calumnies persisted, indeed intensified after a jury, at the conclusion of one of the most remarkable trials in history, acquitted him and co-defendants of

all 240 counts of criminal fraud and other wrongdoing brought against them. The trial lasted 289 days and was punctuated by confessed-to government-falsified testimony. The jury, in acquitting, went to the extraordinary length of stating that Krebiozen should be tested, that it did not believe the government. But what it couldn't do in the courts, the cancer establishment carried off effectively enough in the bovine, pre-Watergate Press, persistently planting therein libels and distortions which have left the lasting impression that Dr. Ivy is the very apotheosis of the cancer quack.

The Krebiozen case will be revisted—and perhaps new information revealed—in a future Newsletter.

Iatrogenesis

"Whenever there is a large class of academic professors who are provided with good incomes and looked up to as gentlemen, scientific inquiry must languish. Whenever the bureaucrats are the more learned class the case will be still worse." —Charles Sanders Peirce

"Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing." —Voltaire

A 19th-Century physician presented a bill against the estate of a deceased client. "Do you wish my bill sworn to?" the doctor asked the administrator of the estate. "No," replied the latter. "Death of the deceased is sufficient evidence that you attended him professionally." —Apocrypha

"After a century of pursuit of medical utopia, and contrary to current conventional wisdom, medical services have not been important in producing the changes in life expectancy that have occurred. A vast amount of contemporary clinical care is incidental to the curing of disease, but the damage done by medicine to the health of individuals and populations is very significant. These facts are obvious, well documented and well repressed." —Ivan Illich

Doctor-caused illness—iatrogenesis—is the subject of noted social critic Ivan Illich's forthcoming new edition of Medical Nemesis to be published by Pantheon Books/Random House in May. Meticulously documented, this book promises to be one of the most insightful books on the human condition in years. Consider this brief excerpt, which is not mere rhetoric but true scholarship buttressed with fully ascertainable facts:

> Two things are certain: the professional practice of physicians cannot be credited with the elimination of old forms of mortality or morbidity, nor should they be blamed for the increased expectancy of life spent in suffering from the new diseases. For more than a century, analysis of disease trends has shown that the environment is the primary determinant of the state of general health of any population. Medical geography

> the history of diseases, medical anthropology, and the social history of attitudes towards illness have shown that food, water and air, in correlation with the level of sociopolitical equality and the cultural mechanisms that make it possible to keep the population stable, play the decisive role in determining how healthy grown-ups feel and at what age adults tend to die.

Useful background in approaching the Illich book: Effectiveness and Efficiency: Random Reflections on Health Services by A. L. Cochrane (Nuffield Provincial Hospitals Trust, London 1972).

Other recommended reading: "The American Cancer Society Means Well, But the Janker Clinic Means Better," article in the April, 1976 Esquire by Patrick M. McGrady Jr. This excellent piece by the president of the American Society of Journalists and Authors concludes:

> Poor America. Its money-fat, guts-thin biomedical research establishment has more and more to do with paper and abstract mathematics and fear and less and less to do with new therapies or even with people suffering from cancer. If it would only send some good doctors to the Janker Clinic [in West Germany], it might not only learn something about cancer care, but it might get a good lesson or two on freedom."

Of equal merit is Joseph Hixson's just-published book The Patchwork Mouse (Anchor/Doubleday) on faked test results at our leading cancer research institute, Memorial Sloan Kettering Cancer Center. The final chapters deal briefly with cancer politics in general.

Fluoridation: 30,000 Excess Cancer Deaths a Year?

A case has been made relating a minimum of 30,000 cancer deaths per year in the United States with fluoridation of water. Dr. Dean Burk, until recently chief chemist of the National Cancer Institute (and one of the founders of NCI) and Dr. John Yiamouyiannis, science director of the consumer-oriented National Health Federation, have gathered data (some of it published in the Congressional Record, entered therein by Representative James J. Delaney, Democrat of New York on July 21, 1975 and on December 16, 1975) which they say establish a probable link between certain cancers and fluoridation. One of their studies compared the ten largest fluoridated cities with the ten largest non-fluoridated cities and charted cancer mortality rates in each on a year-by-year basis. Studies were also made of paired communities, fluoridated and non-fluoridated, in close proximity with one another and thus, except for fluoridation, presumably under the same environmental influences. In San Francisco, to cite one example, the investigators noted that in the eight years prior to 1952, when fluoridation was initiated in that city, cancer mortality remained

static. Two years after fluoridation was started there was a three per cent increase in mortality; after four years the rate had doubled to six per cent; after six years the rate was 12 per cent over the 1952 baseline; after 12 years the rate had escalated to 20 per cent, bringing us to 1970, at which point the last fully inclusive statistics were compiled. Meanwhile, just over the bay in equally or even more industrialized Oakland, where the water has never been fluoridated, the cancer mortality rate increased between 1952 and 1970 by only three per cent. NCI officials have denied the existence of a fluoridation/cancer link but have yet to present data that effectively refute the Burk/Yiamouyiannis thesis. Congressional hearings in May will include testimony on this issue. More on this possible cancer link in future Newsletters.

"Goddamned Quackery!"

That's what Helene Brown, president of the California wing of the ACS, calls the anti-cancer substance "Laetrile," which is also known as Vitamin B-17 (recognized as such in McGraw Hill's authoritative Nutrition Almanac), "amygdalin" and, most commonly, "the stuff you get from apricot pits." The "war" against the purveyors of Laetrile has heated up in recent months, with doctors who have dared to use the substance suffering revocation of licenses and legal action, with verified FDA entrapment schemes (mailing the stuff to advocates and then arresting them), even with the spiriting away of apricot kernels from the counters of health-food stores. Meanwhile, over the border in Mexico, Andrew McNaughton, who once sought investigational drug status for Laetrile, is sitting tight, watching some 20,000 Americans flood into the Tijuana Laetrile clinics each year in pursuit of cancer cure or control. McNaughton was imaginatively profiled in the Canadian magazine Maclean's (January 12, 1976) by one Marci McDonald. The piece is clearly a vicious character assassination, a classic example of using information selectively to portray a subject against whom the author nurtures an obvious a priori bias in the worst possible light. McDonald, moreover, makes no serious effort whatever to examine the data that suggest that Laetrile is perhaps at least more useful than, say, radiation in extending the lives of cancer victims while also improving the quality of remaining life. That data—along with a new look at McNaughton and the Laetrile clinics—is, tentatively, the subject of my next Newsletter.

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The Systemic Use of Procaine in the Treatment of the Elderly: A Review*

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ABSTRACT: This article is a review and evaluation of the world literature on the systemic use of procaine in the treatment of the aging process and the common chronic diseases of later life. Included are data from 285 articles and books, describing treatment in more than 100,000 patients in the past 25 years. Except for a possible antidepressant effect, there is no convincing evidence that procaine (or Gerovital, of which procaine is the major component) has any value in the treatment of disease in older patients. If procaine has an antidepressant effect, there is some likelihood that this accounts for the reports of decreased complaints referable to the musculoskeletal, cardiovascular, endocrine, sexual, gastrointestinal and respiratory systems.

During the past 25 years, a lengthy series of papers on the therapeutic effects of systemically administered procaine has appeared in the European and American literature. The pharmaceutical preparation most commonly used in the reported studies has been Gerovital (GH-3), which is basically a 2 percent solution of procaine. The majority of these publications claim a beneficial effect of procaine in delaying the aging process or in favorably altering the common chronic diseases of middle and later life. A minority of the papers assert that procaine has no such benefits.

So large and complex has this literature become that a detailed and comprehensive review of the subject appears appropriate. The purposes of this paper are to review the pharmacology of procaine, to examine the therapeutic claims made for it in the fields of aging and chronic illness, including psychiatric illness, and to evaluate these claims as carefully as the literature permits. The paper examines the pharmacologic characteristics of procaine, especially in the doses and by the route employed in much of this literature. The effects of procaine on mood, depressive

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states, altered cerebral function, and chronic diseases of middle and later life are reviewed. Summaries and conclusions are presented in the text at points where their inclusion seems most relevant.

In the preparation of this report, we read and evaluated 285 papers. These included 4 papers in Spanish, 5 in Czech or Polish, 5 in Roumanian, 5 in Portuguese, 44 in French, 81 in German, 12 in Italian and 129 in English. Some of these papers were extremely sketchy, some contained no data, and others represented material published earlier in another language. Therefore, we have not cited all of them in our list of references.

PHARMACOLOGIC CHARACTERISTICS OF PROCAINE

Textbooks, such as that of Goodman and Gilman (1) with the definitive data provided by Ritchie et al (2), contain a comprehensive and accurate discussion of the properties of procaine and other local anesthetics. In addition, there have appeared a number of symposia and review articles on the subject; especially noteworthy are those edited by Fink (3) and the recent basic studies of Cohen et al (4, 5).

As a general conclusion, it can be stated that procaine has effects on all types of neural tissues and excitable cells in concentrations of 2–20 mg/ml (hydrochloride salt). It depresses excitability, increases threshold, slows or blocks conduction of action potentials, decreases or abolishes repetitive activity (such as cardiac arrthymias or sensory nerve discharges) and reduces the efficacy of synaptic transmission, usually without producing major alterations in the resting membrane potential. These effects appear to be due to an interaction with conductance channels of membrane cations (Na^+, K^+, Ca^{++}); especially important is blockade of the increase of Na^+ permeability associated with the action potential and its interaction with Ca^{++} effects.

Because procaine is rapidly hydrolyzed in the body by pseudocholinesterase, one must consider the effects of its metabolites, para-aminobenzoic acid (PABA) and diethylaminoethanol (DEAE). No direct effects of PABA have been identified in man. The graying of the hair found in some PABA-deficient animals has no counterpart in man. DEAE has anti-arrhythmic properties similar to those of procaine but is a very weak local anesthetic. Small doses in man may produce a mild euphoric state (1).

Although these generalizations summarize much of the extensive literature on procaine and its metabolites, they are subject to misinterpretation because of the complexity of the studies. The ionized (cationic) form of procaine is generally believed to be the active moiety; however, closely related compounds (e.g., benzocaine) that cannot ionize can produce local anesthesia indistinguishable from that of classic local anesthetics such as procaine. Ritchie (6) stressed that nitrogenous local anesthetics (e.g., procaine) can act in at least two ways, both in the cationic and in free amino forms, although most experiments reveal an interaction with a receptor internal to the cell that interacts with the cationic form (7). Strichartz (8) concluded that all forms of local anesthetics act primarily by preventing the influx of sodium ions (cf. also 2, 9–15). In addition to blocking conduction, local anesthetics block rapid axoplasmic transport (16). Seeman (17) presented a holistic, comprehensive theory of anesthetic action that includes binding of local anesthetics to the passive Na^+ conductance channel. The effect of procaine on sodium conductance is also seen with slices of brain cortex (18). In addition, local anesthetics inhibit evoked release of glutamate from cortex slices (18) and depress cellular respiration of isolated cortical tissue (19).

With the exquisitely sophisticated techniques of fluorescent probes, Cohen et al (5) analyzed the nature of the binding of local anesthetics to membranes, using isolated membrane fractions from the electric organ of Torpedo marmorata. In such preparations, local anesthetics act allosterically on the binding of the natural neural transmitter. This local anesthetic binding can be abolished by treatment of the membrane fragments with detergents; these observations further support the investigator's theory that local anesthetics do not act directly on the cholinergic receptor site but on other sites on the membrane (4). In addition to an action on Na^+ permeability, the local anesthetics compete with or interfere with Ca^{++} action (13, 20). Moreover, in many respects, local anesthetics act similarly to calcium (4, 5, 21).

The delivery of procaine to the central nervous system (CNS) via the blood stream results in effects dependent upon the concentration and sites to which it is distributed. In experimental studies employing brain and spinal cord preparations, the effects of intravenously administered procaine are transient and require doses of over 2 mg/kg as a bolus of a 20 mg/ml solution. The repetitively active sensory-nerve systems are

among the most sensitive neural systems; depression of tooth afferents (22) or muscle spindle afferents (23) requires a procaine blood level of about 0.25 mg/ml. Analogous data have been obtained from CNS studies (24-26). Such effects are short lasting and appear to be related to blood levels; interrupted infusions incremented every 30 minutes can produce moderately sustained effects for a few hours (23).

The application of procaine (or other local anesthetics) directly to neurons or its injection into the nervous system yields results determined primarily by local anesthetic effects *at the site of application*. Although many references (27-29) describe the actions of local anesthetics on the brain, these effects have little if any relation to the actions of local anesthetics given systemically via the blood supply.

The time course of the action of systemically administered procaine appears, quite plausibly, to be correlated with the blood levels and these, in turn, with procaine's metabolism. Procaine is readily absorbed from subcutaneous or intramuscular sites; in fact, this rapid absorption is the major limitation in its extensive utilization as a local anesthetic. Brodie and coworkers (30) demonstrated in 1948 that the direct intravenous infusion in man of 2,000 mg of procaine over 45-125 minutes resulted in maximum blood levels of only 0.00035 mg/ml or less. This infusion procedure resulted in blood levels analogous to those that might be obtained with an intramuscular dose of approximately 10 ml of a 2 percent solution (200 mg) absorbed completely over a period of 10 minutes. These studies also showed that the human being metabolizes procaine at a rate of approximately 20 mg per minute or more. Once the infusion is stopped, the blood levels drop precipitously, whereas the levels of the metabolites decrease with time somewhat more slowly.

Brodie et al (30) also showed simply and conclusively how rapidly procaine disappears in blood, by adding it in vitro to blood samples. Within one or two minutes after the addition of the procaine, the bulk of the sample had been hydrolyzed; thus, hydrolysis of procaine in plasma is extremely rapid.

That procaine acts as a readily reversible inhibitor of brain monoamine oxidase (MAO) was demonstrated in vitro by a decrease in the metabolism of catecholamines (epinephrine or serotonin) and kynuramine. MacFarlane and Besbris (31) found that this action requires concentrations, even under steady-state conditions, of more than 1 mg/ml for 50 percent inhibition. MAO was derived from rat-brain mitochondrial preparations or from brain homogenates; procaine and Gerovital were of limited potency, with concentrations of orders of magnitude greater than the maximum levels obtained in the blood in vivo. Assuming that upon intramuscular administration procaine reaches a brief period of steady-state equilibrium between brain tissue levels and circulating blood, and that there is ready reversibility, the potency of procaine is so low as to be of doubtful significance, even in relation to the peak concentrations obtainable in vivo.

The evidence (32) that Gerovital is a more effective MAO inhibitor than commercial procaine hydrochloride is not convincing, especially since the differences noted were small. The results and conclusions may be due to sample error or additives present in the Gerovital. Hrachovec is cited in MacFarlane's paper (32) as showing that Gerovital inhibits MAO in vivo and that it is a significantly better MAO inhibitor than procaine. However, none of the references cited contain adequate data to support these claims.

The comparison of Gerovital or procaine with iproniazid (32) is not valid, as the author recognized and emphasized in a subsequent publication. The study of MacFarlane and Besbris (31) essentially showed what had already been assumed by many, that procaine is a *weak, reversible* inhibitor of crude MAO preparations. Reversible enzyme inhibition implies that the inhibitor-enzyme complex is readily and rapidly reversible; to demonstrate such inhibition in vivo requires measuring substrate at given times rather than enzyme activity. After enzyme isolation and dilution, any enzyme-inhibitor complex that might have existed in vivo would be expected to have been reversed in the process.

Under optimal conditions, in vivo concentrations of procaine of 10^{-6} M might be reached. At this level, in vitro and under steady-state conditions, Yau (33) obtained 20-40 percent inhibition of mouse-brain MAO. Also, following single intraperitoneal doses of 90 to 180 mg/kg, Yau (33) found only a "slight, but significant" increase in brain serotonin but no significant change in dopamine or norepinephrine, indicating little if any MAO inhibition. No significant changes were found after chronic dosing with *90 mg/kg* of procaine! Conceding that the positive finding might be pertinent, Yau (33) reported that the animals were *sedated* after these doses of procaine – not stimulated, as has been assumed for man. (This

observation poses questions of the qualitative action of procaine in addition to questions of the quantitative action.)

Thus, although Yau (33) found that certain monoamine oxidase preparations are more sensitive to procaine, only marginal effects could be detected in vivo after intraperitoneal administration to mice of massive doses of 60 mg/kg or more. This dose is a huge one on the basis of any kind of extrapolation to man. Moreover, the relationship clinically between antidepressant properties and inhibition of MAO remains a point of some contention; it may well be that clinical antidepressive activity is not directly the consequence of MAO inhibition.

A review of these data leads to the hypothesis that if the claim can be verified that procaine solutions have demonstrable effects in man when administered intramuscularly in daily doses of 10 ml of a 2 percent solution, then the actions are probably the consequence only of the local effects of the injections since the maximal systemic levels of procaine (or PABA or DEAE) achieved would be insufficient to alter neural or enzyme activities.

The claim that Gerovital is specially stabilized in order to increase the biologic half-life of the active ingredient, procaine hydrochloride, has not been substantiated. Although the possibility remains that procaine would reach unusually sensitive brain cells or sites in adequate concentrations, data to support the idea are lacking. It is also possible to postulate a monoamine oxidase unusually sensitive to the inhibitory effects of procaine. That various types of monoamine oxidases are present in brain is now well-established (34). Although one can argue that procaine could act in minute concentrations on specially located and sensitive monoamine oxidases, there is no evidence that this is so.

The frequent claims of the clinical literature that procaine preparations are not detectable by the subjects and that they are without any side-effects are puzzling. Reactions to procaine injected into muscles, joint spaces, or along nerves have long been known to have a number of effects including:

a) numbness at the site of injection (hence its use as a local anesthetic — the 2 percent present in Gerovital is a standard local anesthetic concentration).

b) hypotension or peripheral vasodilation if absorption is especially rapid, and

c) local or systemic allergic reactions in sensitive individuals.

PROCAINE AND GEROVITAL H-3

A wide variety of claims have been made from time to time by various investigators employing Gerovital H-3, both with respect to its composition and to its effects. At present, the claims emphasize that Gerovital H-3 action is due to procaine [for example, Aslan (35)].

The common procedures for verification of the composition of pharmaceutical preparations have not been employed for Gerovital. There is one reference in the literature of an analysis of a single sample of Gerovital [Gordon et al (36)]. This single report of a single sample has been frequently cited as indicating the composition of all Gerovital preparations [for example, MacFarlane and Besbris (31)]. The data obtained by Gordon et al (36), interestingly, do not agree with those provided in the trade literature [Jarvik and Milne (37)] for the composition of Gerovital H-3.

Thus, there exist little if any other analytic or quality control data on samples of Gerovital H-3. In fact, this reviewer suggests that the composition is not consistent; it undergoes at least the variation in procaine concentration due to spontaneous hydrolysis.

In the absence of data to the contrary, it must also be entertained that the commercial preparations may contain other substances or other active ingredients. These questions could be readily resolved by the use of the well established routine techniques for even minimal quality control of pharmaceutical preparations.

The question of the possibility of unique characteristics of Gerovital or GH-3 over procaine has been addressed explicitly by Cherkin (38), Jarvik and Milne (37) and Morin and Cummins (39). With respect to the specific claims, Aslan has reemphasized, as have so many previous authors, that the Gerovital preparation is "specially stabilized" or is "buffer stabilized" so as to provide a "longer half-life of the whole molecule of procaine." Further, the claim is made that use of the low pH of 3.3 reduces the rate of hydrolysis. To date there is no evidence that the procaine of Gerovital is any longer lasting in vivo when administered according to the Aslan techniques than is any other of the commercially available solutions of procaine hydrochloride. This has been experimentally verified by Morin and Cummins (39). Moreover, there is little reason to expect any difference among procaine preparations since the procaine is absorbed into the blood stream, and the blood and body tissues form a vast reservoir relative to the amount of procaine.

Procaine is rapidly split by the action of plasma cholinesterase (30).

The argument regarding the special stability might have some merit if it referred to only the local destruction of procaine, although there is some question of its relevance in view of the extensive buffering capacity of most body tissues.

It is claimed that the benzoic acid added to the preparation forms a complex with procaine which in some way protects it from destruction. This claim also lacks any experimental verification, and such evidence would be easy to generate. It further lacks rationality since such complexes are admittedly weak and readily reversible in plasma or extracellular fluid.

The claim that Gerovital has a uniquely low acid pH as compared with other procaine preparations is erroneous and misleading inasmuch as most manufactured procaine solutions are acid, with a pH not appreciably different from the 3.3 or 3.68 stated for Gerovital [cf. Cherkin (38)].

Thus, the claims for special stabilization, prolongation of half-life, special formulation, buffered stabilization, and less alkalinity than other comparison solutions of procaine [e.g., Zung et al (40) stated that "the usual pH of the commercially available procaine solution varies between 5.5 to 7.6,"] are all false, misleading, or fraudulent. (Claims relating to efficacy due to the metabolic products would also detract from the assertion that the parent substance produces in vivo inhibition of monoamine oxidase as a mechanism of action. If one claims enough different things, it is possible that one of them might turn out to be correct.)

This general criticism is not meant in any way to confirm or deny the presence of potential changes in the clinical status of patients receiving Gerovital. Such claims are appropriately assessed on their own merit!

Taken together, all of the various claims for special pharmacologic qualities of GH-3 are applicable only in increasing its potency or duration of action *at the site of its administration* intramuscularly. Further, such increased stability, if it occurs, would tend to retard the systemic absorption of procaine solution and thus decrease the maximum levels obtainable in such sites as the brain.

The second major issue centers on the possible actions of the metabolic products of procaine, para-aminobenzoic acid (PABA) and diethylaminoethanol (DEAE). With respect to PABA, the levels obtainable are so low as to have minor significance in terms of dietary or other sources of this acid. Moreover, if PABA is the active ingredient, then a far more rational approach to therapy would be its direct administration rather than via the complicated administration of procaine.

With respect to DEAE, this substance has a longer half-life in man than procaine or PABA (30). One can speculate that high levels of DEAE could have pharmacologic effects. However, this is doubtful even though deanol, the dimethylaminoethanol analog, does appear to have some demonstrable clinical effects, at least in tardive dyskinesia (41–43). Pfeiffer et al (44) have long claimed that the latter agent has stimulant effects [see also Ostrow (45) and Connors (46)].

The question of the efficacy of deanol, a congener of DEAE, remains seriously disputed and there are few relevant data on DEAE. What few tests have been carried out have been negative [for example, Verzar (47)].

It should be recognized that the possibility of the metabolic products being active would constitute a direct negation of all the claims of the efficacy of this specially "stabilized" procaine solution, since any procaine solution would give rise to the same metabolic products and should, therefore, exhibit the same therapeutic efficacy.

To summarize: there are absolutely no data relating to the quality control of the composition of Gerovital preparations or of the additives. The absence of such readily obtainable, inexpensive, standard analyses – analyses expected and required by custom and law for all other pharmaceutical and food preparations – greatly restricts the capacity to evaluate and understand the effects of Gerovital.

SUMMARY OF PHARMACOLOGIC CHARACTERISTICS OF PROCAINE

1. Procaine hydrochloride exerts effects on most neural systems and excitable cells in concentrations of 2–20 mg/ml. These effects include: a) a decrease in membrane excitability, b) an increase in threshold, c) slowing or blocking of action potential conduction, d) decrease or loss of repetitive activity such as cardiac arrthymias or sensory nerve discharge, and e) reduced efficacy of synaptic transmission, usually without alteration in resting membrane potential.

2. All neural effects of procaine appear related to changes in membrane ionic conductances involving sodium, potassium, or calcium.

3. Procaine is readily absorbed, distributed and metabolized following intramuscular administration.

4. The actions of procaine on brain and spinal cord are transient and require intravenous doses of over 2 mg/kg in experimental animals.

5. If intramuscular doses of 10 ml of 2 percent procaine solution are eventually proved to have clinical effects in man, then these effects are probably indirect consequences of the local effects of the injection; procaine levels at other than the site of injection are simply insufficient to alter neural or enzyme activities.

6. It has not been proved that Gerovital is especially stabilized, or acts better or differently than other solutions of procaine.

PROCAINE AS A MOOD ELEVATOR

In her original report (35b) Aslan claimed phenomenal improvement in the psychic functioning of 109 elderly subjects who had undergone procaine therapy. Some disoriented psychiatric patients recovered. Memory, concentration, and perception were improved as well as depression.

She noted that many of the procaine preparations used by others were not the same as the Roumanian product, Gerovital. She stated that Gerovital differed from most procaine preparations in its pH and in its content of benzoic acid, potassium metabisulfite, and disodium phosphate. She noted that many clinicians had not followed her suggested dosage regimen and had not continued the therapy long enough to achieve therapeutic effects.

Bucci and Saunders (48) studied 25 chronically psychotic women between the ages of 40 and 80 who had been hospitalized for periods ranging from 2 to 24 years and had failed to respond to phenothiazine drugs. The patients were given procaine hydrochloride three times per week in doses of 100 mg, for six months. Then they were given 160 mg three times per week for the next three months. The evaluations were based on changes during the nine months of treatment. In 3 cases the drug was discontinued because of weight loss and mental deterioration. The results showed alleviation of depression as well as decrease of psychotic symptoms associated with schizophrenia. There was improvement in both the physical and mental status of the patients. Two patients were discharged from the hospital. Seven manifested moderate improvement, 6 slight improvement, 6 no improvement, and 3 became worse. No control group was used.

Kral et al (49) studied 32 hospitalized patients (average age, 81.1 years) with senile and arteriosclerotic psychoses, as well as 20 outpatients (average age, 72) who were being treated for functional or organic psychiatric disorders. Among the inpatients, 11 received 2 percent procaine hydrochloride for 13 months, 11 received it for six months, and 10 received physiologic saline. Procaine in neither group appreciably altered the symptoms and course of the basic senile or arteriosclerotic brain disease. A temporary improvement in depression was noted, as was an increased level of activity. The improvements were not sustained. The outpatients with functional disorders responded equally well to saline and procaine. The three groups were not differentially affected by procaine and saline. In all three groups, behavior became worse as measured by seven items relating to physical condition, memory, mental symptoms, incontinence, appearance, activity and social contact. All showed decreased performance on a memory scale.

May et al (50) studied 107 aged female patients in a double-blind trial. The experimental group received 2 percent procaine HCl at a pH of 3.5–4.0. The patients were evaluated four times: 4–5 months before treatment, 1 month before, 6 months after the start of treatment, and 1 year after the start of treatment. No significant differences for age, length of hospitalization, and memory quotient were demonstrated between the procaine and saline groups. Altogether, 51 of 54 patients in the experimental group and 49 of 53 in the control group completed the study. For memory quotient, no significant difference was found between the groups after treatment. Basically the study's findings were negative for differences between procaine and saline.

Smigel et al (51) studied 60 nursing home patients (ages 35 to 98) who had arthritis, nervous disorders and senile mental disturbances and who had received little or no benefit from other treatment. They were given 2 percent procaine buffered at a pH of 3.5. Later, 5 patients received Gerocaine, another procaine preparation. This double-blind study of 60 patients was coded by a procedure that can be inadequate. Odd-numbered patients received procaine and even-numbered patients received the control substances. Such a code is easily broken. During the course of the study, unaffected controls were taken out of the trial to see if they would improve with procaine therapy, and vice versa. Of the 29 patients receiving procaine, 25 showed improvement in 5 months. Of the 21 controls (placebo injections), 9 showed improvement. Nine controls and one ex-

perimental subject terminated their participation prematurely. Positive results were found mainly for patients with chronic nervous disorders, but not for those with chronic brain syndrome. The conclusion drawn by the authors was that procaine exerted markedly beneficial effects in the experimental group.

Lewicki et al (52), a group of clinical psychologists in Poland, evaluated the responses of elderly patients to long-term treatment with Gerovital. They assessed memory, thoughts, and associations. Seventy-five percent improved but 25 percent were no better. Improvement was not solely attributable to Gerovital because other measures to improve health were used.

In 1971, Cohen and Ditman (53) reported findings on 41 patients — 17 normal, 17 with psychiatric disorders, and 7 with major medical problems accompanied by depression with or without anxiety. These patients were given 100–200 mg of Gerovital three times per week over a four-week period. They were rated by psychiatric interview, mood scale, and a modified Zung scale of depression. They were well educated, knew of the benefits claimed for Gerovital, and volunteered in the hope that it would relieve their symptoms. Of the 41 patients, 35 reported improvement in one or more of the areas evaluated, e.g., well-being, relaxation, energy, libido, motivation, and somatic discomfort. This was an open study with a highly selected group of patients. Because of placebo effects, the patients were likely to respond positively.

Sakalis et al (54) studied 10 senile arteriosclerotic inpatients with depression of two or more years' duration. They were given Gerovital, 100–200 mg three times per week for three weeks. There were no side effects. The patients were given placebo for one week (baseline), active drug for three weeks, and then post-drug placebo for two weeks. No clinical change was noted till the end of the second week. By then, 6 out of 10 were receiving 200 mg per injection. They were rated weekly on the Hamilton Depression Scale, Clinical Global Impression (CGI) and the Nurse's Observation Scale for Inpatient Evaluation. Altogether six ratings were obtained. Statistically significant positive changes were obtained on the Hamilton Scale for somatization and anxious depression ($p < .05$). Symptoms increased during the first placebo week and then decreased during the second placebo week. The CGI showed no significant changes. No changes occurred for orientation, memory, paranoid ideation, and insight. There was a transient amelioration of depressive symptoms. The authors concluded that Gerovital had a mild and transient beneficial effect in high doses, but this was obscured by the variability of the clinical picture in demented patients.

Zung et al (40) recently published the results of a double-blind study comparing intramuscularly administered Gerovital with orally administered imipramine and with placebo given both intramuscularly and orally. The subjects were volunteers 60 years of age or older. The following measures were used: Clinical Global Rating of Depression (CGRD), Zung Self-rating Depression Scale (SDS), Self-rating Anxiety Scale (SAS), Depression Statue Inventory (DSI), and Anxiety Status Inventory (ASI). Ratings were obtained on day zero and day 28. Patients were drug-free for seven days prior to the 4-week treatment regimen of 5 ml of Gerovital administered three times for the first week and then 10 ml three times per week for the last three weeks — a total dose of approximately 2,100 mg of procaine. The imipramine group received 25 mg at bedtime for day one, 25 mg twice a day for day two, 25 mg three times a day for days three to fourteen, and 25 mg four times a day for weeks three and four.

Although the preparations and rates of administration were different, each patient received the preparations by both routes (Gerovital intramuscularly plus placebo orally, or imipramine plus placebo parenterally, intramuscularly or orally). Three patients of 36 dropped out. Nine completed the Gerovital regimen, 11 the imipramine regimen, and 10 the placebo regimen. The average dose of Gerovital was 2,022 mg (procaine), and of imipramine 74.8 mg. At day zero, there were some differences in test scores. The imipramine group was more symptomatic than either of the other two groups. The Gerovital group improved significantly on the CGRD, the DSI, SDS, ASI, and SAS. The imipramine group improved significantly on all measures except the SAS. The placebo group did not change significantly.

Comparison for differences on the CGRD revealed no difference between the imipramine and Gerovital group or the imipramine and placebo group, whereas the Gerovital group differed significantly from the placebo group. On the DSI, the imipramine group was more symptomatic than the Gerovital group but did not differ from the placebo group. The Gerovital and placebo groups did not differ significantly. At day 28, the Gerovital group scored lower than the imipra-

mine group. The Gerovital and placebo groups and the imipramine and placebo groups did not differ on day 28. For change score, no differences were found between the groups.

For SDS at day zero, the Gerovital group scored lower than the imipramine group. Imipramine versus placebo and Gerovital versus placebo scores did not differ. At day 28 the Gerovital group scored lower than the imipramine group. The other two group differences were still insignificant. For change score, the only significant difference was between the Gerovital and the placebo group.

On the ASI at day zero, no significant differenes were found. At day 28 the Gerovital group achieved a lower score than the imipramine group. According to the test, the imipramine group score was lower than that of the placebo group. This is an inconsistency, since the Gerovital and placebo groups did not appear to differ at 28 days. No significant difference was found for change scores.

For SAS at day zero, scores for the Gerovital group were lower than for the imipramine group and the placebo group. Imipramine versus placebo differences were not significant. At day 28 the differences persisted for Gerovital versus imipramine and Gerovital versus placebo. Placebo versus imipramine differences were not significant. All change score differences were not significant. Although the patients receiving active substances reported more dizziness and more confusion, no significant differences for side effects were demonstrated.

This study was better controlled than earlier ones on Gerovital, and compared the antidepressant effects of Gerovital with those of imipramine, a highly regarded tricyclic antidepressant drug. The statistical analysis reported for these studies was probably inadequate since the groups differed significantly at day zero. An analysis of covariance probably should have been used instead of a *t* test.

SUMMARY OF DATA ON PROCAINE AS A MOOD ELEVATOR

The most tenable conclusion to be drawn from the studies reviewed is that suggestive evidence of a transient antidepressant effect was obtained. Defects in the designs of the studies, statistical analysis, and instruments employed [except for the studies of Sakalis et al (54) and Zung et al (40)] make it impossible to state unequivocally that Gerovital is an effective antidepressant. More carefully controlled studies should be undertaken to determine definitively whether Gerovital is an effective antidepressant agent.

Monoamine oxidase inhibitors block the deamination of norepinephrine, thereby increasing the levels of norepinephrine available to receptors in an active form. However, it is not certain that this is the effect that inhibits depression or that all monoamine oxidase inhibitors have an antidepressant effect. Tricyclic agents, several of which are effective antidepressants, have no effect on monoamine oxidase, but work by interfering with the uptake of norepinephrine into adrenergic neurones, both central and peripheral (1).

PROCAINE IN SENILE DEMENTIA AND CEREBRAL ATHEROSCLEROSIS

A large number of publications have dealt with the relative effectiveness of procaine and Gerovital in senile dementia and cerebral atherosclerosis. Those studies without controls will be discussed first. Galindez (55) noted improvement in depression when procaine was combined with dehydroandrosterone. Bizzi and Albonetti (56) reported similar improvement when procaine was combined with multiple vitamins.

In a study by Pascal and Bezusso (57), 19 of 29 elderly patients showed slight improvement in senile psychosis; 11 of 29 felt better and had less anxiety; 4 of 29 slept better, and 3 of 20 hallucinated less frequently. Giore (58) reported that 7 of 10 elderly women treated with procaine improved on a vocabulary test and 8 of 10 did better on the Progressive Matrices Test.

Silbergleit (59) treated elderly asthenic and depressed patients with a combination of procaine, vitamins, and reserpine. He noted improvement in asthenia and depression as well as increased appetite, weight gain, euphoria and an optimistic attitude. Balganon (60) combined procaine with para-aminobenzoic acid and noted great improvement in about a third of a group of patients. Nearly half of the group improved moderately. Similar results were reported by Greppi (61), Paule (62), Student and Vlach (63), Aslan (64), Skula (65) and Letourmey (66). Oury and Delvaille (67) treated 1,000 inpatients and 16,200 outpatients and observed increased memory and attention span.

Not all the uncontrolled studies reported beneficial effects. Piro et al (68) treated 31 patients and concluded that procaine was of no help in neuropsychiatric deterioration due to aging. Scardigli and Guidi (69), and Scardigli (70) and

Giore (58) reached similar conclusions. Gericke et al (71) reported no benefit in a study of 39 patients. O'Connell and Offner (72) and Friedman (73) were unconvinced that procaine was beneficial in chronic brain syndrome.

Among the controlled studies, Kant and Sterne (74) carried out a double-blind trial of procaine versus sterile sodium chloride. There were 10 patients in each group and ages ranged from 60 to 93, with a mean of 76. The patients had various physical diseases and manifested intellectual deterioration. They received nine series of procaine injections over a year. Changes in both groups on physiologic indices over a year were recorded. No differences were found between the placebo and procaine groups for changes in physiologic measures, memory, and intellectual functions. Procaine was not more effective than saline.

Long and Gislason (75) studied 33 patients in a state mental hospital in a double-blind protocol for one year. Patients were disoriented for time and place. Seventeen received procaine, and 16 saline solution. There was a trend to increased orientation, attention, and memory in the group treated with procaine, whereas a decrease in orientation, attention, and memory were noted in the control group.

Berryman et al (76) conducted a double-blind study. The subjects were 40 women over age 50 who received four 12-week courses of treatment, with 24 injections of 100 mg of procaine per course. There was no evidence of benefit from procaine therapy.

Isaacs (77) carried out a double-blind crossover study, using patients as their own controls. Twenty-four patients with cerebral atherosclerosis participated. Ten psychologic characteristics were assessed on 3-point or 4-point scales. Two courses of injections of 10 weeks each were given. Ten patients prematurely stopped treatment. No significant changes for procaine were noted, and no significant differences were found between procaine and a control substance. With procaine, 3 of 14 patients improved in more than two characteristics; 6 of 14 deteriorated in more than two characteristics. With saline, 4 of 14 patients improved in more than two characteristics and 8 of 14 deteriorated in more than two characteristics. No significant effect of procaine was observed.

Hirsch (78), in a double-blind study, used procaine versus sterile water, 5 ml three times a week for four weeks. There were 34 subjects (18 controls and 16 receiving active substance). Premature termination occurred in 8 controls and in 1 procaine patient. No differences were found between the two groups for change in status. With the control substance, 1 subject deteriorated, 3 showed no change, 3 improved, and 2 showed marked improvement. With the active substance, none deteriorated, 7 showed no change, 3 improved, and 2 showed marked improvement.

Fee and Clark (79) conducted a double-blind study in which procaine hydrochloride and isotonic saline were compared in a group of hospitalized inpatients and a group of residents in welfare accommodations. The substances were given intramuscularly three times a week for nine trials of four weeks each. Mental status, mobility, and incontinence were rated. The hospitalized group consisted of 12 men and 12 women. All showed confusion and incontinence. After one year, 10 of the patients had died, 5 were worse, and 8 were stationary. The results showed no difference between placebo and procaine effects. The group living in welfare accommodations consisted of 20 men and 20 women. Half deteriorated or died. With the control substance, 9 died or were worse; with procaine, 10 died or were worse. Eight receiving the control substance and four receiving procaine remained unchanged. Three improved with the control substance, and 6 with procaine. Clinical ratings revealed that 4 improved with the control substance, and 2 with procaine. Seven receiving the control substance and 3 receiving procaine remained stationary. Nine receiving the control substance and 10 receiving procaine became worse. The patients' subjective reactions and the clinicians' ratings both showed no significant differences. Clearly, procaine was not beneficial.

Gitman et al (80) reported a study in which procaine (5 ml) three times a week was given for 12 injections, followed by 10 days of rest and a second series of 12 injections. Ten subjects were studied. One of the 10 showed significant improvement, mainly in dyspnea associated with asthma; 2 gained weight, and 1 lost weight. Only 2 of the 10 could be considered to have shown any clinical improvement.

In a study by Cashman and Lawes (81), the Wechsler Memory Scale, Bender-Gestalt, Raven's Progressive Matrices, and the Mills Hill Vocabulary Definition Scale were used to compare 6 control patients with 6 procaine patients. Five of the 6 control subjects improved; 4 of the 6 procaine patients deteriorated. The study was not double-blind, and other treatments were administered.

Abrams et al (82) reported a double-blind study

starting with 121 subjects, of whom 70 were recruited and 63 were volunteers. Of the 63 volunteers, 60 started and 40 finished. Eight died and 22 refused to continue or ended the trial prematurely. Twenty-two received "European" procaine (Gerovital) and 18 received "American" procaine. Pre- and post-study evaluations involved ratings of the face-hand test, degree of brain impairment, degree of disorientation in time and space, memory defect, affect depression, delusions, capacity to articulate through speech, capacity for interpersonal relations, and extent of ego and intellectual impairment; these ratings were made by psychiatrists. Psychologists rated psychologic integration, energy, physical appearance, memory, and state of mind. Nurses and family members also rated patients. Only positive changes were considered. The "European" procaine group showed more improvement than did the "American" procaine group. The differences in improvement scores were significant at the .007 level for psychiatric ratings. No significant differences were found for psychologic ratings or the nurses' ratings. Relatives' ratings showed a trend favoring the "European" group, which did not quite reach significance. Several statistical analyses were involved. An overall score was obtained from the ratings which demonstrated that 49.1 percent of the "European" group showed improvement in contrast to 19.4 percent of the "American" group. No statistical control for differences in initial states was attempted. Attrition was large; one-third of the group finally was selected for study. Psychologic tests could not be administered. The ratings were impressionistic and the variables rated were global, ambiguous, and somewhat redundant. Only the psychiatric ratings showed a significant effect of "European" procaine.

Gordon et al (36) collected a wide variety of physiologic measures obtained on the same group as the Abrams et al (82) sample. Measures included urinary 17-ketosteroids, 16-hydroxy steroids, uric acid, urea nitrogen, inorganic phosphate, pulmonary ventilatory functions, and motor-nerve conduction velocity. Only 17-ketosteroids and motor conduction differed. The "European" group showed a greater decrease of 17-ketosteroids; motor conduction was increased in both samples. "Results of the present investigation do not justify the use of either procaine preparation as eutrophic treatment of the aged," was the conclusion that these investigators drew from the study.

SUMMARY OF DATA ON PROCAINE IN SENILE DEMENTIA AND CEREBRAL ATHEROSCLEROSIS

The results for patients with organic brain syndromes, particularly those with cerebral arteriosclerosis or senile dementia, do not indicate that any procaine preparation is particularly or consistently effective for these disorders. Results of the more adequately controlled studies were generally negative for procaine; the findings of Abrams et al (82) and of Gordon et al (36) for "European" procaine were at best equivocal. The studies reporting clearly positive findings usually were either less well controlled or without controls.

PROCAINE IN CHRONIC DISEASE OF MIDDLE AND LATER LIFE

Much of the literature on the beneficial effects of procaine is concerned with such common chronic diseases as atherosclerosis, parkinsonism, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, high blood pressure and senile keratoses. Bodily changes common in aging (though probably not specific diseases) are also frequently addressed in the same literature. These include depigmentation and loss of hair, wrinkling and atrophy of the skin, reduction in sexual interest and function, and decline in strength and endurance.

There is little reason to doubt that thousands of elderly people who have been treated at the Geriatric Institute in Bucharest do indeed report that they feel better and do look better to physicians. The modes of treatment commonly employed at that institution include a good diet, vitamin and mineral supplements, application of the interest and care of well motivated persons in the health professions, the company of other old people, an atmosphere radiant with hope and empathy, and the administration of a drug for which patients and staff have the highest expectations. A central question about the efficacy of Gerovital may be phrased in this way: Do the pharmacologic effects of procaine contribute to the benefits of all other measures employed at the same time?

PROCAINE EFFECTS ON ARTHRITIS

In 1949, encouraged by the work of Parhon and Leriche, Aslan began to use intra-arterial injections of procaine in patients with arthritis and

arthrosis. The usual method of administration consisted of 0.10 gm of procaine in the form of a 1 percent solution injected directly into the artery supplying the joint. By 1956, 50 patients, not all elderly, had been treated by this method, with results that were described as excellent (83).

In 1951 Aslan began to use procaine intramuscularly for the severe degenerative diseases of old age, including arthritic disease, both degenerative and rheumatic. The usual dosage schedule consisted of 5 ml of a 2 percent solution three times weekly in a series of 12 injections with a ten-day interval in between. By 1960, several hundred arthritic patients had been treated. Restoration of joint mobility, reduction of pain, decrease of contractures, increase in muscle strength, and improvement in periarticular functions were reported (83–86).

In parallel with these clinical observations, an animal model of experimental arthritis was studied. Modifying the method of Selye, the investigators injected formalin into the joint space of the white rat and both therapeutic and prophylactic benefit was claimed (87) for procaine by Aslan and her colleagues.

Since 1951, procaine, usually by the intramuscular route, has been employed in a number of countries as a treatment for rheumatoid arthritis and osteoarthritis, rheumatoid spondylitis, psoriatic arthritis and other musculoskeletal disorders. The regimen has usually been that of Aslan, although in some cases the procaine employed had a higher pH than that preferred by Aslan. Scardigli and Guidi (69) reported a decrease in articular pain after procaine in 55 patients. Similar results were noted by Aslan when a 2 percent solution was infused into the arteries supplying diseased joints in 20 subjects. The Roumanian group seems to prefer the intra-arterial route when arthritic disease is the major problem, but the intramuscular route when multiple system disease is present.

Other authors have employed procaine according to Aslan's method and reported improvement in arthritic symptoms in nearly all cases. These include Destrem (88), Letourmey (66), Tchebotarev (89), Oury and Duche (90), and Kohler and Mampel (91). More recent contributions from Roumania, all of them enthusiastic about the benefits of procaine in joint disease, have appeared regularly over the years (83, 92–94).

Not all the reports are positive, however. Paule (62) found no x-ray changes in a patient with osteoarthritis of both hips but observed that the subject voluntarily took fewer drugs for pain. Kant and Sterne (74) noted no improvement in joint function in 20 elderly persons, and Fee and Clark (79) had no success treating 65 elderly persons. Luth (95) found no improvement of joint disease after procaine in 470 old people, and O'Connell and Offner (72) reported negative results in 10 patients. Gericke et al (71) treated 39 state hospital patients and observed not only no clinical improvement, but more abnormalities in x-ray films of the joints.

In one of the rare partly controlled studies with procaine, Smigel et al (51) found that procaine was beneficial. However, the protocol was changed in the middle of the trial, the coding of preparations was inadequate, and a flu epidemic struck the patients in the middle of the trial, so the results mean little or nothing.

In the past 15 years, a number of well designed and executed controlled clinical trials of drugs in arthritic diseases have been carried out. Essential to obtaining significant results are a number of elements in the trial. The criteria for disease must be rigidly defined, and the reliability and validity of the diagnosis determined. Rheumatoid arthritis, for example, has been defined in terms of morning stiffness, pain on motion or tenderness in at least one joint observed by a physician, swelling of joints, subcutaneous nodules, specific x-ray changes, positive results with agglutination tests, and characteristic changes in synovial membranes (96). Restriction categories such as the rash of disseminated lupus erythematosus, scleroderma, clubbing of the fingers, evidence of sarcoid or of infectious joint disease help to increase the precision of trials based on these criteria. The activity of the disease should be carefully determined before, and at intervals after treatment by such standard measures as questionnaires, grip strength testing, time required to walk a specific distance, degree of swelling, tenderness, and pain on passive movement of each afflicted joint, x-ray studies and erythrocyte sedimentation rate (97). There is agreement that trials must be double-blind, with a code that cannot easily be deciphered by those making judgments about improvement. Placebos and standard agents as controls are usually necessary. Methods of assessing joint status before and after treatment should be standard, participation rates should be high and dropouts low, both nonparticipation and dropout problems should be clearly described, and their potential effects on the trial should be carefully considered. The

method of analysis of results should follow logically from the protocol and rest on sound biometric and clinical principles (98–100).

There is not a single paper on the effect of procaine in an arthritic disease which contains even two of these requirements for an interpretable clinical trial. Aslan herself writes (83) that bone remineralization and increased joint spaces are important in evaluating procaine therapy. But most of her numerous reports contain no systematic descriptions of x-ray findings before or after procaine administration, or any other objective findings for that matter, except grip strength in some cases. Even when grip-strength measures were used, the reports indicate no concern about the reliability of the measure and no appreciation of the effect that motivation or fluctuations in hand pain can have on grip strength.

Procaine has been given for 26 years to thousands of arthritic patients, and the quality of the work is such that it is not possible to state whether the agent is beneficial or not. With few exceptions, the papers claiming that procaine is worthless as a treatment for arthritis are not substantially better than those claiming the drug is beneficial.

PROCAINE EFFECTS ON SKIN AND HAIR

Aslan (93) in 1951, while studying the effects of procaine on experimental arthritis in the rat, noted that the furry coats of the animals were improved. This led to her long-term observations on procaine in man and to a study of the effects of the drug on skin and hair as a major focus of those observations. There is some rationale for believing that procaine may have a beneficial effect on the skin. It dilates cutaneous vessels and raises skin temperature in acute experiments (1).

In a series of articles, the Roumanian group described their observations on procaine both in diseases of the skin and in the usual changes in the skin and hair with aging (64, 83, 84, 93, 94). They reported that skin turgor and color were improved and that hair regained pigment and sometimes regrew in previous areas of hair loss. A large number of skin diseases were also benefited from procaine. These included vitiligo, scleroderma, ichthyosis, psoriasis, and senile keratosis. In a few cases serial photographs illustrating the skin and hair changes were included in the publications. Aslan and colleagues reported that the skin and hair changes were among the most consistent and striking beneficial effects of procaine in their extensive experience.

Others agreed with the Roumanian investigators about the effects of procaine on the skin and hair changes of the usual aging process (49, 66, 71, 72, 101, 102) and in specific skin disorders (103). One critical observer, who doubted many of the alleged benefits of procaine, believed that skin appearance and muscle turgor were improved (104). However, as with all other effects of procaine in this literature, some authors believed that there were no beneficial effects on the skin (74, 78, 79). These negative trials were all double-blind and placebo-controlled, and in one of them repeated standard colored photographs showed no benefit from procaine (79).

One group of observers noted that skin turgor improved both in patients receiving procaine and in those receiving repeated injections of saline solution in another double-blind placebo-controlled study of 107 old women (50). The authors believed that repeated intramuscular injections alone over a long period of time may have had some beneficial effect on the skin. They offered no explanation of the mechanism.

If procaine has an antidepressant effect or if patients are hopeful about effects of treatment, this characteristic alone may explain some or all of the alleged beneficial effects on skin and hair. With improved appetite, both weight gain and increase in subcutaneous fat may make the skin look better. Combed hair, especially if water or hair-grooming preparations are used, looks darker than unkempt hair. People who are not depressed will wash and comb their hair, get haircuts, smile more, and have brighter eyes. Women free of depression are more likely to use cosmetics. All these factors can make the skin and hair look better. It is not necessary to postulate a trophic effect of procaine to explain them.

The spontaneous regression of skin lesions has not been studied thoroughly. Vitiligo is reversible in a small proportion of cases (perhaps 10 percent), and occasionally senile keratoses, actinic keratoses, or lentigo may also regress (105, 106). The extent to which such spontaneous regression may have influenced the results with procaine is conjectural.

PROCAINE EFFECTS ON HYPERTENSION

The known effects of procaine include both lowering and raising of the blood pressure. Procaine has a direct vasodilator action, best studied in skin and skeletal muscle (1). The effect is quite

transient. Procaine has sympatholytic properties [illegible]1) and diethylaminoethanol exhibits hypotensive effects of short duration. On the other hand, repeated intravenous injections of large doses of procaine in rabbits produces significant increases in hemoglobin levels and smaller increments in erythrocyte counts (107). Such effects may be expected to increase blood viscosity and therefore raise peripheral resistance and blood pressure. Furthermore, weight gain after procaine therapy in man is described as one of the more consistent effects (99–101, 108–112). This ought to raise blood pressure in some cases in view of the well known correlation between weight and blood pressure (113). Aslan and Vrabiescu (85, 114) noted opposing effects of procaine on blood pressure in the dog. Intra-arterial injections lowered pressures but intravenous injections increased sensitivity to adrenalin.

The reported effects of procaine on blood pressure in hypertensive patients likewise vary. Aslan, whose experience is most extensive of all, reported that a drop in blood pressure is common (108, 112). Oury and Duche (90) observed decreased pressure in 20 old people with hypertensive and cardiorespiratory disorders. Nebo also reported lowering of blood pressure in preliminary observations on 86 elderly patients (101) and in more numerous observations on 1985 patients seven years later (109). Bucci and Saunders (48) observed a drop in blood pressure in 5 of 6 hypertensive patients but in no normotensive patients after procaine treatment.

Negative reports on the effectiveness of procaine as an antihypertensive agent are almost as numerous as positive reports. For example, 86 old patients treated with procaine (Seurocaine) exhibited no change in blood pressure (115). Negative results were also described in a study of 34 patients (78) and in observations on 75 older persons treated with procaine (91).

The data on blood pressure in the articles on procaine are negligible. Usually there is simply a sentence or two indicating that the authors observed a fall or no change in blood pressure. No raw data or analyses of results are presented. The method of measuring pressure is not described and the time, frequency and circumstances of the measurements are not reported. Factors known to affect blood pressure acutely are fear, pain, a full urinary bladder, a heavy meal, body position, appearance and attitude of the examiner, hearing acuity of the observer, rate of fall of Hg in the manometer, digit preference and several others (116–119). There is no evidence that these factors were taken into account in the observations with procaine.

A controlled clinical trial of a potentially effective antihypertensive agent is one of the most difficult of all therapeutic studies to carry out. The recent Veterans Administration trials in the United States (118, 119) enumerate many of the relevant problems. The information on blood pressure changes in the reports on procaine in no way constitutes any kind of disciplined evaluation of antihypertensive effects. Procaine may or may not lower blood pressure. The truth of the matter is not in sight.

PROCAINE EFFECTS ON SEXUAL AND ENDOCRINOLOGIC FUNCTION

Procaine has been reported to be beneficial in the management of several kinds of sexual dysfunctions in men and women. Destrem (88) stated that 17 of 17 persons with depression, weakness and sexual problems were helped, and Portias (115) observed improvement in sexual interest and capacity in some of 86 persons treated with procaine. Aslan et al (120) reported a 9 percent increase in egg production in hens treated with 10 mg/kg of procaine daily as compared to a control group, but it is impossible to determine from the abstract if the difference in egg production was statistically significant.

Whereas some publications limit themselves to ascribing an estrogenic and androgenic effect to procaine (66, 112) or to procaine combined with multiple vitamins and magnesium pantothenate (121), some from the Bucharest Institute of Geriatrics are more explicit. Against the background of an extensive morbidity survey (122), Aslan reported some details of procaine effects on endocrine glands (83). She stated that vaginal smears have shown that small amounts of estrogen appear to be circulating in old women. Stimulation of pubic-hair growth with normal sex distribution and improved testicular function were also listed as effects of procaine. In some cases, Aslan noted that genital atrophy in elderly women was slowed and in others a return of normal appearance of the vulvovaginal mucosa and repigmentation of the labia minora occurred. Three cases of amenorrhea in women aged 35–40 were successfully treated by one or two series of intramuscular procaine injections, and several cases of failure to conceive were likewise successfully treated.

All the work performed with procaine in this field consists of preliminary observations which

did not reach the point of controlled clinical trials. The specific endocrine or sexual problems are not described in detail. Relevant histories on pregnancies, deliveries, frequency of sexual intercourse, and degree of sexual interest and function are not specified. Moreover, except for the paper on chickens (120), there are no attempts to follow an experimental protocol. It is appropriate again to state only that procaine may or may not have beneficial effects in endocrine and sexual function. The data are inadequate to support any conclusions.

PROCAINE EFFECTS ON ATHEROSCLEROTIC DISEASE

One of the most important issues about procaine is whether it prevents, delays, or reverses the atherosclerotic process. A closely allied and equally important question is the extent of its benefit on the clinical forms of atherosclerosis, myocardial infarction, angina pectoris, peripheral vascular disease, atherosclerosis of the head and neck, brain infarction, the lacunar state, and pseudobulbar palsy. The literature on procaine deals with both these issues.

Aslan and her colleagues attempted both laboratory and clinical research on the effects of procaine in atherosclerosis. They believed that Starling's concept of transcapillary permeability of proteins (123–128) needs modification. In studies on the effect of aging on capillary filtration of proteins, the differential filtration of serum proteins in atherosclerosis and the influence of prolonged procaine administration upon capillary filtration of proteins, they concluded that atherosclerosis was associated with reduced capillary permeability and that the process was reversed by procaine's permitting an extracellular fluid enriched with serum proteins to bathe tissues. A modified view of this hypothesis is presented elsewhere by Aslan (126). She also believed that the normal function of the vascular endothelium is lost in aging so that, in the elderly, larger molecules such as serum proteins are permitted to penetrate the vascular wall (127). She suggested that aged vascular endothelium permits both albumins and globulins to enter the vessel wall and that procaine selectively inhibits filtration of gamma globulin and enhances the filtration of albumins.

The Roumanian group induced atherosclerosis in rabbits by cholesterol feeding and studied the aorta and blood lipids in a control group and in a cholesterol-fed group, part of which was treated concomitantly with procaine intramuscularly (128). They reported that procaine inhibited aortic atherosclerosis after cholesterol feeding and had the effect of increasing alpha lipoproteins and decreasing beta lipoproteins when compared with the cholesterol-fed animals not treated with procaine. The data were not presented in sufficient detail to determine if the effects were significant. Similar results were reported by David (129).

The Roumanian group has maintained that procaine therapy in elderly men has been followed by an increase in the serum cholesterol level (64, 83, 104, 129). They attributed this to a mobilization of lipid from atherosclerotic plaques and fat depots. Other authors have reported no change or a decrease in serum cholesterol concentration after procaine treatment (51, 66, 71, 80, 115). In one study, the cholesterol level rose if it was low before treatment and fell if it was high (130). In living man, it is impossible to tell what happens to atherosclerotic plaques except by such procedures as serial coronary angiography — procedures which are unjustified in such a situation. In a series of papers reporting increasing numbers of observations over longer periods of time, the Roumanian group described improvement in the atherosclerotic diseases (83, 86, 94, 126, 131). In these accounts, peripheral arterial circulation was improved and intermittent claudication reduced. Anginal attacks were reduced in frequency, myocardial infarction was improved, and digitalis requirements in patients with congestive heart failure were reduced. They also cited unexpected return of muscular strength and dexterity after stroke, diminution of the symptoms of the lacunar state and pseudobulbar palsy, and beneficial effects on disorders more difficult to define (e.g., cerebral atherosclerosis and cerebral angiospasm). This experience now extends to many thousands of patients treated for as long as 24 years.

Other authors have reported favorable results in diseases related to atherosclerosis. Nadel (132) observed improvement in peripheral circulation, generalized atherosclerosis, pseudobulbar palsy and the shoulder-hand syndrome after percutaneous procaine blockade. Vascan et al (133) noted beneficial effects in 127 elderly patients with similar disorders and with cerebral hemorrhage as well. Portias (115) observed moderate improvements in generalized atherosclerosis after procaine, and Letourmy (66) following Aslan's method found lessened angina, reduced intermittent claudication and regression of hemiplegia

and spastic states during procaine therapy. A similar favorable effect was observed on angina and intermittent claudication in 86 middle-aged and old persons after procaine by Nebo (109). Lassman and Plenck (134) were impressed with the beneficial effects of procaine given orally in cerebral atherosclerosis. Tsoukas and Papantoniou (135) believed that procaine helped recovery from cerebrovascular attacks, and advocated its use. Hartin (136) reported that 80 percent of 243 middle-aged and elderly persons were improved or exhibited stabilization of their disease when procaine was employed to treat various cardiovascular disorders. Paule (62) noted improvement after procaine in 6 elderly patients with heart failure. Dryagin (137) noted beneficial effects of procaine in 200 patients with cerebral atherosclerosis.

There are also many studies in which no improvement in atherosclerotic diseases occurred after procaine. Tchebotarev (89) warned that patients felt better and were more active after procaine treatment but their electrocardiograms (ECGs) became worse. Scardigli and Guidi (69) could not confirm beneficial effects of procaine in 76 elderly patients treated 12 to 15 months for cerebral atherosclerosis. O'Connell and Offner (72) reported improved mood but unchanging atherosclerotic disease in 30 elderly persons. In two well controlled clinical trials, Hirsch (78) and Kant and Sterne (74) observed no change in the manifestations of cerebral atherosclerosis or in the ECG. Siggelkow (138) observed that symptoms attributable to cerebral ischemia improved only temporarily.

With a few exceptions, all the reports on the effect of procaine on the atherosclerotic process and on the clinical manifestations of atherosclerosis can only be described as preliminary, sketchy, unstructured, and almost completely uninterpretable. Generalized atherosclerosis and cerebral atherosclerosis, two conditions reported improved by procaine, are diagnostic wastebaskets; the criteria and manifestations vary widely from physician to physician. In any definitive study, angina pectoris, intermittent claudication, cerebral infarction, congestive heart failure, myocardial infarction and related terms require precise definitions of known reliability applied in a standard manner (139). Because angina pectoris and intermittent claudication are usually diagnosed from the medical history alone and can be improved by placebos, controlled clinical trials with double-blind placebo-controlled methodology are essential. Return of the function of muscle groups after stroke depends in part on the patient's morale and sustained effort and can be influenced by such nonspecific beneficial factors as: attention from a variety of persons in the health professions; emotional support from the family, friends and other patients; and an optimistic attitude. Without disciplined clinical trials, it is impossible to separate these effects from those of procaine.

In the early stages of the work with procaine, lipid transport and the atherosclerotic process were poorly understood. Recent improvements in technology (including paper electrophoresis, the preparatory ultracentrifuge, and the autoanalyzer) and the increase in our knowledge of lipid transport disorders and the atherosclerotic processes have been substantial (140–142). The limitations and inaccuracies in some of the usual laboratory methods of measuring cholesterol have become apparent. We have learned that blood lipid concentrations may vary with diet, alcohol intake, and psychosocial stress (143) and that only carefully controlled clinical trials can indicate benefit to the atherosclerotic process (144). None of these advances in methodology, with the partial exception of paper electrophoresis, has been employed in the studies of procaine and atherosclerosis. We must conclude that the work performed so far does not permit any decision as to whether or not procaine is beneficial in atherosclerotic disease.

PROCAINE EFFECTS ON OTHER DISORDERS

A relatively small number of reports deal with the beneficial effects on peptic ulcer, chronic pulmonary disease, parkinsonism, ulcerative colitis, asthma, and longevity (64, 83, 145, 146). Because of the paucity of data, no survey of the effects of procaine in these disorders is attempted, although the atropine-like effects of procaine provide a rationale for its benefit in these disorders.

There has also been relatively little published about the effects of procaine on the lifespan. In two reports (145, 147), Aslan and David claimed that procaine lengthened the life of the rat. In a controlled trial of the effects of procaine, PABA and DEAE on the rodent lifespan, Verzar (47) observed no beneficial effects on survival, body weight at death, or on thermic contraction of tendons. Another aspect of Verzar's work is worth citing. Among the control rats for the procaine group, 50 percent survived 708 days and 20 percent survived 900 days. Among the control

rats for the PABA group, 50 percent survived 866 days and nearly half lived 900 days or longer. With this kind of variation in lifespan between two groups of control rats, the need for precise design and careful analysis of such experiments is demonstrated.

A study of the effects of procaine on human longevity is a complex issue. It involves sensitive, precise and long-term follow-up of such a large number of subjects, and the published data are so meager, that no discussion is warranted here.

Over the past three decades, the methods of controlled clinical trials have evolved to the point of becoming standard (148). First the disease to be treated must be given an explicit definition, and it must be demonstrated that several observers agree on independently-made diagnoses in a number of patients. Then the characteristics of patients recruited for the trial must be determined. Such characteristics include age range, sex, socio-economic status, severity of disease and method of recruitment. The patients, after giving informed consent, are categorized by severity of disease – and possibly other characteristics – and members of each category are randomly assigned to receive a drug believed to be active, or an inert preparation. It may be desirable to administer both preparations, drug and placebo, to all participants in random order. Neither the patient nor the experimenter should know what any participant is receiving. The double-blind methodology requires that drugs be coded by an identifying system that can be consulted only in cases of suspected drug toxicity. Care must be taken to ensure that participants are taking their medicines, and the dropout rate must be minimized. Those who collect the data on which a judgment of effectiveness is to be made must also be unaware of what any subject is receiving. Finally, the results must be subject to disciplined statistical analysis of a type determined before the beginning of the trial. All aspects of the clinical trial should be explicit so that the work may be repeated exactly.

SUMMARY OF PROCAINE EFFECTS ON CHRONIC DISEASES

There is little reason to doubt that many patients have been treated at the Geriatric Institute in Bucharest and have felt and looked better. However, there is no compelling reason to believe that procaine, aside from a possible antidepressant effect, contributed to this improvement. The evidence that procaine has a prophylactic or therapeutic effect in aging or the diseases of later life is unconvincing. The drug has been used for these purposes for 24 years in over 100,000 patients, and there is still no sound evidence upon which to conclude that it has value.

CONCLUSIONS

This review of the literature yields no convincing evidence that, except for a possible antidepressant effect, the systemic use of procaine (or Gerovital, of which the major component is procaine) is of value in the treatment of diseases in older patients.

The literature on procaine reveals that the quality of clinical trials of new agents in the treatment of the elderly may be very poor. There is need for conferences and symposia to discuss the current status of evaluating new drugs in the elderly and the special problems of clinical trials in the aged.

If procaine has an antidepressant effect, there is some likelihood that this may account for the impression among some observers that in procaine-treated patients there is a decrease of complaints attributable to the musculoskeletal, cardiovascular, endocrine, sexual, gastrointestinal and respiratory systems. Depression may play a greater role than previously suspected in these multiple discomforts of the elderly. Controlled clinical trials of standard antidepressant drugs among aged persons deserve careful consideration.

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Exhibit "C"

JAN 12 1976

IND 8681

Rom-Amer Pharmaceuticals, Ltd.
Attention: Alfred T. Sapse, M.D.
233 South Beverly, Suite 100
Beverly Hills, California 90212

Gentlemen:

Reference is made to your communication dated October 27, 1975, regarding your Notice of Claimed Investigational Exemption for a New Drug for procaine hydrochloride, IND 8681.

We have reviewed your comments and arguments and offer a further explanation of the issues that led to our September 5 1975, action of not allowing Phase III studies to begin.

The following is our evaluation of the individual studies which you claim are adequate to support Phase III testing:

> Molloy Study - (50 patients) You advised us on April 28, 1975, that "after examining the records and also upon advice from our consultants, we decided that this study is unacceptable to our company due to non-observance of certain agreed upon provisions of the protocol....".
>
> Swerling Study (13 patients) Deals primarily with organic patients; fails to show significance and on April 3, 1975, you advised us that "our company does not intend to use this study."
>
> Cohan Study - (254 patients) Consists of an open safety study from which we received summary reports but no final report or case report forms. After having been reviewed both in-house and by a consultant, it was noted that the information relates primarily to side effects observed in an open trial and the population consists of a wide age range with a variety of psychiatric diagnoses. Since procaine hydro-

chloride was primarily intended for older patients, it would have been more meaningful to have a detailed analysis of side effects in patients 65 years of age and older excluding such concomitant diagnostic labels as "senile deterioration", "severe arthritis", "chronic brain syndrome", "schizophrenic reaction" etc. It also is necessary to know how the side effect data were obtained, i.e., were patients asked direct questions or were these reports based on information volunteered by patients during the course of the usual psychiatric interview? Were more of these side effects reported in patients diagnosed as chronic brain syndrome than in those diagnosed as anxiety state or depression? It has been noted that this is an important issue for a drug which is intended to be used with older patients who are likely to have one or more physical ailments in addition to their psychiatric problems.

Jarvik Study - (24 patients) This submission consists of case report forms for 24 patients, a one paragraph narrative description of the findings and twenty-one tables of data analysis. After reviewing the information submitted, we believe that the data are incomprehensible in the absence of a formal description of the meaning of the various tables. It was also noted that the values in tables 8 and 11 are not the same. For example, the mean for the pretreatment of the procaine hydrochloride group on the Obsessive Compulsive Factor in Table 8 is 1.8 whereas the value noted in Table 11 is 1.5. It is also necessary to have the final adjusted means listed for the covariance analysis as well as for the F-ratios and degrees of freedom. It is not stated whether the P values listed are for one-tail or two-tail tests. Finally, none of the so-called significant differences on the covariance analyses exceeded the .10 level and the significant differences on the three SCL 90 scores, where variances are large, are probably due to a few patients.

Cammer Study - (40 patients) This study consisting of a 22 page summary and no raw data was submitted on August 22, 1975. Considering the fact that this study arrived after the original request for a conference and with no raw data, it was not possible to make a decision as to the adequacy of the Cammer study prior to September 8 or 9. Subsequently, the Cammer study (without case reports) has been reviewed.

Both in-house and consultant reviews note that in the results of the covariance analysis (Table 9), there are significant pretreatment differences between the procaine hydrochloride and placebo groups on four of the major variables. In at least one case, these pretreatment differences (on the covariates) are greater than the differences between the final adjusted means. It will also be necessary to have the final adjusted means for the covariance analyses as well as the F-ratios and degrees of freedom. The above mentioned issues must be resolved before the study can be evaluated.

Zung Study - (30 patients) This study was presented and reviewed at both the August 2, 1974, Division Conference and the October 4, 1974, Geriatric Panel Advisory Meeting. While the study may show a degree of efficacy in favor of the drug over placebo the following methodological problems were noted:

1. On both the Depression Status Inventory (DSI) and the Self Rating Depression Scale (SDS), and the Anxiety Status Inventory (ASI) and Self Rating Anxiety Scale (SAS) both the imipramine patients and placebo patients were worse before and after treatment.

2. The Clinical Global Impression as a global rating was not felt to be adequate, in itself, to characterize the type and kind of depression or the level of depression.

3. There was not enough information on the duration and type of the patients' depression prior to the study.

4. Only total scores (DSI, SDS), etc.) were analyzed; there was no factor analysis on individual items on the scales.

5. The definition of depression did not specify the necessity of having any particular item (dysphoric mood, etc.) or level of condition.

The consensus was that the Zung study was valuable in providing information on which to revise protocols for future studies.

Kurland Study - (64 patients) While this study may show efficacy in favor of the drug, it utilized the same protocol as that of the Zung study. As such, many of the problems noted above are applicable. In addition, there was a significant placebo effect for both the HRD and the SDS at the .01 level. Randomization of patients may also have been compromised since there was an exact reversal of M-F ratios between the drug group and the placebo group.

In general, like the Zung study, this study was valuable in providing information on which to revise future protocols.

J. Overall Pooled Analysis (Zung, Kurland and Jarvik Studies) Dr. Overall attributes the significant differences among the studies solely to chance even though there were enormous differences between the Jarvik and Kurland studies (see Tables 2a and 2c of Overall). It was also noted that in both the Jarvik and Zung studies roughly half of the placebo patients show significant improvement whereas only a fourth of Kurland's placebo patients show significant improvement. It is also questionable to be pooling data from three studies when one study (Kurland) is contributing 63 cases and the other two are contributing 24 and 19 cases. There was no discussion of the differences among studies in the type of patient sampled, age ranges, pretreatment differences, etc. This is important since it was previously noted (see above) that

in the Zung study there were significant pre-treatment differences between the imipramine and procaine patients.

In response to your comments regarding the Zung and Kurland studies, the specific deficiencies are discussed above. It is our belief that the appropriate criteria for admission into these studies and the definition of depression, etc. are of fundamental and critical importance in the design of studies which are attempting to establish the efficacy of a drug in the treatment of depression. In this regard, both the Zung and Kurland studies have played a very valuable part by helping to revise future protocols in regard to definition, entry criteria, etc.

While it may be argued that the standards of research are continually changing as science evolves in an effort to improve itself, it also should be noted that this Administration has a responsibility to demand research consistent with the highest standards available. As such, the new protocol proposed by this Division reflects the recommendations made in the Guidelines for the Clinical Investigation of Anxiolytic and Antidepressive Substances. In reference to the validity of the Zung and Kurland studies, it should be emphasized that in no way is a precedent being set. Rather, it is in accord with the experience of others that the usefulness and purpose of early phase II studies are to improve the design and execution of later studies.

In regard to animal toxicity studies, please refer to our conference of August 2, 1974, and our letters of December 5 and 9, 1974, and September 5, 1975. However, to reiterate: three-month toxicity studies in animals support clinical studies of no longer than 3 months duration regardless of phase. It should be noted that the number and length of animal studies do not determine phase of drug development. Phase III clinical trials depend on the outcome of Phase II trials.

We have attempted to outline the issues that formulated our September 5, 1975 decision. However, if you feel that further discussion of the issues is needed, our staff is available to meet with you on short notice.

Sincerely yours,

Barrett Scoville, M.D.
Director
Division of Neuropharmacological
Drug Products
Bureau of Drugs

cc:
HFD-120
HFD-120/GHajarian/12/17/75
HFD-108
HFD-120/JCinque ✓
HFD-120/HPostman
HFD-120/VGlocklin
HFD-120/Dr. Raskin
HFD-120/FT:mf:1/8/75

Exhibit "D"

CLINICAL TESTING FOR SAFE AND EFFECTIVE DRUGS

INVESTIGATIONAL DRUG PROCEDURES

Before 1962, there was no requirement that the Food and Drug Administration be notified that drugs were being tested on humans.

The 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act greatly strengthened the Government's authority over clinical (human) testing of new drugs.

With this new regulatory authority, the Food and Drug Administration has taken steps to:

1. Provide added safeguards for those on whom drugs are tested.
2. Improve reports by drug investigators.
3. Establish investigative procedures to supply substantial scientific evidence that a drug is safe and effective.

First Steps

Before a new drug may be tested on humans, the sponsor (usually a pharmaceutical firm, sometimes a physician) must give the FDA the information specified as a "Notice of Claimed Investigational Exemption for a New Drug" (Forms FD 1571, 1572, and 1573), known as an "IND." Copies of these IND forms may be obtained from:

Document and Records Service Section
(HFD-106)
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

The IND should include the following information:

a) Complete composition of the drug, its source, and manufacturing data, to show that appropriate standards exist to insure safety.

b) Results of all preclinical investigations, including animal studies. Initially, these should be directed toward defining the drug's safety, rather than its efficacy. The data must demonstrate that there will not be unreasonable hazard in initiating studies in humans. Further animal studies may be conducted concurrently with clinical studies. The Bureau of Drugs will, on request, comment on the adequacy of the proposed animal studies. The FDA generally requires as a minimum: (i) pharmacological profile, (ii) acute toxicity be determined in several species of animals and that the route of administration be that which will be used in the animal trials, (iii) short term studies ranging from two weeks to three months depending upon the proposed use to evaluate toxicity. Additional animal studies are frequently necessary.

c) A detailed outline (protocol) of the planned investigation.

d) Information regarding training and experience of the investigators. (See "Qualifications of Investigators.") Investigators are responsible to the sponsor and are required to submit, to the sponsor (not the FDA), either Form FD 1572 for clinical pharmacology or Form FD 1573 for clinical trials.

e) Copies of all informational material supplied to each investigator. (The type of information is listed in Form FD 1571.)

f) An agreement from the sponsor to notify the FDA and all investigators if any adverse effects arise during either the animal or human tests.

g) The investigator's agreement to obtain the consent of the person on whom the drug is to be tested before the test is made.

h) Agreement to submit annual progress reports and commitments regarding disposal of the drug when studies are discontinued.

Physician-Sponsored IND

When an investigator wishes to act as sponsor for the use of a drug solely as a research tool or for early clinical investigation of a drug of therapeutic or diagnostic potential (clinical pharmacology—phases 1 and 2) a simpler abbreviated form of submission is acceptable. An example would be the study of a drug that no manufacturer is interested in sponsoring. An outline of such a study should provide the following information:

1. The identity of the compound or compounds, together with the facts that satisfy the investigator that the agent may be justifiably administered to man as intended.

2. The purpose of the use and the general protocol.
3. Appropriate background information, including a brief statement of the investigator's scientific training and experience and the nature of the facilities available to him.

The physician sponsoring this form of IND deals directly with the FDA. The FDA has no authority over the practice of medicine and cannot require a physician to prescribe or not to prescribe a drug for a particular illness. But physicians are encouraged to submit an IND when they use a drug for purposes other than those approved by the FDA, when the drug was marketed. This enables the FDA to accumulate data on the safety and efficacy of the drug for that kind of treatment and to share the information with other physicians.

The Clinical Investigation

The kind and extent of the investigational drug tests are crucial to producing the substantial scientific evidence of safety and effectiveness needed to approve the drug for marketing. This evidence is obtained in three phases:

Phase I

Pharmacology studies are used to determine toxicity, metabolism absorption and elimination, and other pharmacological actions; preferred route of administration, and safe dosage range. These studies involve a small number of persons and are conducted under carefully controlled circumstances by persons trained in clinical pharmacology.

Phase II

Initial trials are conducted on a limited number of patients for a specific disease treatment or prevention. Additional pharmacological studies performed concurrently on animals may be necessary to indicate safety.

Phase III

Proposals for this phase, involving extensive clinical trials, are in order if the information obtained in the first two phases demonstrates reasonable assurance of safety and effectiveness, or suggests that the drug may have a potential value outweighing possible hazards. The phase III studies are intended to assess the drug's safety, effectiveness and most desirable dosage in treating a specific disease in a large group of subjects. The studies should be carefully monitored, no matter how extensive.

The FDA receives constant reports on the progress of each phase. If the continuation of the studies appears to present an unwarranted hazard to the patients, the sponsor may be requested to modify or discontinue clinical testing until further preclinical work has been done.

30-Day Delay

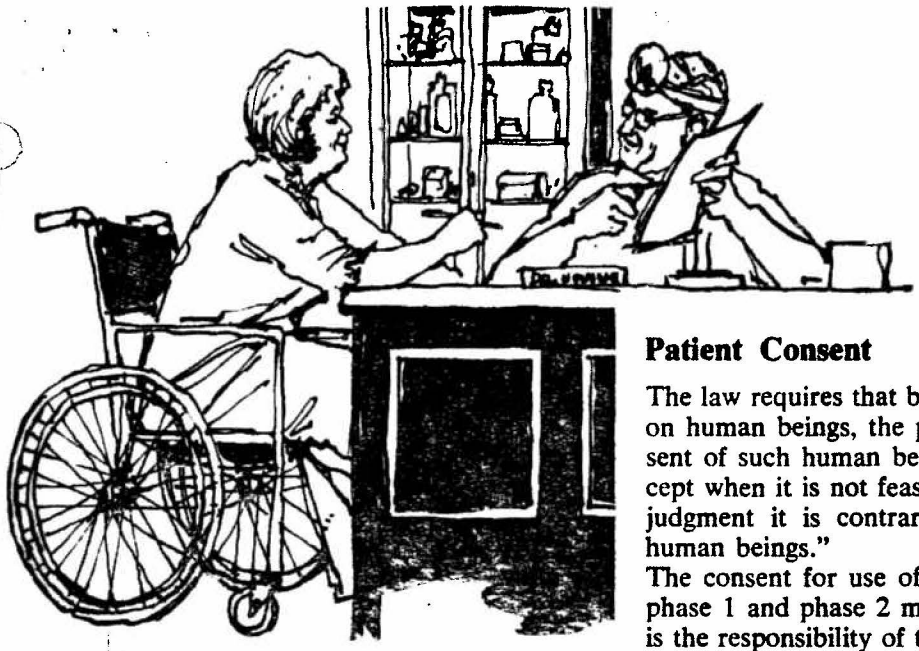
After the sponsor submits his IND, he must wait 30 days before beginning clinical tests. This delay enables the FDA to review the protocol to make certain it contains all of the necessary information and to assure that patients are not exposed to unwarranted risks. The 30-day period may be extended if the FDA feels additional time is needed for the sponsor to correct deficiencies in the protocol. The FDA also may waive the delay requirement if it feels such action is justified.

Sponsors may discuss their protocols at any time either before or during the tests with the Office of Scientific Evaluation, Bureau of Drugs.

Tests in Institutions

Drug tests on persons in hospitals, prisons, research facilities, and other institutions must be carefully supervised by institutional review committees.

The committees must be composed of persons with varying backgrounds, such as lawyers, clergymen or laymen, as well as scientists. They are appointed by the institution involved in the study. The FDA inspects the institutions periodically to determine if the committees are operating properly.



Qualifications of Investigators

The sponsor of an investigational new drug (usually the manufacturer) will ask the clinical investigator to supply the following information on Form FD 1572 (for the clinical pharmacologist engaged in phase 1 or 2 trials) or Form FD 1573 (for the physician engaged in phase 3 clinical trials):

A statement of his education, training and experience.

Information regarding the hospital or other medical institution where the investigations will be conducted; special equipment and other facilities.

The training and experience needed will vary, depending upon the kind of drug and the nature of the investigation. In phase 1, the investigator must be able to evaluate human toxicology and pharmacology. In phase 2, the clinicians should be familiar with the conditions to be treated, the drugs used in these conditions and the methods of their evaluation. In phase 3, in addition to experienced clinical investigators, physicians not regarded as specialists in any particular field of medicine may serve as investigators. At this stage, a large number of patients may be treated by different physicians to get a broad background of experience.

Obligations of Investigators

The investigator must keep careful records of his study and retain them for at least two years after the NDA is approved. The records must be made available promptly to the drug sponsor and to the FDA when required. Regular progress reports must be sent to the sponsor.

Reports must be sent to the sponsor immediately when dangerous adverse effects are observed, so the FDA and the other investigators can be notified, and the study stopped if the hazard warrants.

The regulations regarding consent of human beings when investigational drugs must be observed.

Patient Consent

The law requires that before using investigational drugs on human beings, the physician must "obtain the consent of such human beings or their representatives except when it is not feasible or when in his professional judgment it is contrary to the best interest of such human beings."

The consent for use of an investigational new drug in phase 1 and phase 2 must be in writing. In phase 3, it is the responsibility of the investigator, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form.

If written consent is not obtained, the investigator must obtain oral consent except as provided above, and record that fact in the medical record of the person receiving the drug.

Causes for Termination of Investigation

The FDA may direct the sponsor to terminate an investigation at any stage under certain conditions. These include:

Evidence of significant hazard.
Convincing evidence that the drug is ineffective.
Submission of false data.
Omission of material information.
Unsatisfactory manufacturing practices.
Failure to conduct the investigation in accordance with the plan submitted by the sponsor-and approved by the FDA.
Commercialization of the drug. The IND regulations are not intended to provide a way of marketing a drug for profit without an approved NDA.
Failure to submit progress reports at intervals not

exceeding one year.

Failure to report serious or potentially serious adverse reactions.

Failure to meet requirements for patient consent.

The Commissioner may notify the sponsor of any of the above conditions and invite immediate correction. A conference may be arranged. If the corrections are not effected immediately, the Commissioner may require the sponsor to terminate the investigation and recall unused supplies of the drug. The drug in question may not be reintroduced into clinical testing in man until additional data have been submitted to the FDA and the Commissioner has approved the proposed resumption of the study.

The Investigator and "Promotion"

The regulations forbid manufacturers or any persons acting for or on their behalf to disseminate any promotional material concerning a new drug prior to completion of the investigation.

This is not intended to restrict the full exchange of scientific findings in scientific or other communications media. Its purpose is to restrict promotional claims by the sponsor until the safety and effectiveness of the investigational drug have been established. Violation of the regulations by an investigator may result in FDA action to deny him further supplies of the drug. The manufacturer may also jeopardize his right to sponsor the investigation.

Special preclearance before Human Trials

Before starting an investigation in any of the following categories, FDA approval is required for:

a) Substances controlled under Schedule I of the Controlled Substances Act (PL 91-513).

b) Investigations of drugs so toxic that their use may be justified only under special conditions.

c) Substances proposed for treatment of drug dependence.

d) Reinstitution of drug investigations which had been terminated by the Commissioner.

Use of Drugs for Laboratory Procedures

New drugs used only for studies in vitro (test tubes) or in laboratory animals are exempted from the new-drug provisions of the Act provided they are labeled "C tion—Contains a new drug for investigational use o in laboratory research animals, or for tests in vitro. N for use in humans."

The exemption does not apply, however, for a new drug used in vitro when this use will influence the diagnosis or treatment of disease in a human patient—for example, discs to determine the sensitivity to antibiotics of bacteria in culture, or a stick or strip of paper incorporating a reagent to test for sugar in the urine. Apparent ineffectiveness of an antibiotic sensitivity disc or a false negative test for glycosuria might well lead to an incorrect diagnosis and deprive the patient of appropriate treatment.

Before such a preparation can be marketed there must be certification (in the case of antibiotics) or approval of a New Drug Application (in the case of other drugs). For that reason, it is necessary to submit adequate proof of the effectiveness of these preparations before they can be marketed.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELF
Public Health Service
FOOD & DRUG ADMINISTRATION
5600 Fishers Lane

A Primer On New Drug Development

A Primer On New Drug Development

by Wayne L. Pines

The development of a new drug product is a long, complex process that can begin in many places—a drug manufacturer's laboratory, a chemical company, research at the National Institutes of Health—and that hopefully will end with benefits to the public.

By the time a new medicine becomes available to the general public, it has been thoroughly tested in both animals and humans under carefully controlled circumstances, and information has been approved for physicians to help them prescribe the drug correctly.

The Food and Drug Administration is responsible for approving the marketing of all new drugs that are sold in the United States, and for monitoring their use after approval.

This primer provides a simplified view of how a new drug is developed and approved for general marketing. Much of this applies only to prescription drugs, although some parts could apply to nonprescription medicines.

The First Step

The first step in the development of a new drug is research into the chemistry or anatomy of a disease, or the discovery of possible drug effects for a chemical. Recently, most drugs have been developed in the laboratories of pharmaceutical companies.

The chemical is subjected to screening tests and to testing in animals. Initial animal studies are performed to see whether the chemical has any desired drug effects. If it does, additional testing is done to determine what effects it might have, what dosage levels are poisonous, what the safe dosage range might be for humans, and whether there is a reason for testing the chemical in humans.

FDA initially requires that sufficient animal studies be performed to show it is reasonably safe to begin human testing. Additional animal tests are required as the human tests progress.

FDA does not monitor animal tests. But if they indicate the drug can be safely tested in man and that the chemical may be useful therapeutically, the drug sponsor will then proceed to the next step, which does involve FDA. This step makes the drug an Investigational New Drug (IND), which means the sponsor wants to test it in humans.

Before human tests can start, the sponsor must submit to FDA a form known as a "Notice of Claimed Investigational Exemption for a New Drug." The sponsor must tell FDA the complete composition of the drug, its source, and how it is made.

In addition, the sponsor must submit the results of all animal studies to document that enough testing has been performed in animals to indicate that the drug shows promise of being useful in humans, and that no test subject will be exposed to an unreasonable risk.

The IND also contains a detailed outline, called a protocol, describing the planned testing in humans. The sponsor must wait 30 days after submitting the IND to enable FDA to review the materials to make sure patients are not being subjected to unwarranted risks.

Before testing is done on humans, FDA requires that, at the institution where the drug is to be tested, a committee composed of a broad spectrum of disciplines such as physicians and clergymen review the protocol to assure that patients' rights are adequately protected.

Human testing is divided into three phases.

Phase I

The first phase of human testing is directed at determining what chemical actions a drug has, how it is absorbed into the body, how it should be given (by mouth or injection, for example), and what the safe dosage range is. These tests involve a small number of patients —usually fewer than 10.

The basic approach during Phase I is to begin with doses one-tenth or less of what might be expected to be useful, and gradually increase the dose with the patient carefully watched. Much of this testing is done in normal, healthy volunteers.

The safety record of such research is excellent. FDA knows no volunteer patient who has be

permanently harmed as a result of Phase I testing of hundreds of new compounds under the FDA procedures established in 1962. Some patients do become ill as the dosage is increased.

The main things investigators are looking for during Phase I studies are to see that the chemical does act in the body, that it is safe, and that further testing can continue. Once Phase I studies are completed successfully, Phase II studies can start.

Phase II

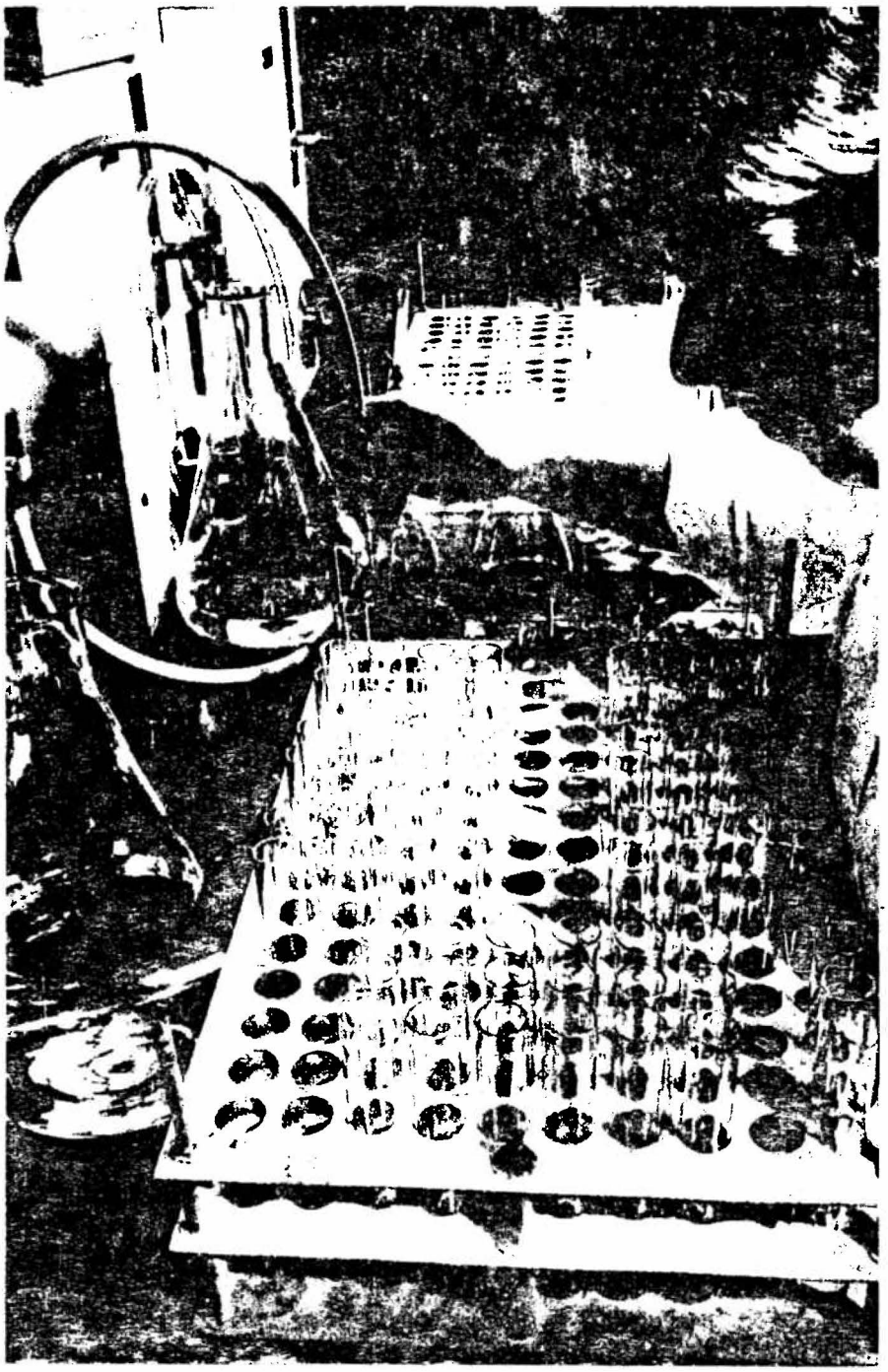
Phase II studies involve human testing on a limited number of patients for treatment or prevention of a specific disease. The number of patients depends on the nature of the drug.

This is the time when investigators evaluate the effectiveness of the drug. Additional testing usually continues on humans or animals to indicate the drug's safety.

If the Phase II tests show the drug may be useful in treating a disease and the long-term animal testing indicates no unwarranted harm, then the sponsor proceeds to Phase III.

Phase III

This is by far the most extensive testing. Phase III studies are intended to assess the drug's safety, effectiveness, and most desirable dosage in treating a specific disease in a large number of patients. As with earlier human studies, these tests are carefully controlled—that is, the investigator must have a basis for determining that the drug itself is causing the desired effect,



"No matter what system we set up, as technical knowledge grows, presently acceptable procedures and systems will appear inadequate. This is part of scientific progress."

rather than other variables or chance.

In Phase III, the drug is used the way it would be administered when marketed. Once Phase III is completed and the sponsor believes the drug is safe and effective under specified conditions, the sponsor applies to FDA for approval to market the drug. This application is called a New Drug Application (NDA).

The New Drug Application

By the time an NDA is submitted, a drug usually has been studied in several hundred to several thousand patients. An NDA contains all the information the sponsor knows about the drug. Often the NDA runs into thousands of pages.

The NDA is reviewed by the division in FDA's Bureau of Drugs responsible for evaluating that category of drug. There are six divisions: cardiopulmonary-renal, neuropharmacological, metabolic-endocrine, anti-infective, oncology-radiopharmaceutical, and surgical-dental.

Each division is composed of physicians, pharmacists, chemists, and other professionals experienced in evaluating new drugs. FDA makes extensive use of advisory committees composed of experts from outside the Agency.

The NDA is reviewed by a team who determine whether the drug is safe and effective and whether the drug sponsor can manufacture the drug properly and consistently, batch after batch.

Among the information submitted in the NDA are: chemical structure of the drug, scientific rationale and purpose the drug is to serve, all animal or laboratory studies, and all tests in humans.

FDA reviews the entire NDA to determine whether the benefits of the drug when used properly outweigh the risks. This is the crucial determination in evaluating a new drug.

If a drug is indicated for a cancer patient, for example, a relatively high degree of risk and adverse reactions may be tolerated if some benefit may ensue, because the alternative to use of the drug might be death. If a drug is used as a minor tranquilizer, then a much lesser degree of risk would be acceptable.

The benefit-risk judgment that goes into approval of a new drug is one of the hardest anyone can make. It involves not only medical but also societal considerations. How much risk is the public willing to take to obtain the benefits of a new drug, when no drug is completely free from risks?

Very often manufacturers of drugs —who may have spent considerable sums to develop a drug—complain that the review process for an NDA takes longer than it should. Legally, once an application is filed, FDA has 180 days to review it. In many cases, the application is not approved in the initial review, and the review period is extended.

The reason for most delays in the past has been that the data submitted to FDA were inadequate. Studies were not well controlled or there were not enough. In a large number of cases there was inadequate information about the manufacturing and quality control.

In making an important decision such as authorizing the sale to the public of a potent new chemical, it is imperative that FDA make sure the drug's benefits outweigh the risks and that the product will be made properly.

In the past, too, there may have been some unnecessary delays in the approval of a new drug. The Bureau of Drugs has taken steps, such as computerization, the use of project officers, and the use of advisory committees, to try to reduce the time delay. All the problems have not been solved, but the Bureau is working on them.

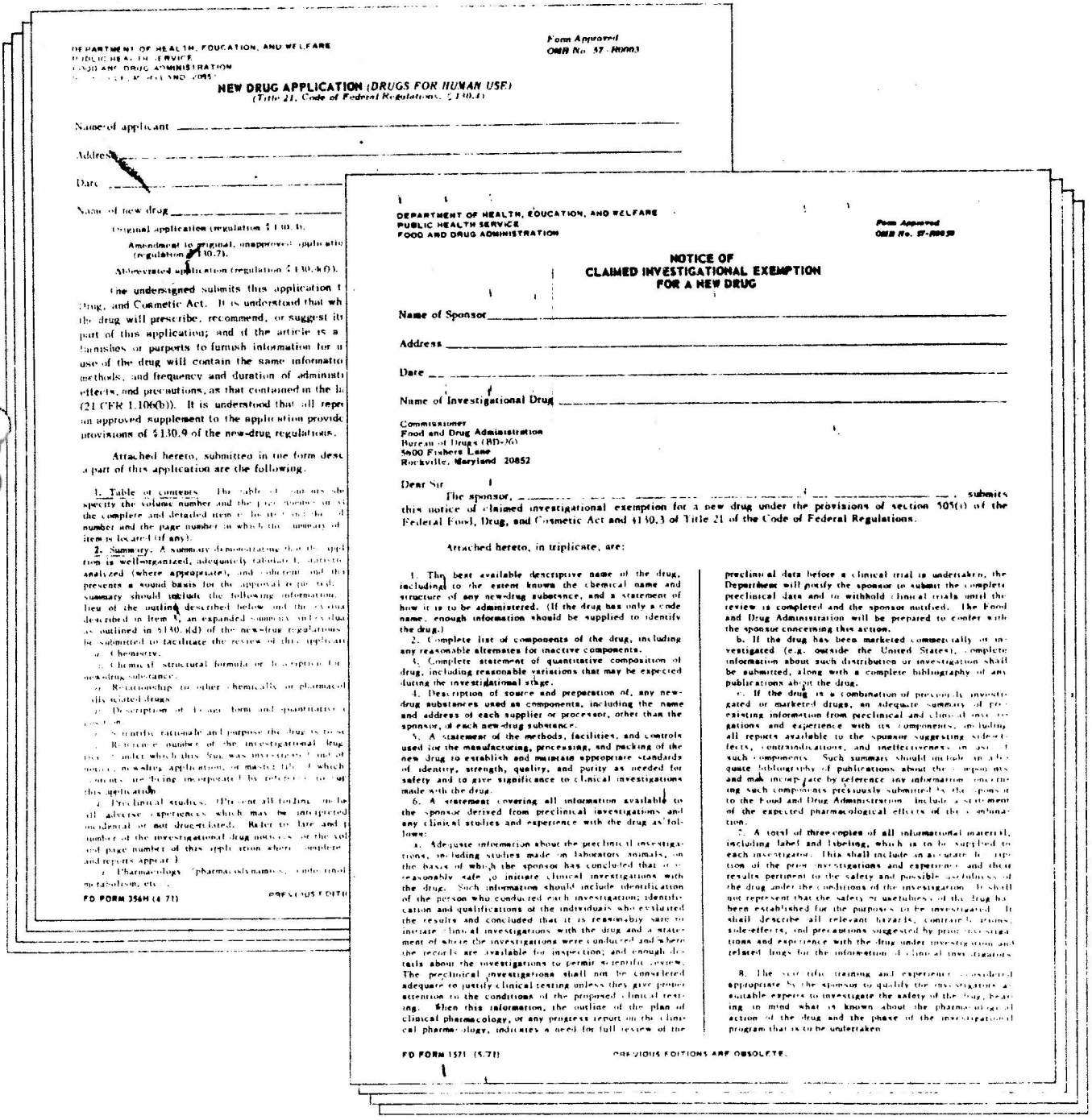
One of the final steps in the approval of an NDA is the review of the package insert or labeling. This is a detailed explanation of what the drug is, how it works, what it has been proven useful for, adverse reactions, means of administration, dosages, and other pertinent information.

The package insert must accompany the drug whenever it is shipped in interstate commerce. It also serves as the basis for all information on the drug disseminated by the manufacturer. The company may not make any claim for the drug which is not in the approved labeling.

A summary of many package inserts appears in the Physician's Desk Reference, a widely distributed book to which physicians often turn for information about prescription drugs.

Once an NDA is approved, the company is required to keep records relating to production methods for the drug and its safety and effectiveness. Any information in-

These are the forms that sponsors of Investigational New Drug (IND) and New Drug Applications (NDA) must fill out. The forms explain what types of information are required for each application. The information submitted in support of the application is considerably longer.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*
(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant _____

Address _____

Date _____

Name of new drug _____

Original application (regulation § 130.4).

Amendment to original, unapproved application (regulation § 130.7).

Abbreviated application (regulation § 130.4(f)).

The undersigned submits this application t
Drug, and Cosmetic Act. It is understood that wh
the drug will prescribe, recommend, or suggest its
part of this application; and if the article is a
furnishes or purports to furnish information for u
use of the drug will contain the same informatio
methods, and frequency and duration of administr
effects, and precautions, as that contained in the la
(21 CFR 1.106(b)). It is understood that all repo
an approved supplement to the application provide
provisions of § 130.9 of the new-drug regulations.

Attached hereto, submitted in the form desc
a part of this application are the following:

1. Table of contents. The table of contents sh
specify the volume number and the page number in th
the complete and detailed items of the application and
number and the page number in which the summary of
item is located (if any).

2. Summary. A summary demonstrating that the appl
tion is well-organized, adequately tabulated, accurate
analyzed (where appropriate), and coherent and that
presents a sound basis for the approval of the drug.
summary should include the following information
lieu of the outline described below and the narrative
described in item 3, an expanded summary may be sub
as outlined in § 130.4(d) of the new-drug regulations
be submitted to facilitate the review of this applicati
a. Chemistry.
1. Chemical structural formula or description for
new drug substance.
2. Relationship to other chemically or pharmacol
ally related drugs.
3. Description of dosage form and quantitative c
position.
4. Scientific rationale and purpose the drug is to be
5. Reference number of the investigational drug
(s) under which this drug was investigated and of
notice, new drug application, or master file in which
current information incorporated by reference for the
this application.
6. Preclinical studies. (Present all findings on ha
all adverse experiences which may be interpreted
incidental or not drug-related. Refer to date and i
number of the investigational drug notices or the vol
and page number of this application where complete
and reports appear.)
7. Pharmacology (pharmacodynamics, underlying
metabolism, etc.).

FD FORM 356H (4-71) PREVIOUS EDITI

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0059

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor _____

Address _____

Date _____

Name of Investigational Drug _____

Commissioner
Food and Drug Administration
Bureau of Drugs (BD-56)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir

The sponsor, _____, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug. Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pertaining information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of three copies of all informational material, including label and labeling, which is to be supplied to each investigator. This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

FD FORM 1571 (5-71) PREVIOUS EDITIONS ARE OBSOLETE.

A summary of many package inserts appears in the Physician's Desk Reference, a widely distributed book to which physicians often turn for information about prescription drugs.

dicating that the drug may pose an unexpected hazard must be reported.

A manufacturer must report to FDA every 3 months during the first year after approval, every 6 months in the second year, and once a year after that. Immediate reports are required in cases of drug mixups or contamination, or when unusual or especially severe adverse reactions are reported.

For some drugs, FDA requires more than recordkeeping. FDA can require additional studies to test the long-term effects of the drug. For example, FDA is requiring long-term studies for levo-dopa, a new and powerful drug used for Parkinson's disease.

"Me-Too"

If a drug has previously been marketed, another company's version is called a "me-too" drug. In some cases, it is unnecessary for a company wanting to market a "me-too" drug to go through the same type of extensive testing required of the original drug. FDA therefore has established an Abbreviated New Drug Application (ANDA). Depending on the nature of the drug, FDA requires varying amounts of information from a manufacturer who wants to make the drug.

In the same vein, it is important to note that FDA does not issue patents for drugs. They are issued by the U.S. Patent Office and last for 17 years. If a firm develops a new drug, it can get a patent and take legal action against any company that tries to market the identical drug during the 17-year period. Once the original patent expires, any other company can market a "me-too" version of the drug under its "generic" name or under a new trade name if the drug meets all the requirements of the law.

Changes in the NDA

Whenever a company wants to change any part of the procedure for making a drug, it must seek FDA approval. This is because even what appears to be a minor change in the manufacturing process can affect the final product. This type of approval, which is sought frequently, is called a supplemental New Drug Application.

The same applies to labeling. Very often after a drug has been in use for some time, new information develops about it. Perhaps there are new purposes for which it can be prescribed, or new warnings that need to be included. Any change must be approved by FDA.

Withdrawing NDA Approval

If an approved drug is found to produce an unexpected side effect or to be less safe or effective than anticipated, FDA can seek to withdraw approval. FDA gives the firm an opportunity to present its views. In some cases, this may involve a hearing.

In landmark rulings in five "drug effectiveness" cases June 18, 1973, the U.S. Supreme Court supported FDA's authority to be the final judge of whether a drug is safe and effective, and to deny a hearing to a company that cannot show that significant facts are at issue.

Labeling for Patients

In 1970, FDA took a major step to provide information about prescription drugs directly to patients. The Agency decided that manufacturers of oral contraceptives—"The Pill"—must include in all packages received by patients a statement summarizing the potential risks of the drug. Physicians were provided with brochures listing the benefits and risks of the drug in greater detail.

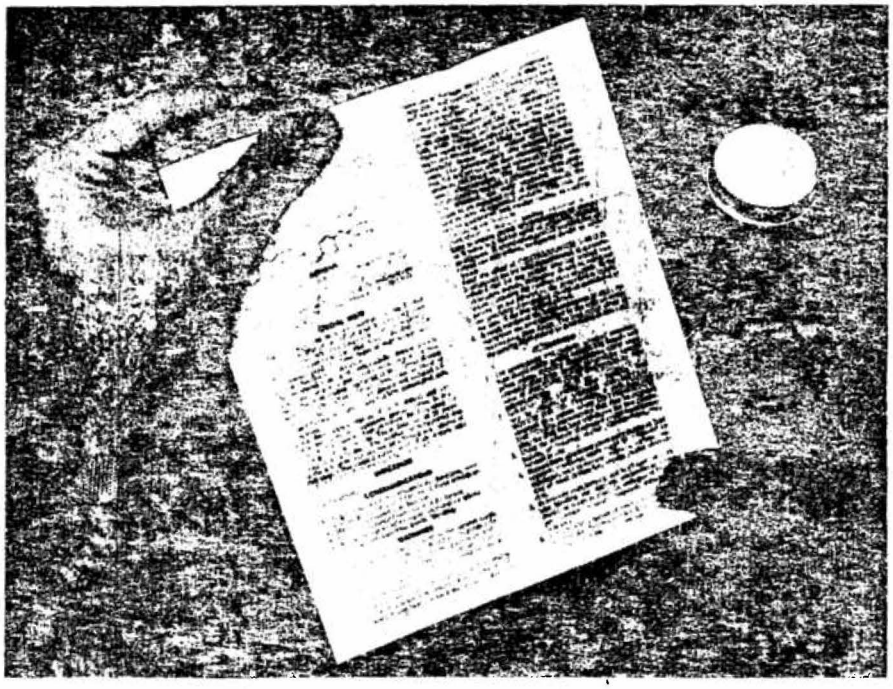
The reason for this decision was that FDA believed women should participate in the decision on whether to take "The Pill." Drugs used for contraception are different from others in that they are given to healthy women, not to treat disease, and there are nonchemical alternatives.

In 1973, FDA decided that information should be provided directly to patients on two other contraceptive drugs, diethylstilbestrol (DES) as a "morning after" pill and Depo-Provera as a long-acting injectable contraceptive. Information may be provided directly to patients on other prescription drugs in the future.

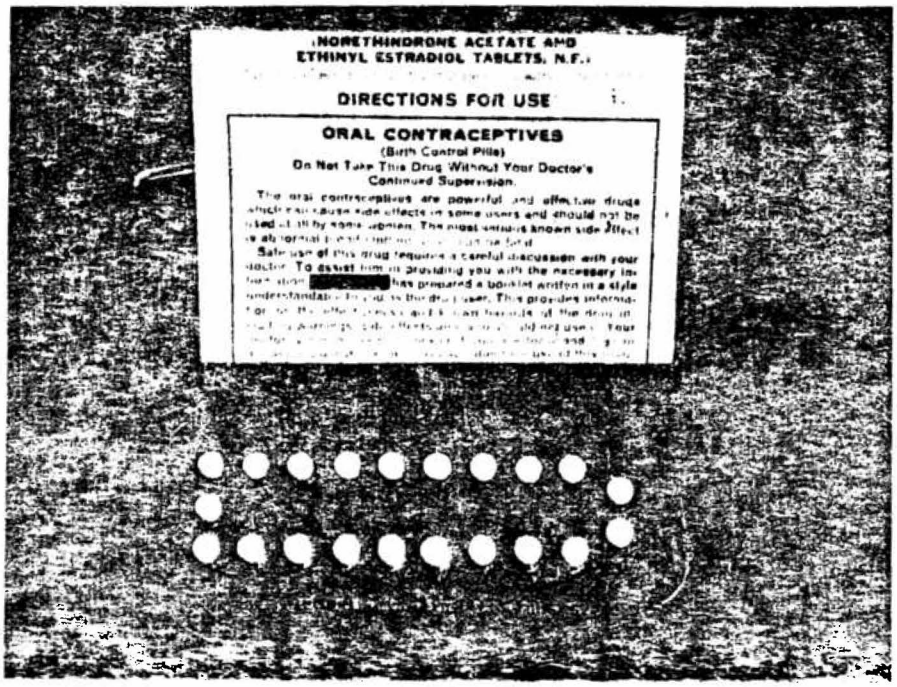
Patient Consent

Increasing concern has been expressed in recent years about the use of prisoners and other institutionalized people for drug studies. People in institutions are the most convenient volunteers for some studies because they are in controlled environments.

However, FDA does not believe that any person should be required to participate in a study involving investigational drugs, or duped into taking a drug he does not need. The law requires that before using investigational drugs on humans,



The package insert must accompany the drug whenever it is shipped in interstate commerce. It also serves as the basis for all information on the drug disseminated by the manufacturer.



In 1970, FDA decided that manufacturers of oral contraceptives must include in all packages received by patients a statement summarizing the potential risks of the drug. This has become known as a "patient package insert."

To help improve medical communications, FDA publishes a Drug Bulletin for all physicians, dentists, pharmacists, and other health professionals.

the physician must obtain the person's consent. That consent must be informed—that is, the patient must know what the risks are. The only exception is when consent is not feasible or when in the physician's judgment it is contrary to the best interests of the person.

Drugs for Pregnant Women and For Children

FDA is concerned about the use of drugs by all persons, but especially about drugs being taken by pregnant women and by children. A drug can have a very different effect on the fetus than on the mother, since the fetus is particularly sensitive to biological change.

Investigators who believe a drug may be useful in pregnant women have to be extra careful in testing them. Most drugs have not been tested in pregnant women, and the labeling is required to indicate that. However, extensive testing is required in pregnant animals.

Thus, many physicians know which drugs pass through the placenta to the fetus. In treating a pregnant woman, physicians have to make a delicate benefit-risk decision.

The same problem applies to drugs for children. Many drugs available for adults are also prescribed for children. Some labeling and standard charts provide guidance for the physician.

However, FDA believes that drugs to be used in children should be tested in them under very carefully controlled circumstances. The only children who would ever receive a drug in a test situation are those who need it for a disease. This area is now receiving considerable attention at FDA.

Certification

The law provides that two types of drugs—antibiotics and insulin—must not only be approved generally for marketing by FDA, but must be certified batch-by-batch. The manufacturers pay for this service. FDA tests random samples from each batch for purity and potency. The manufacturer may not release the batch until FDA certifies it.

Advertising

One of the most significant sources of information about prescription drugs is information supplied by the drug manufacturers to physicians, through advertising in medical journals, direct mail, or salesmen known as "detailmen."

The law requires that information supplied to physicians about prescription drugs be truthful, fully informative, and fairly balanced. Claims for a drug's effectiveness must be balanced with information on its side effects.

FDA extensively regulates prescription drug advertising and mail promotion. Whenever material is found misleading, FDA can seek to seize the drug on the grounds that it is "mislabeled." In virtually all cases, however, FDA seeks alternatives that have proven more effective. Among these are remedial ads required by FDA to be placed by the drug company in the journals in which a misleading ad appeared, or remedial letters sent to physicians.

It is generally acknowledged that the prescription drug information system in the United States needs improvement, so that physicians are assured of having accurate and complete information. FDA publishes a Drug Bulletin for all physicians, dentists, pharmacists, and other health professionals which reports significant new regulatory developments. FDA is developing further systems to try to provide physicians with the best information about drugs.

What Consumers Can Expect

The system of new drug development and control in the United States is far from perfect. Admittedly, improvements are needed.

No matter what system we set up, as technical knowledge grows, presently acceptable procedures and systems will appear inadequate. This is part of scientific progress.

But despite the defects in the system, consumer exposure in the United States to drug products of unproven safety and effectiveness is minimal. This does not mean that patients are never exposed to unnecessary hazards from prescription drugs. All medicines have the potential to harm as well as benefit, and despite all precautions, prescription medicines at times are misused or misunderstood.

Looking beyond FDA's responsibilities in the regulation of drugs, ultimately it is up to the "three P's"—physicians, pharmacists, and patients—to make sure that drugs are used wisely and that FDA's regulatory efforts result in true benefits to the public.

Wayne L. Pines is editor of FDA CONSUMER.

REPRINT FROM FEBRUARY 1974
FDA CONSUMER
U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service, Food and Drug Administration

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DHEW Publication No. (FDA) 74-3021
U.S. GOVERNMENT PRINTING OFFICE: 1974 - 544-192/ 79

Exhibit "E"

Reprinted from Second Qtr. issue, *Psychosomatics*, 1976, Volume XVII, Number II.

A Procaine Derivative for the Treatment of Depression in an Outpatient Population

MORTON L. KURLAND, M.D. AND MAX HAYMAN, M.D.

In 1946, Ana Aslan of Romania reported her work with procaine hydrochloride in the aged.[1] By 1956 she was utilizing Gerovital H3 and published a provocative paper entitled "A New Method for a Prophylaxis and Treatment of Aging with Novacaine: Eutropic and Rejuvenating Effects."[2] Since that time, thousands of patients have been treated with this compound. There have been innumerable magazine and newspaper stories extolling the value of this treatment in the aged. A promise such as this, contrary to all human experience, rapidly polarized the population into believers and doubters. Among the doubters must be included the medical community. With the dearth of controlled double-blind studies, the work emanating from the Romanian group has been looked at askance by medical workers. This was particularly true since early double-blind studies by English and American workers indicated there was no value to the treatment.

Gericke and coworkers[3] followed two groups of geriatric mental patients whom they treated for two courses with 10 injections of procaine for each course. They found no definite improvement in either group. Kant and Stearne[4] in a double-blind study with procaine hydrochloride treated 20 chronically ill geriatric patients, 10 on active medication, 10 on placebo. They saw no significant differences between the groups. May and coworkers[5], with using procaine hydrochloride, matched pairs of female geriatric psychiatric patients, found no significant difference after one year of treatment according to the Aslan method, but not the Aslan preparation. Fee and Clarke[6] did a one-year controlled study with 10 elderly male and female patients with procaine hydrochloride. No improvements were noted. Berryman and coworkers[7] did a one-year controlled study with female patients. In the 15 procaine hydrochloride patients and 13 control patients, no significant differences were found. Hirsch[8] did an eight-month controlled study with 21 male and female geriatric patients. There was no detectable difference between the 12 procaine hydrochloride and 9 control patients who completed treatment. These were the controlled studies which reported negative results.

Other double-blind studies were more positive. Kral and coworkers[9] carried out a double-blind study with procaine hydrochloride in a group of senile and arteriosclerotic patients with a mean age of 81. There were two groups, a hospital group of 32 with 10 controls and a clinic group of 10 with 10 controls. They reached the conclusion, after 6 to 13 months of treatment, that it was temporarily helpful in the improvement of mood and level of activity, as well as in depressive symptoms. Smigel and coworkers[10] did a double-blind study on 60 patients with arthritis, nervous disorders, and senile mental disturbances. Thirty were in the active treatment group and thirty were controls. Two had allergic reactions in preliminary tests. Patients were treated with 5 cc of GH3 intramuscularly three times a week for four weeks. Four courses were given with ten days intervening. Improvement of some kind compared to 30% of the controls. Improvement in mood, mental attitude, muscle power, arthritis, parkinsonism, cerebral arterio-sclerosis and multiple sclerosis was also reported.

Long and Gislason[11] restricted their study of the effects of procaine hydrochloride to problems of orientation, attention and memory in patients over 65 and selected some severely ill subjects. There were 30 males and 30 females. Theirs was a double-blind one-year study using the Aslan technique although not the Aslan preparation. They found a 45% loss of patients because of the severe illness of the patients and other factors, such as nurses' attitudes. They completed the project with an active group of 17 and a control group of 16. They found significant improvement in orientation, attention and memory. No attempt was made to measure clinical behavioral improvement. The investigators felt that their results lent support to Aslan's thesis.

Abrams and his coworkers,[12,18] in a study of the European procaine preparation, noted that Aslan and her coworkers had no double-blind studies nor controls for the attitude of her staff. They also mentioned that many of the English and American writers who got negative results did not use Gerovital H3, the preparation of the Romanian group. This, they stated, could have altered the therapeutic results. They studied

Desert Psychiatric Medical Group, Palm Springs, California 92262.

Dr. Kurland is Associate Clinical Professor of Psychiatry, USC School of Medicine; Medical Director, Desert Hospital Mental Health Center, Palm Springs, California.

Dr. Hayman is Medical Director, Desert Alcoholism Coalition, Palm Springs, California.

This study was supported by Rom-Amer Pharmaceuticals Ltd. Beverly Hills, California.

such criteria as psychiatric functioning, family estimate, nurses' estimate, and psychological integration. They administered 5 cc of the two different preparations, the European (Gerovital H3) and American (procaine hydrochloride), which were injected intramuscularly three times weekly for four weeks. It was withdrawn for ten days and then repeated. Evaluations were made after six months of treatment. In all phases of the results, the European preparation was significantly better than the American. The improvement was most pronounced in the psychological evaluation where the improvement approached significance.

A very careful study was made recently by Zung and his coworkers.[13] He used outpatients 60 years or over who had depressive disorders which were at least mild in Clinical Global examination. This was a double-blind study of four weeks duration utilizing Gerovital H3, the European preparation. They administered 5 cc three times in the first week and 10 cc three times a week in each of three subsequent weeks. The total dosage was 2100 cc mgm of GH3. Thirty patients completed the study, of whom 9 received GH3, 11 received imipramine and 10 received placebo (sterile saline). The placebo patients showed no significant changes although both GH3 and imipramine patients improved when compared pre versus post treatment; only the GH3 patients' mean change scores were different from that of the placebo treated patients. They reached the conclusion that the treatment differences showed Gerovital H3 superior to imipramine.

MODE OF ACTION

Gerovital H3 has been demonstrated by Hrachovac,[14] MacFarland,[15] and MacFarland and Besbris[16] to produce a dose-dependent inhibition of monoamine-oxidase (MAO). This effect was greater than simple procaine hydrochloride, though weaker than iproniazid. Gerovital H3 retards the oxidation of procaine hydrochloride, permitting a more prolonged action. GH3 is essentially procaine with benzoic acid as a preservative and metabisulfate as an antioxidant.

GH3 is a reversible and competitive MAO inhibitor and is a contrast to present irreversible MAO inhibitors. This helps explain the absence of severe adverse reactions of GH3 as compared to other MAO inhibitors in the treatment of depression, such as tranylcypromine (Parnate).

Robinson and colleagues[17] have speculated that since MAO activity increases with age, this might be a factor in the development of depression and explain the benefits of MAO inhibition in the aging.

We are presenting a rather simple, uncomplicated double-blind study which we hope will eliminate some of the ambiguities found in previous studies.

STUDY OBJECTIVE

The purpose of the study was to evaluate the therapeutic efficacy and safety of Gerovital H3 (GH3) in the treatment of mild to moderate depressive disorders in an outpatient population.

MATERIALS AND METHODS

Patient Selection

Suitable for consideration for the study were outpatients 45 years old and over, men and women, who had depressive disorders of at least mild severity. This was determined by using a Clinical Global Impression (CGI) scale of 1 to 7, with 3 = mildly ill.

The following patients were excluded from the study: (1) patients incapable of spontaneous conversation and activity; (2) patients who were severely demented; (3) patients who were schizophrenic or had evidences of a thought disorder; (4) patients who had diabetes, tuberculosis or cancer.

Each patient was informed he was the subject of a double-blind study and that he might not receive the active medication.

Patients were to be free of major psychotropics (phenothiazines, tricyclic antidepressant and MAOI) for ten days, and to be free of minor tranquilizers (meprobamate, benzodiazepines) for 3 days.

It should be noted that our study differed from others in that we accepted patients from age 45 up. Thus we eliminated some severe organic brain deteriorated states. All were outpatients and ambulatory and, therefore, in probably better condition than many of the patents utilized in previous studies. All of the patients were extremely cooperative as indicated by the fact that only one patient dropped out of the study and he was a control patient.

All patients suffered from depression. The types of depression are as follows:

Neurotic Depression	16
Manic-Depressive Reaction	4
Reactive Depression	22
Depression with Organic Brain Syndrome	6
Chronic Depressive Reaction	16
Alcoholism with Depression	

Study Drugs

Gerovital H3 (GH3) was supplied in 5 cc ampules each containing 100 mg. of 2% procaine hydrochloride manufactured in Romania. Placebo in the form of normal saline was supplied in matching ampules.

Study Design

All patients were skin tested for potential sensitivity to GH3 prior to the administration of test preparations. This procedure was carried out by injecting 0.1 cc of known GH3 intradermally. This double-blind study was 4 weeks in duration. All patients received I.M. medication using the following schedule:

Week 1 — 5 cc, 3 times a week. Weeks 2, 3 and 4 — 10 cc (two 5 cc ampules) 3 times a week.

This is equivalent to a total dosage of 2100 mg. of procaine hydrochloride.

The coding and decoding were done by an outside source, and the investigators received coded kits to preserve the double-blind nature of the study. The coded kits were prepared under the supervision of Sidney Cohen, M.D., Professor of Psychiatry, Neuropsychiatric Institute, University if California at Los Angeles, Los Angeles, California.

Patient Evaluation

Patients were evaluated psychiatrically and a diagnosis and a Clinical Global Impression (CGI) of the severity of their illness pre-treatment established. Patients were also evaluated for depressive disorder using the Hamilton Rating Scale for Depression (HRD), and the Zung Self-rating Depression Scale (SDS).

Ratings for CGI, HRD and SDS were repeated weekly and at the end of the treatment period. In addition, a series of examinations were performed before and after the test trials (physical examinations, blood chemistries, blood counts and urinalysis).

RESULTS

A total of 64 patients were studied. One patient dropped out of the study. Of the 63 patients who completed the study, 33 received GH3 and 30 received placebo. Tables 1 and 2 summarize the data collected. In the GH3 group 22 women and 11 men whose ages ranged from 45 years old to 81 (m = 58.5). There were in the placebo group 10 women and 20 men whoses ages ranged from 45 years old to 83 (m = 58.9).

All patients received the scheduled dosage of 21 5 cc injections.

Statistical Analyses

Statistical analyses using the T-test, two-tailed, were performed on the three variables measured (CGI, HRD and SDS) for within group comparison (pretreatment versus post-treatment), and for between group comparisons (GH3 versus placebo).

TABLE 1

Sex, Age and Individual Scores on the Clinical Global Impression, Hamilton Rating for Depression, and Self-Rating Depression Scale for Patients treated with GH3.

Ss#	Sex	Age	CCI		HRD		SDS	
			Pre-	Post-	Pre-	Post-	Pre-	Post-
1	F	47	5	2	68	26	92	34
2	F	47	5	1	55	25	64	38
3	M	51	5	2	62	33	59	58
4	F	69	5	1	58	26	45	39
5	F	57	5	3	67	45	54	39
6	M	54	6	2	66	29	76	54
7	F	61	5	3	62	34	76	51
8	F	63	4	2	47	25	56	41
9	F	62	5	2	54	26	78	38
10	F	60	7	5	75	52	78	38
11	F	50	6	6	59	55	53	41
12	F	58	3	1	49	26	44	28
13	F	48	4	2	45	26	44	38
14	F	68	4	4	47	47	50	59
15	F	76	4	2	58	30	63	50
16	M	56	6	7	70	76	54	70
17	F	53	3	3	54	42	33	36
18	M	61	6	5	81	58	90	83
19	F	55	4	4	63	52	55	59
20	M	56	5	2	74	29	81	49
21	M	66	5	1	63	27	63	58
22	F	76	5	2	57	35	53	48
23	M	63	4	2	62	30	75	61
24	F	71	5	1	64	28	83	29
25	M	48	4	2	57	35	50	53
26	F	50	4	2	54	32	48	30
27	M	55	3	2	40	32	55	35
28	M	45	3	1	50	29	38	30
29	F	75	4	4	54	51	79	66
30	F	49	4	3	69	51	69	46
31	F	53	3	3	47	41	49	34
32	M	81	4	1	57	30	60	68
33	F	46	4	3	52	35	51	30
m	F-22	58.5	4.5	2.5	53.8	36.9	61.5	47.1
s.d.	M-11		1.0	1.5	9.4	12.3	15.5	14.0

TABLE 2

Sex, Age and Individual Scores on the Clinical Global Impression, Hamilton Rating for Depression and Self-Rating Depression Scale for Patients Treated with Placebo

Ss#	Sex	Age	CCI		HRD		SDS	
			Pre-	Post-	Pre-	Post-	Pre-	Post-
1	M	46	3	3	51	38	58	38
2	M	54	5	6	51	60	63	61
3	M	58	6	5	70	58	74	61
4	M	62	5	4	68	54	74	61
5	M	64	5	6	64	73	64	74
6	M	52	4	5	60	56	65	69
7	F	51	4	4	61	55	51	54
8	M	61	3	3	42	36	40	36
9	M	58	4	4	57	48	53	53
10	F	45	5	1	60	26	66	38
11	M	65	3	3	44	40	48	28
12	M	59	4	4	47	50	66	35
13	M	83	5	2	63	29	61	44
14	F	55	5	5	65	58	71	66
15	F	60	4	4	51	50	51	56
16	M	47	4	4	55	48	46	51
17	M	64	5	4	68	63	66	75
18	F	55	4	4	58	56	65	64
19	M	69	3	3	41	40	68	54
20	F	55	4	4	51	46	48	53
21	F	65	5	5	66	64	79	65
22	M	61	4	4	53	56	44	53
23	F	47	5	5	64	58	69	56
24	M	49	4	3	54	39	75	44
25	F	61	4	4	55	51	59	38
26	M	73	4	4	51	55	60	58
27	M	52	6	5	67	59	91	84
28	M	63	4	5	51	61	51	51
29	M	72	5	5	55	60	58	56
30	F	61	4	4	45	43	58	56
m	F-10	58.9	4.3	4.0	55.3	51.0	61.7	54.4
s.d.	M-20		0.8	1.1	8.2	10.8	11.4	12.9

Product moment correlations were also performed.

Table 3 summarizes the data on the GH3 treated patients with respect to their pre-treatment and post-treatment results. These patients improved with treatment using GH3 on all three variables measured (CGI, HRD, SDS) at a significant level, with p = less than .001.

Table 4 summarizes the pre and post-treatment results of the placebo treated group. These patients did not improve significantly on the CGI, with p = greater than .05. Of the other two variables measured (HRD, SDS), there was a demonstrated placebo effect with the patients showing improvement up to the .005 level of significance.

Table 5 summarizes the T-tests comparing GH3 treated versus placebo treated patients for their Clinical Global Impression (CGI).

At pre-treatment, the CGI scores for the two groups are not significantly different. At the end of the treatment period, the GH3 group improved significantly over the placebo group with p = less than .01. A change score (difference between pre-treatment and post-treatment) was calculated and a T-test was done on the change scores. The GH3 treated group showed greater improvement, which was significant with p = less than .001.

Table 6 summarizes the T-tests comparing GH3 treated versus placebo treated patients using the Hamilton Rating Scale for Depression (HRD).

At pre-treatment time, the HRD scores for the two groups are not significantly different, with both groups manifesting equivalent psychopathology. At the end of the treatment period, the GH3 group improved significantly over the placebo group with p = less than .01. A change score was calculated and a T-test performed. The GH3 group showed significantly greater improvement, with p = less than .001.

Table 7 summarizes the T-tests comparing GH3 treated versus placebo treated patients using the Zung Self-rating Depression Scale (SDS).

At pre-treatment, the SDS scores for the two groups are comparable and not significantly different, with p = greater than .05. At the end of the treatment period, the GH3 group showed greater improvement which was significantly different, with p = less than .05. A change score was calculated and a T-test performed. The GH3 group showed greater improvement than did the placebo group. This improvement is significantly different using a one-tail T-test, at the .05 level.

Correlations

Table 8 summarizes the correlations calculated for the three variables measured (CGI, HRD, SDS), for

TABLE 3

T-Tests Comparing Pre- and Post-Treatment Variable Measured of Patients Treated with GH3, N=33

VARIABLE	Pre-Treatment m	(s.d.)	Post-Treatment m	(s.d.)	t	P
CGI	4.4	(0.9)	2.4	(1.4)	7.2938	<.001
HRD	57.5	(9.4)	36.0	(12.1)	9.9791	<.001
SDS	61.4	(15.5)	47.3	(13.8)	4.8447	<.001

TABLE 4

T-Tests Comparing Pre- and Post-Treatment Variables Measured of Patients Treated with Placebo, N=30

VARIABLE	Pre-Treatment m	(s.d.)	Post-Treatment m	(s.d.)	t	P
CGI	4.3	(0.7)	4.0	(1.0)	1.6090	n.s.
HRD	54.9	(7.7)	49.7	(10.7)	2.6758	<.02
SDS	61.6	(11.4)	54.4	(12.9)	3.3193	<.005

HRD 0 SDS 0 CGI 28 HRD 28 SDS 28

TABLE 5

T-Tests Comparing Clinical Global Impression (CGI) Between the Two Treatment Groups

	GH3 m	(s.d.)	PLACEBO m	(s.d.)	t	P
CGI PRE	4.4	(0.9)	4.3	(0.9)	0.2963	n.s.
CGI POST	2.4	(1.4)	4.0	(1.0)	4.7884	<.001
CGI CHANGE SCORE	2.0	(1.5)	0.3	(1.1)	4.5964	<.001

TABLE 6

T-Tests Comparing Hamilton Rating Scale for Depression (HRD) Between the Two Treatment Groups

	GH3 m	(s.d.)	PLACEBO m	(s.d.)	t	P
HRD PRE	57.5	(9.4)	55.1	(7.7)	1.0300	n.s.
HRD POST	36.0	(12.9)	49.7	(10.0)	4.4949	<.001
HRD CHANGE SCORE	21.5	(11.6)	5.2	(10.3)	5.5977	<.001

TABLE 7

T-Tests Comparing Self-Rating Depression Scale (SDS) Scores Between the Two Treatment Groups

	GH3 m	(s.d.)	PLACEBO m	(s.d.)	t	P
SDS PRE	61.4	(15.5)	61.6	(11.4)	0.0525	n.s.
SDS POST	47.3	(13.8)	54.4	(12.9)	2.0873	<.05
SDS CHANGE SCORE	14.1	(16.7)	7.2	(11.9)	1.8630	<.05*

* one-tailed t-test

TABLE 8

Correlation of Variables Measured for All Patients Studies, N=63.

CGI 0	77	58	29	27	46
HRD 0		61	21	28	50
SDS 0			09	10	41
CGI 28				94	57
HRD 28					64

All decimals have been omitted and r values that are not significant at the .05 level are underlined.

TABLE 9

Analysis of Covariance of Measured Variables

Clinical Global Impression (CGI)	F	P
Gerovital H3 versus placebo	26.7645	<.001
Hamilton Rating Scale for Depression (HRD)	**F**	**P**
Gerovital H3 versus placebo	23.8841	<.001
Self-rating Depression Scale (SDS)	**F**	**P**
Gerovital H3 versus placebo	5.6843	<.03

pre-treatment (day 0) and post-treatment (day 28).

There is a significant correlation between the CGI, HRD and SDS scores at pre-treatment and post-treatment. There is also significant correlation between the HRD and SDS, both at pre-treatment and post-treatment.

Adverse Reactions

The following table is a summary of *all* adverse reactions noted during the study:

ADVERSE REACTIONS

TREATMENT GROUP	Sweating	Dizziness	Tremor	Palpitation	Muscle Pain
GH3					
Ss + #8	1			1	2
#56		1	1		
PLACEBO					
Ss + #42	2	2		2	

Severity rating of adverse reactions: 1 = mild, 2 = severe.

Ratings that are underlined were thought to be attributed to the drug.

CONCLUSIONS

A double-blind study comparing Gerovital H3 against placebo in an out-patient private practice population with diagnoses of depressive disorders was performed. Using a random design, 63 patients were studied whose ages ranged from 45 years old to 83. Psychometric variables used at pre-treatment and post-treatment intervals included the Clinical Global Impression, Hamilton Rating Scale for Depression, and the Zung Self-rating Depression Scale.

The total dosage for patients who were in the Gerovital H3 treated group was 2100 mg of procaine hydrochloride.

Statistcial analyses using the T-test were performed. The results demonstrated that Gerovital H3 was significantly better than placebo on all three variables measured. This was true for comparisons made within the two treatment groups for pre-treatment and post-treatment scores, and for comparisons made between the two treatment groups, and for the change scores between groups (Gerovital H3 versus placebo). Various examinations pre- and post- treatment were done and will be reported later.

A tabulation of adverse reactions showed minimal side effects reported for both the Gerovital H3 treated and placebo treated groups.

We conclude from the data presented that Gerovital H3 is an efficacious drug in the treatment of mild to moderate depressive disorders in an adult population. Furthermore, we have noted no sensitivity nor significant complications nor side effects.

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160 Luring Drive, Palm Springs, CA. 92262.

Acknowledgment: We are indebted to William W.K. Zung, M.D., for the statistical and computer studies in this paper.

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Printed in U.S.A.

Exhibit "E-1"

Honorable Alan Cranston
United States Senate
Washington, D.C. 20510

NOV 16 1976

Dear Senator Cranston:

This is in reply to your letter of July 2, 1976, concerning the drug Gerovital H3, and the letter of June 4, 1976, to Senator Kennedy, from Alfred T. Sapse, M.D., former President of Ron-Amer Pharmaceuticals, Ltd., the U.S. sponsor of investigational studies with this drug. We apologize for the delay in our response to you which was due in part to the fact that we were in the process of reaching an internal decision on requirements for further investigational study of this drug.

Some brief background may be helpful to your understanding of the issues involving this drug. Gerovital H3 is procaine hydrochloride. Procaine hydrochloride has been marketed as an injectable local anesthetic by many firms for many years in the U.S. It is sold under brand names as well as its generic name of procaine hydrochloride.

Gerovital H3 is the trade name for the product promoted by Dr. Ana Aslan of Rumania as being effective in treatment of the various manifestations of the aging process. Patients come from all over the world to the various treatment centers in Rumania which specialize in the use of Gerovital H3. Many articles have appeared in the lay press in the U.S. on the use and effectiveness of Gerovital H3 as a rejuvenant in elderly individuals. It was claimed by Dr. Aslan that Gerovital H3 is not ordinary procaine hydrochloride but that it has special qualities by virtue of its compounding. As far as we can determine, the drug is identical to procaine hydrochloride as we know it in the U.S. Ron-Amer agreed with us on this point in the meeting held at the Food and Drug Administration (FDA) on May 17, 1976, to which Dr. Sapse alludes in his letter of June 4, 1976.

Several years ago, Ron-Amer submitted a Notice of Claimed Investigational Exemption for a New Drug (IND) to FDA for permission to study Gerovital H3 in depression in elderly patients. Mental depression, as you know, occurs in people of all ages. The drugs currently used for its treatment can cause serious adverse reactions in some individuals. Procaine hydrochloride is a rather safe drug when used in appropriate doses and in patients who are not allergic to it. Consequently, FDA was genuinely

interested in ascertaining whether the drug is effective in the treatment of mental depression, and various scientists in FDA's Division of Neuropharmacological Drug Products spent considerable time advising the sponsor on appropriate study designs. (It should be noted that the sponsor was quite naive with respect to designs for adequate and well-controlled studies.)

While these studies were continuing, publicity claiming remarkable rejuvenating properties for the drug also was continuing. It was entirely reasonable to conclude that the public, and perhaps practicing physicians, might become persuaded that the drug was useful in altering the aging process itself, even though it was being studied only as an antidepressant in the elderly. Further, an effect on the aging process also would be implied by the trade name, Gerovital H3, i.e., vital old age, a name which the U.S. sponsor, Rom-Amer, had no intention of changing and was using in its investigational studies. In addition, although mental depression is not restricted to the older age group, and there is no obvious reason to believe that a drug effective in mental depression in an elderly individual would not also be effective in a young or middle-aged adult, Rom-Amer made no move to extend its studies to younger patients.

All of these factors led to a concern on our part that the studies of Gerovital H3 be directed at the true indication for the drug, and that if the drug was intended for broad, vague "geriatric" use, such use be investigated. When we became aware of reports in the lay press of plans to dispense the Rom-Amer product in the U.S. through a network of health resorts, we felt it desirable to express our concern and to meet with Rom-Amer representatives to discuss the firm's future plans. A copy of our April 6, 1976 letter to the firm is enclosed.

The proffered meeting was held on May 17, 1976. Following the meeting, FDA considered its position on further clinical studies by Rom-Amer with procaine hydrochloride. A letter issued to the firm on August 6, 1976 (copy enclosed) advises that we are prepared to permit continued clinical trials for the indication of "depression" without additional requirements for studies in various conditions associated with aging. This decision was based on our feeling that, absent evidence that Rom-Amer is responsible for the extravagant publicity surrounding Gerovital H3, it would have been unreasonable for the Agency to require that the extravagant claims be tested. However, in order for the firm to continue studies in depression, we imposed a number of conditions required by the law and regulations and dictated by good science, including extension of studies to younger depressed patients and use of the established name, procaine hydrochloride.

I should like to address myself to the contents of Dr. Sapse's letter of June 4, 1976 to Senator Kennedy, because it contains many misunderstandings, unfounded allegations, and undocumented scientific conclusions on the part of Dr. Sapse.

In the first place, although Rom-Amer has vowed that its only interest in Gerovital H3 is to determine whether the drug is effective in treatment of mental depression in the elderly, even a casual reading of the first few pages of Dr. Sapse's letter leaves no doubt as to his true feelings concerning the indications for use and the value of this drug, although he does temper his remarks somewhat by stating that the broad claims for Gerovital H3 may be largely due to its antidepressant properties. He states that "With Gerovital H3, and later, other procaine-based products, the era of geriatrics began - meaning an era of healthier, happier aging...." There are no adequate scientific studies to our knowledge which would support this claim. Although Dr. Sapse admitted in our May 17, 1976 meeting that Gerovital H3 is no different from the well-known local anesthetic procaine hydrochloride, in his letter to Senator Kennedy he refers to Gerovital H3 only as a "procaine-based" product. We also find his equating of the importance of the therapeutic "break-through" provided by Gerovital H3 to that of the life-saving drug penicillin thoroughly unfounded.

Dr. Sapse's letter implies that the clinical studies supported by Rom-Amer in the U.S. have shown that procaine hydrochloride is indeed effective as an antidepressant. This conclusion is premature. While there is some preliminary evidence that this may be so, methodologic flaws in the studies prevent any definitive conclusions and much additional work is required to determine whether or not the drug is effective. Furthermore, the dosages used in the clinical trials to date were chosen empirically by the firm and its investigators, based upon the dosages in widespread use in Rumania for the treatment of the aging process. Accordingly, as indicated in our letter of August 6, 1976, to the firm, studies of additional doses are needed to determine the appropriate dose for the claimed indication of depression.

Dr. Sapse, on page nine of his letter to Senator Kennedy, quotes two sentences out of context from our letter to Rom-Amer of April 6, 1976. Specifically, the quote "We will be unwilling to approve procaine HCl as an anti-depressant solely for use in the elderly" is used by Dr. Sapse to imply that the FDA had determined that it would never approve the drug for marketing for that use when actually our letter stated: "We would be unwilling to approve procaine HCl as an antidepressant solely

for use in the elderly, since younger patient populations do suffer from depression, unless evidence were presented that the drug has a unique antidepressant effect in this age group."

The other quote taken out of context by Dr. Sapse, "your drug product be demonstrated to be safe and effective in some definable way in altering the aging process...before it can be approved for marketing" was used by him to imply that a decision had been made by FDA that indeed this was a condition for approval for marketing of Gerovital H3 when, in actuality, the aforementioned sentence was preceded by the words "Consideration is being given to a requirement that your drug product..." etc. This consideration was the basis for our request for a meeting with Rom-Amer to discuss the firm's plans with respect to further studies and its understanding of how it proposed to market the drug. As noted above, our request was based on a well-founded concern that the drug might be studied as an antidepressant but promoted as a panacea for the illness of the aged.

On page 12 of his letter Dr. Sapse states that Dr. Crout "is angry" that Rom-Amer was not able to "police" the American press and prevent it from publishing material about Gerovital H3. In fact, Dr. Crout never stated or even implied that Rom-Amer could prevent publications in a free press. Dr. Crout's point was that the articles appeared to be intended to create an expectation in the minds of the public that Gerovital H3 is particularly useful in the aged, and if Rom-Amer expects to market the drug with such a claim, then the law requires that appropriate studies be done in support of this claim.

On page 13 of his letter, Dr. Sapse alleges that Dr. Crout "...feels that Gerovital H3 should not be approved in the United States at all." This is a patently false statement. The conditions under which the Bureau of Drugs feels the drug should be investigated for potential marketing are stated in the enclosed letter of August 6, 1976 from Dr. Crout to Dr. Manfred Mosk of Rom-Amer.

On pages 13 and 14, Dr. Sapse alleges that Dr. Crout has behaved entirely differently when a large pharmaceutical company is involved and he cites, as an alleged example, a case in which Dr. Crout rejected the advice of an FDA advisory committee not to approve a new indication for a drug which had "negative effects to (sic) the patient," and, then stated to the drug firm that the advisory committee had recommended approval. This allegation is entirely false. The drug to which Dr. Sapse apparently alludes is Inderal (propranolol), a drug marketed for several indications. The specific indication of concern to

Dr. Sapse is angina pectoris. FDA's Cardio-Renal Advisory Committee recommended inclusion of this indication in labeling of this drug and Dr. Crout concurred with the Committee's recommendation.

On pages 14 and 15 of his letter, Dr. Sapse alleges that FDA officials, when another pharmaceutical firm appeared to be interested in entering into an agreement with Rom-Amer on eventual marketing of Gerovital H3, recommended that the firm "stay away" from the drug because FDA had no intentions of approving Gerovital H3 in the U.S. This allegation is a total fabrication by Dr. Sapse. The members of the Division of Neuropharmacological Drug Products, who met with the pharmaceutical firm (Carter-Wallace), informed the firm of certain potential difficulties which it might encounter if the drug were approved for marketing. A copy of the minutes of that meeting is enclosed.

Finally, Dr. Sapse indicates that the hopes of 32 million Americans over the age of 60 to enjoy a "happier, healthier aging" are dashed because Gerovital H3 will not be available. As I have tried to make clear, we are willing to approve the drug for mental depression provided there is adequate evidence of safety and effectiveness for such use and provided the drug is labeled as required by law with the established name, procaine hydrochloride, and with a brand name which is not false or misleading.

If we can provide any further information, we would be pleased to do so.

Sincerely yours,

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

Enclosures
Cy Crout/Rom-Amer ltr. 4/6/76
Cy Crout/Rom-Amer ltr. 8/6/76
Memorandum of Conference 12/12/75
Constituent's Ltr.
cc: Congressional Liaison Office

cc: HFL-10 (2) (w/cy inc)
HFD-1
HFD-2
HFD-100
Drafted by:HFD-100/MFinkel/jmb/9/13/76
Revised by:RTemple/9/13/76 and R. Crout 9/22/76
Init:PJSavino:9/24/76
MFromer:9/27,28/76
R/D:MFromer:11/11/76
f/t:vbw:MAG II: 11/11/76

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

IND 6691
10,635

APR 6 1976

Rom-Amer Pharmaceuticals, Ltd.
Attention: Alfred T. Sapse, M.D.
233 South Beverly Drive
Suite 100
Beverly Hills, California 90212

Gentlemen:

There have been a number of reports in American publications which discuss the future availability of Cerovital for the treatment of various ailments related to the aging process. For example, there have been reports, inter alia, in the Detroit Free Press, August 17, 1975; Argosy, August, 1973; and the TWA Ambassador Trans World Magazine, September 1975.

We have reviewed the protocols and development of clinical data in INDs 6691 and 10,635. These provide for the study of procaine HCl in the treatment of depression in an elderly population. As you are aware, procaine HCl differs substantially from the antidepressant drugs currently approved, both in chemical and pharmacologic properties. None of them is limited to use in the elderly. We would be unwilling to approve procaine HCl as an antidepressant solely for use in the elderly, since younger patient populations do suffer from depression, unless evidence were presented that the drug has a unique antidepressant effect in this age group. In addition, we would be unwilling to extrapolate evidence of antidepressant effect in the elderly to non-elderly patients in the absence of clinical trials which demonstrate that such an extrapolation is valid. The appropriate method for so demonstrating would, of necessity, require the performance of controlled clinical trials in patient populations other than the elderly. But the choice of populations for study of antidepressant effects is not our primary concern in writing to you at this time.

We find that the principal usage of your drug product as marketed abroad is in the prophylaxis and treatment of symptoms and manifestations associated with the aging process. Usage in Europe has been exclusively for these purposes, and it was our concern with this aspect which prompted our letter of December 19, 1975 regarding use of the European trade name for your products. Thus, if the drug were found to be safe and effective for the treatment of depression and were so labeled, we have no doubt that, based upon the reported European experience and the plethora of published articles similar to those referenced above, the major use of your products

uld be for the aging process. There have been reports of plans to dispense the Ron-Vuer brand of procaine HCl in the United States through a network of health resorts or facilities whose clientele would, in effect if not by intention, be restricted to older individuals interested in treatment for aging. Inquiries reaching the Bureau from persons wishing to receive treatment with your products under the I.D protocols attest to the widespread interest in this drug and indicate that the public perception of its use is for other than antidepressant effects.

Accordingly, I request that you meet with us to review the status of your research studies and investigations to date. We are interested in your plans for further studies and marketing for this drug. This meeting would not be viewed by the Bureau of Drugs as marking the end of Phase II.

We believe that the investigational goal should reflect what is clearly the principal intended usage of your product - the effect of the drug on aging. Consideration is being given to a requirement that your drug product be demonstrated to be safe and effective in some definable way in altering the aging process before it can be approved for marketing. Since such studies would undoubtedly require larger numbers of patients participating in controlled trials for an extended period of time, we request that you be prepared to participate in at least a preliminary discussion of the effect of this projected requirement on your drug investigatory efforts at the meeting which is scheduled for April the fourteenth with Dr. Finkel.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

IND 8681
IND 10,685

AUG 6 1976

Roa-Amer Pharmaceuticals, Ltd.
Attention: Manfred Fesk, Ph.D.
233 South Beverly Drive
Suite 100
Beverly Hills, California 90212

Gentlemen:

Reference is made to your Notices of Claimed Investigational Exemption for a New Drug for procaine hydrochloride Injection and Tablets, INDs 8681 and 10,685 respectively. We also refer to your letter dated June 25, 1976.

As requested at the conference between representatives of your firm and this Administration on May 17, 1976, we have given further consideration to the requirements for testing of your drug products prior to possible approval for marketing, and we have reached the following conclusions in this matter.

Should procaine hydrochloride prove to be a safe and effective drug in the management of depression, it would provide an alternative choice for the physician among the currently approved drugs for this disorder. Consequently, we are prepared to permit continued clinical trials with procaine hydrochloride for the management of depression, without additional requirements that the drug be studied in various conditions associated with aging.

There are certain conditions, however, which must be fulfilled by your firm relative to the continuation of clinical trials in depression:

1. Since your drug products are not intended to be used for, nor have they been shown to be effective in, the aging process, they cannot be referred to, or labeled as, Gerovital. To do so would cause these products to be misbranded. (See section 502(a) of the Food, Drug, and Cosmetic Act.)

2. It appears that the composition of your injectable product fulfills the criteria established by the U.S. Pharmacopeia XIX for Procaine Hydrochloride Injection. Accordingly, as required by Sections 501(b) and 502(e) of the Food, Drug, and Cosmetic Act, we request that you:

a. Perform, or assure that your supplier performs, all of the tests and assays required by the U.S.P. XIX monograph for Procaine Hydrochloride Injection and the General Tests and Assays required for injections as described in U.S.P. XIX.

b. Label your injectable product prominently as Procaine Hydrochloride Injection USP, 2%. In this connection, your letter of June 25, 1976, stated that, instead of Gerovital H$_3$ you would now label the drug as PA-3. Possibly you are thinking of this as a trade name. We believe it inappropriate to consider trade names at this stage of the investigation.

c. State all of the ingredients on the label, including the inactive ingredients and all other information as required by 21 CFR Section 201.100.

d. State on the label (since you are performing double blind studies), that "This vial contains either Procaine Hydrochloride Injection USP, 2%, or a placebo."

e. Add to the label the statement: "Caution - This drug product is limited by United States law to investigational use."

f. Add to the label the appropriate study number.

3. Since procaine hydrochloride tablets are not the subject of a USP monograph, this product should be labeled as follows: "Procaine Hydrochloride Tablets - 100 mg."; the statement "Caution: New Drug - Limited by United States law to investigational use"; the lot number; the study number; and the statement "This bottle contains either Procaine Hydrochloride, 100mg. per tablet, or placebo."

4. The patient codes for the double-blind studies should be in the form of individual sealed labels prepared in a manner which would make it obvious whether any of the seals had been tampered with. The sealed labels should be returned to your firm at the completion of the studies.

5. As required by 21 CFR Section 312.1(a)(2) we request that you prepare an investigator's brochure which informs the investigator of the nature of the drug he is investigating, the relevant hazards of the drug and the results of the clinical trials to date with regard to the treatment of depression.

6. So that we may be certain that patients are being adequately informed about the investigational drug studies, as required by Section 505(i) of the Act and 21 CFR 310.102, we request that you prepare a patient informed consent form to be used by each investigator which informs the patient of the name and nature of the drug he may be receiving in the clinical trial, any relevant hazards of the drug, the nature of the proposed clinical trial, including the fact that it is placebo-controlled (or controlled with a known active drug, if applicable) and a statement that the patient may withdraw from the study at any time. This form (suitably modified depending upon the protocol) should be signed by each patient who participates in a clinical trial and should be dated and witnessed.

7. There is no current evidence which would lead one to believe that procaine hydrochloride, should it be found to be effective in depression, is specifically indicated only in depression in elderly patients. Accordingly, it will be necessary to revise your protocols to include study of depression in young and middle-aged adults.

8. Good therapeutic principles dictate that patients be treated, with the lowest dose which provides both effectiveness and maximum safety. At the same time it is desirable to ascertain a range of effectiveness so that the highest safe and effective dose is also determined. This provides the prescribing physician with optimum information on appropriate dosage regimens. See page 23 of the enclosed FDA Guidelines entitled "General Considerations for the Clinical Evaluation of Drugs". Accordingly, it will be necessary (1) to study dosage regimens other than those you have previously used in order to determine the lowest effective dose and the maximum interval of administration; (2) and to perform dose response studies.

9. We have recently become aware (material presented at the Control Substances Advisory Committee, April, 1970) that Procaine HCl has reinforcing properties in regard to self-injection in primates. We are unaware of any clinical studies which might elucidate reinforcing properties in man. We therefore will require clarification through clinical studies of these issues.

10. Copies of the new labels, the investigators' brochure, patient informed consent form and revised clinical protocols should be submitted before proceeding with any new studies.

We are also enclosing a copy of the draft guidelines for the study of antidepressant drugs prepared by our Psychopharmacology Advisory Committee. We hope these will prove helpful.

[illegible]

If further clarification of any of the above requests is required, please contact Dr. Thomas Hayes, Group Leader, Psychopharmacologic Drug Group, Division of Neuropharmacological Drug Products, Bureau of Drugs.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

MEMORANDUM OF CONFERENCE

PRESENT:	Dr. Joseph Harun	Carter-Wallace
AND:	Dr. Scoville	FDA
	Dr. Hayes	
	Dr. Glocklin	
	Dr. Rosloff	
	Mr. Cinque	
	Mr. Hajarian	

SUBJECT: IND 8681, 10,685 - Gerovital H_3

DISCUSSION:

Carter-Wallace Labs. is exploring the possibility of investigating Gerovital H_3 through a secrecy agreement with Rom-Amer Pharmaceuticals, Ltd. the only sponsor of an IND for this drug.

We stated that since we had no official letter of authorization from Rom-Amer, we could only discuss abstract issues.

It was emphasized that extensive clinical studies were needed to determine substantial evidence of efficacy for clearly defined conditions.

The firm was alerted of potential difficulties in marketing the drug if approved:

1. The trade name Gerovital H_3 would probably not be acceptable if the drug is approved only for mild depression.

2. The indiscriminate use of the product for non-approved indications.

The firm promised to get a letter of authorization from Rom-Amer in order to discuss specific aspects of the IND's.

Gerald R. Hajarian

Gerald R. Hajarian
Consumer Safety Officer

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Exhibit "F"

ALFRED T. SAPSE, M.D.
420 NORTH PALM DRIVE
BEVERLY HILLS, CALIFORNIA 90210
U.S.A.

G. R. HAJARIAN
HF9-120

June 4, 1976

Sen. Edward M. Kennedy
Chairman
Senate Health Sub-Committee
Washington, D.C.

Dear Senator Kennedy:

Allow me to introduce myself. My name is Alfred T. Sapse, M.D. From June 1971 to May 18, 1976, I was President of Rom-Amer Pharmaceuticals, Ltd., a small research and development company in the field of geriatric drugs. The purpose of this letter, Senator Kennedy, is to bring to your attention what I feel is a grave injustice which has been perpetrated against this Company by the Food and Drug Administration - an injustice which ultimately led to my resignation as President and Director.

I offered my resignation reluctantly, after 5 years of dedicated service, so that I would be free to bring this injustice to the attention of persons such as yourself, Senator Kennedy, as well as to the American people at large. I want to emphasize the fact that in writing this letter, I do not represent or engage in any way Rom-Amer Pharmaceuticals, Ltd. I do this on my own initiative, and I am taking full responsibility for its contents.

In this letter I want to acquaint you with certain activities and actions directed against Rom-Amer Pharmaceuticals, Ltd. by Dr. J. Richard Crout, M.D., Director of the Bureau of Drugs.

Should the facts enumerated below provide enough background for this action, I respectfully request a full investigation into Dr. Crout's activities and actions be taken by the Senate Health Subcommittee.

Rom-Amer Pharmaceuticals, Ltd. was formed as a private company in 1970. It went public in November 1971, after acquiring from a foreign trade agency of the Romanian government the rights to distribute the drugs Gerovital H_3 in the United States. Early in 1972, in order to pass the U.S. FDA regulations, a requirement of that acquisition, the Company started the Gerovital H_3 injectable research program. What follows is the story of Rom-Amer's relations with the Food and Drug Administration between 1972 and April 1976 in connection with this research program.

Gerovital H_3 is a procaine based drug that was developed twenty-three years ago by Dr. Ana Aslan, Professor of Medicine, and Director of the Geriatric Institute of Bucharest, Romania. In the 1950s extraordinary claims were made for the new drug - ranging from slowing down or reversing some of the manifestations

of aging, to later, lesser claims of alleviating some of the miseries of aging; such as depression, pain, etc.

Due to these claims, a controversy developed around Gerovital H_3, a controversy which is, in fact, still going on today. In spite of the fact that the drug has been in existence for twenty-three years, and also in spite of the controversy around it, the use of Gerovital H_3 spread slowly all over the world, until it is presently used by millions, especially by those in the 60+ age bracket. It has also been approved by most FDA equivalents in the world, including those in France, Germany, Switzerland, the United Kingdom and others.

During the stages of its formation, the Company knew that getting Gerovital H_3 approved in the U.S. would not be an easy task. We also knew that it was not the first time that a drug had fought hard to gain acceptance. Penicillin, discovered in 1928, was scorned for many years before it was finally accepted. Penicillin, after its approval, opened a new era in medicine, the era of antibiotics. With Gerovital H_3, and later, other procaine-based products, the era of geriatrics began - meaning an era of healthier, happier aging - at least for most of the world if not for the United States. My connection with GH_3 started years before - in Romania in the 1950s - when I was involved with the early testing of this drug and had a chance to watch the results.

In 1971, two scientists from the University of Southern California (U.S.C.) reported developing some preliminary evidence that might shed some light on one of the pharmacological actions of Gerovital H_3 and explain its broad range of claims. After reviewing this research data, representatives of the Company approached the FDA to inquire about the possibility of submitting an Investigational New Drug (IND) application, and to find out what claim would be acceptable to the FDA. At that meeting, in Washington, D.C., we met Dr. Barrett Scoville, Acting Director, Division of Neuropharmacological Drugs, Dr. Alice Campbell and others. The meeting was important to the Company - we were gratified to hear from Drs. Campbell and Scoville that if Rom-Amer would research an "anti-depression in a geriatric population" claim, they would whole-heartedly support our efforts. We were impressed with their statements that the FDA is open-minded regarding Gerovital H_3 and that they would treat our results with no bias and decide upon them in good faith. The selection of the "anti-depression in an aging population" claim was not incidental. Depression hits every age, but especially the aging. It has a paralyzing effect on their capabilities and their will to cope with everyday activities and stress. As you know, Senator Kennedy, the word "depression" encompasses many symptoms - perhaps as many as thirty - including depressed mood, inability to experience pleasure, sleepless nights, gradual loss of mental and physical energy to the point of

being too tired to take any action or make a decision, decrease in libido, loss of interest in usual activities, gradual loss of memory, etc. The present anti-depressant drugs on the market, while effective, are not very well tolerated by aging people. They create problems and side effects. Thus there is no safe anti-depressant geriatric drug on the market, and there is a vital need for one; a vital need for a drug such as Gerovital H_3, with practically no side effects. The safety of Gerovital H_3 was never challenged, since the FDA knew that it is among the most devoid of side effect drugs. The positive feelings of the FDA towards the Company's claim of anti-depression in an aging population was expressed publicly by Dr. Elmer Gardner, Director of the Division of Neuropharmacological Drugs. He stated in an interview, published April 6, 1973 in the Medical World News, that "There is no safety problem with the drug...Fighting geriatric depression is a perfectly viable rational for testing a new drug, and such a limited claim makes valid testing possible."

Later on, three university professors expressed the same opinions. Dr. Lissy Jarvik (U.C.L.A.) in an exhaustive review of Gerovital H_3 and procaine therapy, (Aging, Vol. 2, 1975), which was requested by Dr. Samuel Gershon, Professor of Psychiatry at N.Y.U., and Dr. Allen Raskin from the Psychopharmacology Research Branch of the FDA concluded "...the most promising feature of Gerovital H_3 treatment at this time appears to be its potential

anti-depressant effect." In October of 1975, at the first Workshop of the Veterans Administration Geriatric Research, Education and Clinical Center, Dr. Ostfeld of Yale University, (after having reviewed both English and foreign language literature on Gerovital H_3 and procaine) concluded "... procaine therapy probably has some anti-depressant effects, resulting in improvements of morale, appetite, physical activity, sexual interest, weight gain, improved memory and return to work. Most important, reduced depression usually means less preoccupation with pain and other bodily symptoms, increased optimism and a greater willingness to work and interact with others. It is important that evaluation of procaine properties continue." Dr. Sidney Cohen (U.C.L.A.), who had supervised clinical work with 475 subjects using Gerovital H_3, stated at the same meeting "...It is my impression that claims of life prolongation might really mean mood elevation, anti-depression and energy enhancement."

In 1972, based upon encouragements by Drs. Elmer Gardner, Barrett Scoville and others, and after our first protocol on depression as delineated in our Investigational New Drug Application had been formally approved by the FDA, Rom-Amer Pharmaceuticals started the first phase of testing Gerovital H_3. As the subjects were informed at that time that they were receiving Gerovital H_3, this type of study belongs to the "open studies" phase. The initial protocol, which is the

vital document in any research clinical program, and in accordance with which any research program is carried out, was not very complicated at this time. It consisted of a few scales, a thorough medical examination, urine and blood laboratory tests etc.

When a number of subjects had completed this first study, we considered the results indicative enough to continue our research program. So the Company went back to the FDA to obtain their approval for further studies, and to negotiate new protocols - this time for the "double-blind" studies. Clinical investigators (who were well-known to the scientific community, as well as to the FDA) submitted two proposals for protocols. These new protocols on depression were much more detailed than the first ones. They included scales filled out by a battery of two or three doctors per subject, and also, on a weekly basis, by the subject himself. Physical, medical, psychiatric examinations, and nurse evaluations were included, as well as EEG, laboratory, and other tests. The protocols were approved by the FDA in 1973. In these studies the subjects received coded injections containing either plain water or Gerovital H_3, but neither the doctors nor the patients knew what each patient was receiving. One study also compares Gerovital H_3 with a well-known anti-depressant drug presently on the market. During 1974 the Company completed a number of double blind studies carried out in accordance with this protocol and submitted the results to

the FDA. By that time Dr. Gardner had left the FDA. Dr. A. Campbell joined the group of FDA officials objecting to drug review irregularities that are occurring within the FDA. Dr. Richard Crout became Director, Bureau of Drugs, on May 21, 1973.

Late in 1974, the FDA suggested changes in the protocol on depression - the protocol which they had previously approved. These changes would put GH_3 to a much tougher, but proper test and we agreed with most of them. In spite of our eagerness to utilize this changed protocol as soon as possible, due to the FDA's foot dragging it took the Company over six months - at a substantial cost in money and time - to have the FDA sign the letter approving this protocol - which they finally did in June of 1975. We went ahead and started two double blind studies using this latest protocol. One study is in progress at McGill University in Montreal, Canada (Drs. Thomas Ban and Heinz Lehman). The other one was carried out by Leonard Cammer, M.D., psychiatrist in private practice and Clinical Associate Professor of Psychiatry, New York Medical College, and Flower and Fifth Avenue Hospitals. Late in 1975, Dr. Cammer completed his study, which used Gerovital vs. placebo in 40 subjects, and we submitted his results to the FDA. While the final evaluation of the Cammer study is still in progress and some computer evaluations are still being requested by the FDA, it is our estimate that the Cammer study is a very successful one.

Even before the results of the Cammer study became known to the FDA, Dr. Hayes, presently Acting Director, Division of Neuropharmacological Drugs stated: "First results of the American tests indicate that Gerovital H_3 seems to have some ability to treat mild depression. If future results confirm this, the FDA may have no choice but to license Gerovital H_3." (The Cleveland Press, Thursday, April 3, 1975). That quote was made before the Cammer study. We do not know what happened at the FDA after submission of Dr. Cammer's study. In retrospect, I now feel that someone at the FDA apparently tried to sink the "Gerovital H_3 project" through tougher and tougher protocols. Apparently, this strategy did not succeed, as out of a clear blue sky Rom-Amer was hit with a very unexpected letter, which was signed by Dr. J. Richard Crout, Director, Bureau of Drugs. It was the first time that he had by-passed the FDA's Division of Neuropharmacological Drugs - with which we had regularly corresponded for almost five years - and written directly to us. In this letter, dated April 6, 1976, Dr. Crout made these statements among others: "We will be unwilling to approve procaine HCl"(he forbade us even to use the word Gerovital H_3, a trademark which is legally registered with the U.S. Patent Office)"as an anti-depressant solely for the use in the elderly"...and also, "your drug product be demonstrated to be safe and effective in some definable way in altering the aging process...before it can be approved for marketing." If it sounds unbelievable Senator Kennedy - well

it is! After almost five years of research, after encouraging us to do the testing for a claim and use that is desperately needed by an aging population, after Rom-Amer spent all its money following the FDA's instructions and after all projects which it now appears to me were used to discredit the Gerovital H_3 program had failed - Dr. Crout decided to interpret the law his way, and thus renegue on everything the FDA has solemnly promised before. Now he wants Rom-Amer - which is broke financially - to start a new program to prove that Gerovital H_3 can alter the aging process. How long can this program take? 40 years? 50 years? Who knows.

However, since the FDA letter dated April 6, 1976 invited representatives of our Company to come to Washington, D.C. for a discussion about the Gerovital H_3 program, on May 17, 1976, Manfred Mosk, Ph.D., myself, and two officials of a company specializing in the testing of new drugs in the U.S. were present at this meeting. A team of seven FDA officials participated at the meeting: Dr. Crout; Dr. Marion Finkel, Associate Director, Bureau of Drugs; Dr. Carl M. Leventhal, Deputy Director, Bureau of Drugs; Dr. Thomas A. Hayes, Acting Director, Division of Neuropharmaceutical Drugs; Mr. Jay Cinque, Medical Officer in charge of the Gerovital H_3 program; Mr. Hajarian, Consumer Officer; and Dr. Barry Rosloff, Pharmacologist. Dr. Finkel chaired the meeting. I would like to give you a few highlights of this meeting.

Though the explanations we heard were most unclear, apparently the reasons Dr. Crout now wants an anti-aging claim for Gerovital H_3 are:

1. The principal usage of Gerovital H_3 products marketed abroad since 1953 is "in the prophylaxis and treatment of symptoms and manifestations associated with the aging process." In other words, although Gerovital H_3 has been used in Europe since 1953, it was only in 1976 that Dr. Crout found out about it. So while Dr. Crout mentioned in page one of his April 6, 1976 letter that "the principal usage of Gerovital H_3 in Europe is the treatment of symptoms and manifestations associated with the aging process", on page two he concluded that "your drug product be demonstrated to be safe and effective in some definable way in altering the aging process." Dr. Crout is not bothered by the fact that he contradicts himself; going from usage of Gerovital H_3 in Europe in the treatment of manifestations associated with the aging process (page 1) (in our opinion geriatric depression is associated with the aging process) to his conclusion that this means "altering the aging process", (page 2), which is an entirely different situation. That is just one of the examples of the "massaged" ways of arriving at Dr. Crout's "altering the aging process" idea.

2. Dr. Crout is angry that we were not able to "police" the American press and keep them from publishing material about Gerovital H_3. I have written to the FDA on numerous occasions and assured their staff members that Rom-Amer Pharmaceuticals, Ltd. has not initiated or been involved in any way with articles in the U.S. lay press regarding Gerovital H_3. However, despite my letters, Dr. Crout went ahead and referred in his letter of articles published "inter alia" in Argosy in 1973, the Detroit Free Press in 1975, and the TWA Ambassador in 1975. These articles, as Dr. Crout put it, "discuss the future availability of Gerovital for the treatment of various ailments related to the aging process." While we have no way of stopping any American newspaper from publishing whatever it wants, it is of interest to note that the articles mentioned by Dr. Crout talk about the "treatment of various ailments related to the aging process" and not about "altering the aging process", which according to Dr. Crout's letter to us is what he wants.

3. Another source of concern for Dr. Crout is that should Gerovital H_3 be approved in the U.S. for anti-depression geriatric claims, it is possible that medical doctors in private practice will utilize Gerovital H_3 for other uses than geriatric depression. It should be remembered

that Gerovital H_3 under our IND program is in injectable form and delivered by pharmacists only on medical prescription. That means that because Dr. Crout makes believe he is worried because he cannot control what the medical practitioner does in his own office, he feels that Gerovital H_3 should not be approved in the United States at all. It is a strange argument to say the least! Especially since the representatives of the Company stated that they will accept - in the event the product is approved - any restrictions that the FDA finds necessary to be put on the Gerovital H_3 label and insert.

When the meeting turned to the reason we had been invited to the FDA meeting; namely to have a preliminary discussion about Dr. Crout's requirements on anti-aging ideas, Dr. Crout and Dr. Finkel made a number of very confusing statements. We stated that we were utterly confused, and we think that Dr. Crout himself did not know what to say. Finally, to put an end to this uneasy situation, the representatives of the Company were told to go home and wait for a letter.

What is strange, Senator Kennedy, is that Dr. Crout behaves entirely differently when a big drug company is involved. The Kennedy Health Subcommittee's investigations had uncovered evidence that when a big drug company submitted a request to

Dr. Crout to have a drug they were manufacturing approved for a new use, and when Dr. Crout's own advisory committee rejected it because of negative effects to the patient, Dr. Crout did not hesitate to answer the drug company that the advisory committee had recommended the approval. (Chemical and Engineering News, August 26, 1974, p. 14).

Why is Dr. Crout so eager to approve a new use for a drug even knowing that it has negative effects to the patient, when a big drug company is involved, and why is he trying to prevent the approval of a drug which is safe and effective, and desperately needed by so many Americans over the age of 60, when a small drug company is involved?

There are other aspects to be considered of Dr. Crout's and/or some of his staff associates actions against Gerovital H_3 and Rom-Amer. As you know, Senator Kennedy, we are a small company continuously in need of additional financing to carry on with research on Gerovital H_3, while at the same time, we are looking for business cooperation from other drug companies to jointly develop Gerovital H_3 for commercialization in the U.S. In this respect, we had some preliminary discussions with a pharmaceutical company and found that they have a certain interest in our drug, provided that : (1) An analysis of our research data by their medical staff would be satisfactory; (2) They can discuss the data directly with Rom-Amer's clinical

investigators, and; (3) We will let them informally contact officials at the FDA to learn their thoughts about the Gerovital H_3 program. We agreed with these requests. Then, after signing a non-disclosure agreement with this pharmaceutical company, all our research data - both experimental and clinical - was submitted to them for evaluation. They needed about four to five months to check out the various aspects of our research data. Then the company informed us that "we have completed our review of your data package and were impressed with the substantive content, particularly the more recent clinical studies which were better controlled and double-blinded." Accordingly with our agreement, and after they had met privately with the Gerovital H_3 clinical investigators, they made a request to informally contact FDA official(s) to find out their feelings towards the Gerovital H_3 program. We agreed. The meeting with an unknown FDA official(s) took place shortly thereafter. Some time later, we were informed that the company was not interested in pursuing the matter any further. We did not ask their reasons for dropping the project after they had been "very impressed" with our work - and they did not volunteer to tell us.

I realize only now that the FDA official(s) apparently told them to stay away from Gerovital H_3, perhaps telling them about their intentions of not approving Gerovital H_3 in the U.S. - intentions that they did not tell us. If what I now suspect is true, then someone at the FDA, on the one hand was keeping us busy spending

our money for a research claim that the FDA had agreed to previously but now had no intention of approving, and on the other hand, they were creating a financial vacuum around us - (the drug company situation is not the only one) - scaring away interested parties so that no future help would come from the outside.

We would like at this point, Senator Kennedy, to bring up a situation that goes beyond Dr. Crout's crushing a small research pharmaceutical company. That point is that if the Gerovital H_3 research program comes to a halt, it will also stop the hopes of more than 32 million Americans in the over-60 generation who have been awaiting the results of our research with hope and expectations. Gerovital H_3 is the first drug for geriatric depression to be tested in the U.S.; but most certainly, should the results be positive, many other geriatric drugs would follow. The Gerovital H_3 program has tested the willingness of the FDA to allow "the geriatric" or "happier, healthier aging" era to start in the United States - an era that has already begun in many, many other countries. Dr. Crout, for his own reason, said "no". The American people should know that all over the world geriatric drugs are abundant, and accessible to everyone who needs them, and indeed, in some Western European countries Social Security ays for these treatments. Moreover, major trade unions are sending their members to sanatoriums to take these treatments, and are paying the bill. Rom-Amer had hoped that this

would happen in the U.S. too. If Gerovital H_3 program is stopped, it will squash for many years to come, the hopes of so many millions to have a healthier, less depressed, more cheerful aging. I am firmly convinced, Senator Kennedy, that Gerovital H_3 would have helped millions of people to better enjoy their "golden age", have less of the miseries of aging and derive more enjoyment and satisfaction from their pro-retirement and retired years.

Where do they stand now?

Well, for those Americans who are fortunate enough to go to Europe to get Gerovital H_3 or other geriatric drugs, or those who smuggle it into the U.S., not having Gerovital H_3 here will make little difference. For the rest of the Americans over age 60 who could benefit from use of this drug - the great majority - the march through a more and more depressed life to the "rest homes" and graves that had stopped for a moment of hope now will recommence again. I think Dr. Crout can be proud of that.

Dear Senator Kennedy, I think that what is going on in this respect is a crushing blow. Not only for Rom-Amer Pharmaceuticals, Ltd., but for those too over the age of 60. I know that something is wrong with Dr. Crout's decision vis-a-vis Rom-Amer, but I do not have the means to find out what. The only hope I have is that based upon your own investigation, you will prove

my allegations to be correct.

I am not alone in this respect. I am sure that many, many millions of Americans will follow your endeavors with utmost attention. Your success in this matter will rekindle again their hopes that means for a healthier, happier aging will become available to them too, after all.

Respectfully submitted,

Alfred T. Sapse, M.D.

cc: Dr. Alexander M. Schmidt, Commissioner, FDA

Dr. J. Richard Crout, Director, Bureau of Drugs, FDA

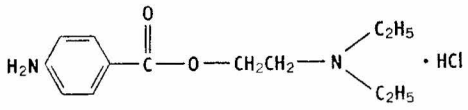
tricular ectopic beats represent typical examples of therapeutic aims. The use of the drug is always potentially dangerous.

Procaine amide

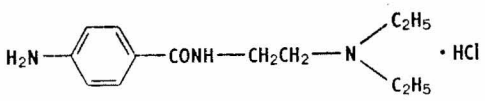
Development as cardiac drug

The commonly used local anesthetic procaine was shown by Mautz[15] in 1936 to elevate the threshold to electrical stimulation when applied to the myocardium of animals. In subsequent years thoracic surgeons and anesthesiologists frequently used topical procaine in surgery to reduce premature ventricular and atrial contractions during surgery. Procaine was even administered intravenously for this purpose.

The chemical structures of procaine and procaine amide are shown below.



Procaine hydrochloride



Procaine amide hydrochloride

Encouraged by these studies, investigators studied the antifibrillatory activities of compounds related to procaine, including the effects of the two hydrolysis products of procaine, para-aminobenzoic acid and diethylaminoethanol. The most fruitful consequence of these studies was the finding that, if the ester linkage in procaine was replaced by an amide linkage, the resulting compound had distinct advantages as an antiarrhythmic drug. The main advantages consist of greater stability in the body and fewer central nervous system effects.

Cardiac effects

The actions of procaine amide on the heart are similar to those of quinidine, although on a weight basis the drug is less potent. Excitability to electrical stimulation of both the atrium and ventricle is depressed by the drug.[21] The refractory period is prolonged, more in the atrium than in the ventricle. Conduction is slowed, particularly across the A-V node. Experimentally the drug protects against ventricular tachycardia induced by the cyclopropane-epinephrine sequence and suppresses ectopic beats following coronary artery ligation.[10]

There has been great interest in the possibility of using procaine amide to suppress ectopic ventricular activity in digitalis intoxication. Although it is possible to do this in experimental studies,[9] the drug should not be considered a true antidote to digitalis intoxication, since there is doubt that it can significantly alter the median lethal dose of digitalis.

The clinical reports on the effectiveness of procaine amide in digitalis intoxication are somewhat conflicting. Several groups recommend its use, but it should be remembered that in large doses ventricular fibrillation has been precipitated in patients having digitalis intoxication, possibly because of slowing intraventricular conduction.

Electrocardiographic changes. Procaine amide may cause prolongation of the P-R, QRS, and Q-T intervals. These effects are explainable on the basis of prolonged conduction and increased refractory period.

Extracardiac effects

Procaine amide can cause a fall in blood pressure, particularly following intravenous injection. This blood pressure change may be due to a ganglionic block.[16] The drug has local anesthetic properties but does not appear to be as effective for nerve block as procaine itself.

Preparations, dosage, and metabolism

Procaine amide hydrochloride (Pronestyl) is available in 250 mg. capsules and in 10 ml. vials containing 100 mg./ml.

The drug is rapidly absorbed from the gastrointestinal tract. About 60% of it is excreted in the urine unchanged, a situation quite different from procaine, which is largely hydrolyzed by an esterase. Plasma levels decline at a rate of 10 to 15% per hour, more slowly in renal damage or severe congestive failure.

Therapeutic plasma levels are 10 to 20 mg./L. and are available on a dosage schedule of 500 to 750 mg. of the drug every six hours. On such a schedule the drug is not cumulative in normal persons but would become so in the presence of defective renal function.

Toxicity

In addition to the cardiotoxicity discussed previously, procaine amide can produce gastrointestinal and central nervous system disturbances and may also depress the bone marrow.

The clinical literature contains reports of such disturbances as nausea, anorexia, mental confusion, hallucinations, skin rash, and occasionally agranulocytosis. The occasional appearance of chills and fever also suggests a hypersensitivity reaction.

Therapeutic aims in relation to those of quinidine

From a pharmacologic standpoint procaine amide appears to act as a weak form of quinidine. Nevertheless, it is a valuable therapeutic adjunct. Its intravenous administration may be safer than that of quinidine. In addition, it may prove a safe replacement in cases of quinidine purpura. The major therapeutic uses of procaine amide consist of management of ventricular arrhythmias and prophylaxis against such arrhythmias during treatment of myocardial infarction.

Conversion of atrial fibrillation to sinus rhythm by means of electric countershock is gaining popularity. Maintenance of normal rhythm following conversion often requires the use of quinidine.[23]

Other drugs having a quinidine-like effect

In addition to procaine amide, there are many drugs which have some quinidine-like effect. Dawes[5] has shown that local anesthetics such as procaine, spasmolytics such as atropine and papaverine, and the narcotic analgesic meperidine can prolong the refractory period of the heart muscle. The antihistaminic drugs also have a similar effect.[13]

All of these drugs have other important primary sites of action, and their possible cardiac effect is generally disregarded. This action may become important, however, when several drugs are used in special situations such as premedication to anesthesia.

The antiepileptic drug diphenylhydantoin sodium (Dilantin) has also been shown to exert an antiarrhythmic effect both in experimental preparations and in patients.[4]

Beta adrenergic blocking drugs such as propranolol have antiarrhythmic properties in addition to what might be expected from their antagonism to the actions of the catecholamines on the heart.[11a]

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Exhibit "H"

HOWARD W. CANNON
NEVADA

COMMITTEES:
ARMED SERVICES
COMMERCE
AERONAUTICAL AND SPACE SCIENCES
RULES AND ADMINISTRATION

United States Senate

WASHINGTON, D.C. 20510

August 12, 1976

Mr. Roland Bartlett
1710 Seneca Lane
Las Vegas, Nevada

Dear Mr. Bartlett:

Thank you for sending me the tape containing your thoughts on Gerovital, Laetrile, and the Food and Drug Administration.

I have done some checking into the status of Laetrile and find that it is classified as not generally safe and effective for use under the Federal Food, Drug and Cosmetic Act. The main controversy surrounding the drug is that, while a substantial number of people report Laetrile has helped in retarding cancer, there is no organized clinical evidence to support that fact. Tests conducted by the National Cancer Institute have not yet been able to demonstrate Laetrile's ability to retard tumor development.

In regard to Gerovital, the Romamer Company which has exclusive rights to market the drug in the United States has been testing it as an anti-depressant. However, because Gerovital is most commonly known for alleged age arresting properties, FDA advised the company that they had to demonstrate it actually had such properties. Negotiations are currently underway to reverse that decision and I will certainly stay alert to developments in this area.

With regard to the Food and Drug Administration you are clearly correct to observe that there are some serious problems in that agency. Congressional hearings have been held to look into some of the abuses which have been alleged and the Health Subcommittee plans to continue the investigations.

While there is no legislation currently before the Congress that addresses issues specifically related to Gerovital and Laetrile, Congressman Symms of Idaho has introduced a bill which would eliminate the requirement that new drugs be regulated according to their effectiveness. The bill states that such

drugs should be regulated solely to assure their safety. While it does not appear that this bill will win approval this year, it is my view that if a drug is not harmful, people ought to be able to use it.

I do appreciate your concern and willingness to discuss these matters with me and please do not hesitate to contact me again whenever you have additional thoughts to share on this or any other issue.

With best wishes, I am

Sincerely,

Howard W. Cannon

HOWARD W. CANNON

HWC/JSsa

— Exhibit "I" —

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

IND 6734

APR 1970

The McNaughton Foundation
of California
P. O. Box "A"
Sausalito, California 94965

Attention: Andrew R. L. McNaughton

Gentlemen:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for the following:

Sponsor: The McNaughton Foundation of California

Name of Drug: Amygdalin

Date of Notice: Undated (Cover letter dated April 6, 1970)

Date of Receipt: April 7, 1970

Please identify all future communications concerning this Notice with the IND number shown above.

All submissions should be forwarded in triplicate.

As sponsor of the clinical study proposed in this exemption, you are now free to obtain supplies of the investigational drug and to initiate clinical studies. If deficiencies are found during our review of the information you have furnished, you will be notified and invited to make corrections.

The use of the assigned IND number may assist you in obtaining shipment of the drug from your supplier or in clearing import shipments through U. S. customs.

The interstate distribution of this drug for investigational use is subject to all of the applicable provisions of the Act and regulations. This includes the immediate reporting of any alarming reaction in either animal or human studies and submission of progress reports at intervals not to exceed one year. A copy of the Investigational Drug Regulations is enclosed for your information.

Sincerely yours,

Earl L. Meyers

Earl L. Meyers, Ph.D.
Director
Division of Oncology and
Radiopharmaceuticals
Office of New Drugs
Bureau of Drugs

Enclosure

NINETY-FIRST CONGRESS

Congress of the United States

House of Representatives

INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE
OF THE
COMMITTEE ON GOVERNMENT OPERATIONS
RAYBURN HOUSE OFFICE BUILDING, ROOM B372
WASHINGTON, D.C. 20515

Exhibit "J"

March 16, 1971

Honorable Elliot L. Richardson
Secretary
Department of Health, Education
and Welfare
Washington, D. C.

Dear Mr. Secretary:

The President has requested $100 million in special cancer research funds for fiscal year 1972, in addition to a larger regular appropriation for the National Cancer Institute. A study group sponsored by a Senate Committee has proposed spending many times that amount.

Unquestionably, the American people would support expenditures of any magnitude if such expenditures offered promise of a cure or prevention for cancer. The sad truth is that over a period of years the Federal Government has spent vast sums on cancer research and the results of this effort have been rather meager.

It is with this perspective that I strongly urge your Department to make an objective evaluation of the demonstrated efficacy claimed for and the potential of the drug Laetrile (Amygdalin) as an anti-cancer agent. The use of this drug for cancer therapy has been banned in the United States for a number of years.

I and many other Members of Congress have received a large volume of mail from individuals who claim they or members of their families have benefited from Laetrile treatments, and from people who believe the Government is party to a conspiracy to suppress an inexpensive, non-toxic, and effective anti-cancer drug. Whatever

the merits of these claims, public confidence in our Government has not been strengthened by the highly unusual actions of the FDA in first advising the sponsor of IND 6734 on April 20, 1970 that clinical studies with Laetrile could be initiated, and then terminating this authorization on April 29, 1970. Copies of these FDA letters are enclosed.

According to the McNaughton Foundation of California, the sponsor of IND 6734, Laetrile (Amygdalin) has already been used successfully in the treatment of cancer by 10 physicians and cancer researchers in approximately 1000 cases. The McNaughton Foundation states that the most recent clinical work with Laetrile has been done by Dr. Ernesto Contreras in Mexico, and Dr. Hans A. Nieper in Hanover, Germany.

In view of this background and the deeply held conviction of a large number of Americans that they are being forced by their Government to leave the country in order to obtain therapy with a drug that is both safe and effective for the control of cancer, I believe it imperative that HEW take immediate steps to review the clinical records of patients treated by Doctors Contreras and Nieper. This review should be done by cancer experts who have no conflicting interests and who are able to evaluate the evidence objectively. There is precedent for a retrospective study of patient histories in the evaluation of Krebiozen cases some years ago under the auspices of the National Institute of Health. The cost of such a study would be relatively small. Also, the Food and Drug Administration has the organization and the experience in gathering of patient case history records to assist in this undertaking.

In addition, there would appear to be merit in the National Cancer Institute's performing further animal tests with Laetrile. I note that in writing to Congressman Edwin W. Edwards on January 26, 1971, Dr. Carl G. Baker, Director of the National Cancer Institute, stated that the preclinical data provided by the McNaughton Foundation does indicate some activity for Laetrile in animal tumor systems. While I understand that the Cancer Institute at one time did conduct studies with Amygdalin in a small number of tumor-bearing mice, it is alleged by Dr. Dean Burk of the Cancer Institute that these animals were tested at inadequate concentrations of a drug of questionable origin and chemical authenticity. In the light of the

tremendous sums of money that have been spent with relatively little productivity in the Cancer Chemotherapy Program, I find it very surprising that the Cancer Institute has not sought on its own initiative to do further animal testing with this drug which apparently has shown some activity in the tests sponsored by the McNaughton Foundation.

It should be clearly understood that I am not endorsing Laetrile (Amygdalin), since I have no basis for judging whether or not it is safe and effective for the treatment of cancer. However, the public has a right to know if any of the therapeutic claims made for this drug are justified. I am sure you are fully aware of the anguish and desperation experienced by those persons who are given no hope for the cure of cancer through conventional means, and the great temptation for them to try unorthodox remedies which are said to be non-toxic. In the fight against cancer we surely cannot afford to ignore any leads, whatever their source.

Your Department can render an important public service by arranging for a thorough investigation of the recent clinical experience with Laetrile. I hope you will agree with me that an appropriate study should be initiated without delay.

Sincerely,

L. H. Fountain

L. H. Fountain, Chairman
Intergovernmental Relations Subcommittee

Enclosures

DEPARTMENT OF
NATIONAL HEALTH AND WELFARE
HEALTH PROTECTION BRANCH

CANADA

MINISTÈRE DE LA
SANTÉ NATIONALE ET DU BIEN-ÊTRE SOCIAL
DIRECTION GÉNÉRALE DE LA PROTECTION DE LA SANTÉ

Exhibit "K"

402 - 2431 - 11th Avenue,
Regina, Saskatchewan.
S4P 0K4.

File 930-6

February 21, 1977.

Mrs. Joan Lloyd,
2620 Lougheed Drive,
CALGARY, Alberta.

Dear Mrs. Lloyd:

This is to acknowledge your enquiry about importing medication from Mexico for your own personal use.

We do not issue permits in this regard, but see no reason to refuse entry of this proposed importation.

Products such as B-17, and Laetrile, can not legally be sold in Canada because there is insufficient evidence to establish their safety and effectiveness. However, at the present time it is legal to bring medication into Canada for personal use, unless it is in a specific restricted category, such as narcotics or controlled drugs.

Yours truly,

for H. R. Harries,
Food and Drugs Inspector,
Regina District.

HRH/lem

cc: Regional Office, Winnipeg.

cc: Canada Customs, Calgary, Alta.

— Exhibit "L" —

UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

STATE OF CALIFORNIA) AFFIDAVIT
)
CITY AND COUNTY OF SAN FRANCISCO)

Chauncey D. Leake, Ph.D., being first duly sworn, deposes and states:

1. In 1917, I received the degree of Litt.B. from Princeton, and in 1920 I received a Master of Science degree from the University of Wisconsin. From the University of Wisconsin, in 1923, I received my Ph.D. in Pharmacology. Between 1923 and 1928, I was an associate professor of pharmacology at the University of Wisconsin. I then transferred to the University of California Medical School, San Francisco, where I organized the Department of Pharmacology. Between 1928 and 1942, I served at the University of California Medical School, San Francisco, as Professor of Pharmacology, Professor of Medical History, and Librarian. Between 1942 and 1955, I was executive director of the University of Texas Medical Branch, Galveston. Since 1962, I have served as Senior Lecturer in Pharmacology at the University of California School of Medicine, San Francisco. A copy of my curriculum vitae is attached hereto as Exhibit A and incorporated herein by reference.

2. Through my many years of research and study in the field of Pharmacology, I have become familiar with the substance known as amygdalin. Indeed, I have made a special study of amygdalin, and I am familiar with both the scientific and popular literature on the subject, and I also have personally discussed the nature and effects of amygdalin with

numerous medical and scientific authorities who personally have researched and experimented with it. Amygdalin is a chemical which has been defined, for example, as follows: (1) "Amygdalin, a glucoside found crystalline in almonds, and amorphous in cherry-laural leaves." [The Shorter Oxford English Dictionary, 2nd edition, 1939, Vol. 1, page 59] (2) "Amygdalin, a white, bitter tasting water soluble glucosidic powder, $C_6H_5CHCNOC_{12}H_{21}O_{16}$, usually obtained from bitter almond seeds and the leaves of the genus Prunus and related genera; used chiefly in medicine as an expectorant." [The Random House Dictionary of the English Language, New York, 1966, 51, 3rd column]

3. Amygdalin was discovered in 1830 by Robiquet and Boutron-Charlard when it was isolated from almonds. It has been used medicinally since the middle of the last century. There are numerous historical references to amygdalin per se or substances containing amygdalin. The following are examples: (A) Encyclopedia Brittanica, Cambridge, England, the 11th edition, 1911, Vol. 1, page 716: "Almond is the fruit of Amygdalus communis, a plant belonging to . . Prunae. The genus Amygdala is very closely allied to Prunus (Plum, Cherry) . . . distributed over the Old World . . referred to in the Bible . . Pulvis Amygdalae compositus of the British Pharmacopeia consists of sweet almonds, sugar and gum acacia. It may be given in any dose. The Misturae Amygdalae contains one part of the above to eight of water; the dose is 1/2 to 1 ounce . . . The bitter almond . . contains a ferment emulsin which in the presence of water acts on a soluble glucoside, amygdalin, yielding glucose, prussic acid and the essential oil, benzaldehyde . . . " (Emphasis supplied)

(B) The Greek Herbal of Dioscorides by Robert T. Gunther, Hafner, Ondon, 1968, pp. 86-87 (The text of Dioscorides was

written in the 1st Century AD, the author being a surgeon in the armies of Nero; Englished by John Goodyet AD 1655): "Book I, chapter 176: Amugdale. Amygdalus sommunis. Almond. The (nuts) being eaten, dolores adimunt, they soften ye belly, cause sleep, & are ureticall, & they are good for the reiectio Sanguines . . . They are good also for ye nephriticall and peripneumonicall, being drank with water . . helps such as are troubled with ye Dysurie & ye stone; & the Hepatick, & Coughs, & ye inflationes Coli . . . But the sweet & edible almond commes a great deale short in strength of the bitter; yet that also is extenuating & ureticall."

4. The National Standard Dispensatory by H. A. Hare, C. Caspari & H. H. Rusby, Lea & Febiger, Philadelphia, 3rd edition, 1916, pp. 173-175: "Amygdala Amara - Bitter Almond . . The ripe seed of Prunus Amygdalua amara (Amygdalus communis L. - Fam. Rosaceae. Bitter almond is official in most pharmacopeias . . Constituents. - The brown testa contains tannin, a green resin, and a bitterish acrid yellow substance . . . The kernel contains fixed oil (Oleum Amygdalae Expressum) about 46%, ucilage 3%, sugar 6%, proteids 24 to 30%, amygdalin (the important ingredient) 1 to 3%, and ash (chiefly phosphates of potassium, calcium & magnesium. Starch is wanting. The two proteids are modifications of vegetable casein. Both are soluble in cold water; one, conglutin or amadin being precipitated by acetic acid, the other emulsin or synaptase . . by alcohol. Both act as emulsifying agent in suspending the fixed oils . . . but it appears to be the emulsin only which is capable of decomposing amygdalin into hydrocyanic acid & benzaldehyde .. . Amygdalin ($C_{20}H_{27}NO_{11}$) was discovered by Robiquet and Boutron-Charlard in 1830. . . Liebig & Wohler found in 1837 that grape-sugar was also yielded by amygdalin, this being the first discovery of a glucosi-

Amygdalin occurs sometimes in anamorphous condition, but as obtained from by alcohol from bitter almonds, peach-seeds, etc, it crystalizes with 2 H_2O, this water being expelled at 120 C. It is soluble in about 15 parts of water, has no odor, a bitter taste, and is not poisonous unless decomposed by emulsin. L7 grains of anhydrous amygdalin yield 1 grain of hydrocyanic acid. A heat of 150 C. is said to destroy amygdalin, but long before that temperature is reached the properties of the emulsin are destroyed. The seeds yield nearly 1% of volatile oil and 0.25% of hydrocyanic acid . . . Action abd Uses. - The oil of bitter almond, because of its hydrocyanic acid, has been employed in the coughs of phthisis and in the irritative coughs of children.

5. I have researched the question of whether amygdalin is toxic. I am not aware of any reported cases of amygdalin poisoning. Under certain conditions, amygdalin yields HCN (hydrocyanic acid) which inhibits enzyme action. HCN is liberated slowly from amygdalin in the human body, and it is rapidly detoxified by sulfates in the body to thiocyanate. In Forensic Medicine and Toxicology by R. A. Witthaus and T. C. Becker, New York, 1896, pp. 602-629, there is a long discussion of hydrocyanic acid poisoning, with many case reports and references, but there are no cases of poisoning by amygdalin. In 402 cases of cyanic poisoning collated, five occurred from eating bitter almonds or cherry or plum kernels. A. J. Kunkel in 2nd edition of Handbuch der Toxicologie, Jena, 1901, dismisses amygdalin as being of no significant toxicity. (P. 929)

6. During the 1930s, while I was at the University of California Medical School, San Francisco, I became aware that amygdalin was being studied by Charles Gurchot, Ph.D., at the hospital laboratory of the Medical School. During this time,

I conferred on numerous occasions with Dr. Gurchot and various physicians at the hospital concerning amygdalin and its use in the treatment of cancer. I was aware that as early as the mid-1930s, certainly prior to 1938, it was being used at the Medical School Hospital on cancer patients for treatment of cancer. At this time, it was generally held by physicians, and other scientists familiar with it, that amygdalin was safe when used in the treatment of cancer as well as in its use as an expectorant or cough suppressant.

7. During the 1950s, subsequent to Dr. Gurchot's work at the University of California Medical School, San Francisco, I communicated with Ernst T. Krebs, Sr., M.D., now deceased, about his use of amygdalin in the treatment of cancer patients. Dr. Krebs advised me that he had been using amygdalin in the treatment of cancer in human patients for a number of years and that amygdalin had been used with beneficial effects upon the patients. It is my memory that Dr. Krebs was using the amygdalin during the 1950s in the treatment of cancer patients. Dr. Krebs reported to me that there were no toxic effects from the use of amygdalin on these patients.

8. For years prior to 1938, and also immediately prior to October 10, 1962, as well as subsequent to that date, amygdalin has been commercially used and sold in the United States. It has been available in commercial quantities from various manufacturers of chemicals in the United States, e.g., Merck. It is my opinion, as well as the opinion of other qualified scientists, that amygdalin is safe and non-toxic when administered to humans and animals under commonly recommended dosages. It is my information and belief, based upon my

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discussions and review of reports from physicians who used amygdalin during the 1930s and 1940s at the University of California Medical School Hospital, San Francisco, that those physicians regarded amygdalin as safe for administration to human beings.

CHAUNCEY D. LEAKE, Ph.D.

SUBSCRIBED AND SWORN to before me this 27th day of December, 1976.

Notary Public in and for said County and State

CHAUNCEY D. LEAKE
University of California
San Francisco, California 94143

Born Elizabeth, New Jersey, September 6, 1896. Princeton, Litt.B. 1917; University of Wisconsin, M.S. 1920, Ph.D. 1923; Kenyon, L.H.D. (Hon.) 1959; Medical College of Pennsylvania, D.Sc. (Hon.) 1963; University of California, LL.D. (Hon.) 1965; Philadelphia College of Pharmacy and Science, Sc.D. (Hon.) 1969; Sc.D. (Hon.) 1974, Ohio State University.

Assoc. Professor Pharmacology, University of Wisconsin, 1923-28; Professor of Pharmacology (organized department), Professor of Medical History, Librarian, University of California Medical School, San Francisco, 1928-42. Executive Director, University of Texas Medical Branch, Galveston, 1942-55. Professor of Pharmacology and Lecturer in the History and Philosophy of Medicine, Ohio State University, 1955-62 Coordinator, Medical Student Research Training Program, 1962-65; Senior Lecturer in the History and Philosophy of the Health Professions, Senior Lecturer in Pharmacology, University of California School of Medicine, San Francisco 1962- . Professor of Medical Jurisprudence, Hastings College of the Law, San Francisco, 1962-66. Visiting Member, Institute for Advanced Study, Princeton, 1950, 1952, 1954. Motorola Executive Institute, 1970- . Director, Carter-Wallace, Inc., 1970- .

U.S. Chemical Warfare Service, 1918-19. Consultant, National Research Council and USPHS. Special Award, International Anesthesia Research Society, 1928, and Western Pharmacology Society, 1965. Hon. Fellow, American College of Dentists. Fellow American Association for the Advancement of Science (Vice President and Chairman History of Science Section, 1940; President, 1960). A.M.A. (Chairman, Pharmacology Section, 1937). American Physiology Society. Society of Experimental Biology and Medicine (President, 1961-63). American Society for the History of Medicine (President, 1960). History of Science Society (President 1936-39). American Society Pharmacology (President, 1958-60). American Academy Arts and Sciences. National Association of Science Writers (Hon.). International Academy for the History of Science. International Academy History of Medicine. Law-Science Academy of America, A.M.A. Institute for Biomedical Research - Scientific Advisory Committee 1964-69. Hon. Fellow Hastings Institute Society, Ethics and Life Sciences.

Founder and Editor, Texas Reports on Biology and Medicine, 1943-55. Consulting editor, Excerpta Medica, Current Contents, Perspectives in Biology and Medicine, Arch. Internat. Pharmaco., Research Communications in Chemical Pathology and Pharmacology. Author of seventeen books and some six hundred publications relating to biomedical science, philosophy, and education.

EX. A

— Exhibit "M" —

UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

STATE OF CALIFORNIA) AFFIDAVIT
)
CITY AND COUNTY OF SAN FRANCISCO)

Charles Gurchot, Ph.D., being first duly sworn, deposes and states:

1. In 1917, I received a Bachelor's Degree in Chemistry from the College of the City of New York, and in 1927, I received my Ph.D. in Chemistry and Physiology from Cornell University, Ithaca, New York. I have had graduate experience in research and teaching in pharmacology, biochemistry and chemistry at the following institutions: Stanford University, School of Medicine; University of California, School of Medicine; Cornell University, Department of Chemistry; and Cornell Medical College in Ithaca, New York. In order to become acquainted with medicine for research purposes, I studied medicine at Cornell Medical College at Ithaca for two years from 1927 to 1929, and for one year I studied medicine in Paris at Ecole de Medecine and at one of the Paris hospitals from 1929 to 1930.

2. From 1934 to 1945, I was on the faculty of the University of California, School of Medicine, San Francisco, where I served as an assistant professor of pharmacology. I am a member of the following organizations: The Society for Experimental Biology and Medicine; Fellow of the American Association for the Advancement of Science; Fellow of the American Institute of Chemists; Honorary Scientific Fraternity of Sigma Xi; The California Academy of Sciences. From 1945 to 1955, I did research work on cancer with the John Beard

Memorial Foundation; and since 1955, I have done work with the McNaughton Foundation. I have been semiretired since 1963, but I have continued to research and publish in the fields of pharmacology and cancer treatment. My curriculum ~~vitae~~ is ~~attached hereto as Exhibit A and incorporated herein by reference~~ re-attached.

3. Since 1932, I have had a special interest in the study and management of cancer. In this connection and as a pharmacologist, I have studied, researched, experimented with and utilized various substances intended for the control and management of cancer. Among these is a substance scientifically known as amygdalin.

4. Amygdalin is a chemical substance that is classified as a cyanogenic glycoside. Amygdalin is the chemical name for Laetrile, a substance which occurs in the kernels of bitter almonds, peaches, apricots, and in other plant materials. Cyanogenic glycosides are substances which contain, in their molecular structure, a moiety known as the cyanide group which upon hydrolysis by certain enzymes is released. Although amygdalin contains cyanide, the molecular structure of amygdalin is such that cyanide is not released in any toxic form to humans or animals, when consumed either orally or by injection, unless a group of enzymes contained in the so-called emulsin enzyme complex is administered also and at about the same time.

5. Since 1932, I have made a special study of amygdalin. I am familiar with both popular and scientific literature on the subject. Amygdalin, as an isolated chemical substance, has been known and used medicinally since the 19th century. In 1830, it was discovered by Robiquet and Boutron-Charlard. From my research on amygdalin, I am aware that there is a report in the Gazette Medicale De Paris, tome XIII, Samedi,

Le 13 Septembre, 1845, by Dr. Th. Inosemtzeff, Professor of Surgery at the Imperial University of Moscow. In this report, the professor described two cases of cancer in which amygdalin was utilized, reportedly with some success, in an effort to control the cancer. During the 19th century and into this century, amygdalin also has been used safely and medicinally as an expectorant and cough repressant.

6. In about 1931, it was brought to my attention that Dr. Ernst T. Krebs, Sr., M.D., previously had extracted what he believed were enzyme substances from the kernel of the apricot, and that he had been using these enzymes to treat cancer. Dr. Krebs tentatively identified this enzyme complex as emulsin. The extract also contained amygdalin, among other substances. Dr. Krebs advised me that in the late 1920s he had begun to inject patients with the extract which he previously had tested upon animals. Dr. Krebs is now deceased.

7. About the time of hearing of Dr. Krebs' discoveries, Dr. Leon Lewis, M.D., and I were working at Sonoma State Home, Glen Ellen, California. ~~As a result of~~ Before contacting Dr. Krebs, we had become interested in the use of enzymes in the treatment of cancer. We began to research the use of his "enzyme extract" on cancer; and I tested the extract both in the Sonoma State Home laboratory and with Dr. Lewis in the clinic. In the early 1930s, Dr. Lewis and I moved to the east coast of the United States, and we continued our collaboration on the use of this "enzyme extract" under sponsorship of the International Cancer Research Foundation, headed by Mr. William Donner. Under this sponsorship, we conducted clinical studies at Philadelphia General Hospital, University of Pennsylvania Graduate Hospital and Fox-Chase Cancer Hospital. In addition, we collaborated on laboratory studies at Cornell University, Ithaca, New York. Dr. Lewis did his clinical work in Philadelphia, and I worked

in a laboratory at Cornell University.

8. Between 1933 and 1934, I participated with Dr. Lewis in using amygdalin to treat cancer on approximately 100 patients in the Philadelphia area. The amygdalin was administered variously through intramuscular injection, intravenous injection and orally. Previously, Dr. Lewis and I had determined that there would be no toxic effects from administering the amygdalin in proper dosage. There were no toxic effects on any of the patients who received the amygdalin.

9. I am familiar with the Pharmacopoeia of the United States. I have reviewed several portions of the Pharmacopoeia relating to "amygdala." Amygdala is Greek for almond. For example, in the 1831 edition of the Pharmacopoeia, there is reference to "Mistura, Amygdalae" (p. 146). The English translation of this is "Almond Mixture." (p. 147) It is listed under the general category "Mixtures." A copy of the pertinent portion of the Pharmacopoeia is attached here as Exhibit B and incorporated herein by reference.

10. Various forms of "Amygdalae" or "Amygdala" are mentioned in later revisions of the Pharmacopoeia. For example, in the 7th revision, published in 1893, amygdala is referenced under the heading "Amygdala Amara." (p. 39) Under this heading it is listed as "Bitter Almond." It is defined as follows: "The seed of Prunus Amygdalus, var. amara De Candolle (nat. ord. Rosaceoe)." It is also stated as follows: "When triturated with water, Bitter Almond yields a milk-white emulsion, which emits an odor of hydrocyanic acid." There is a designation or reference to "preparation," stated as "Syrupus Amygdalae." This syrup or milk-white emulsion would contain about 50 milligrams of unreacted amygdalin from each seed processed. Thus amygdalin would be present in a significant quantity.

11. The 9th revision of the Pharmacopoeia, published in 1916, refers to "Oleum Amygdalae Amarae." This is translated as the "Oil of Bitter Almond" (Pp. 284-285). It is described as "A volatile oil obtained by maceration and distillation from the ripe kernels of Prunus Amygdalus amara DeCandolle (Fam. Rosacae), and from other kernels containing amygdalin." Under the heading "Note," the Pharmacopoeia states: "This Oil is intended for medicinal use; it must not be used for flavoring foods." (Emphasis supplied) (p. 285) The average dose suggested is: "Metric, 0.03 mil--Apothecaries, 1/2 minim." This oil also would contain amygdalin. A copy of this section of the Pharmacopoeia is attached as Exhibit B and incorporated herein by reference.

12. The 10th revision of the Pharmacopoeia, published in 1926, also refers to the oil of bitter almonds. It states that the oil is intended for medicinal use and that neither it nor its solution should be used or sold for flavoring foods (p. 249). The substance is again mentioned in the 11th edition, published in 1936, and the 12th edition, published in 1942. It is cautioned in both of these editions that the oil is intended for medicinal use, should not be used or sold for flavoring foods. Although the 1936 edition recommends the same average dosage as the 1916 revision, the 1942 revision does not mention an average dosage.

13. The "oleum amygdalae amarae" or oil of bitter almonds referred to in the above revisions of the official United States Pharmacopoeia contains amygdalin. Today amygdalin exists in both the liquid oil form and a solid crystaline form. The constituent elements of amygdalin are the same under both forms.

14. Prior to October 10, 1962, amygdalin, in both its liquid and solid form, was used and sold in the United

States. Indeed, between 1934 and 1945, I participated in the use of amygdalin at the hospital of the University of California Medical School in San Francisco. While acting under the supervision of staff physicians of this hospital, I personally used it in the treatment of cancer of patients at the hospital. Among these supervising physicians were Drs. Howard Nafziger, M.D., William Kerr, M.D., Glenn Bell, M.D., Salvatore Lucia, M.D., and Robert Stone, M.D. The amygdalin which I used was administered on patients intramuscularly and intravenously. During this time, the amygdalin preparation used by me at the University's hospital also was used by about a dozen physicians throughout California through the University of California Medical Schools and as recommended by members of the Hospital Staff of the University of California Medical School at San Francisco. These physicians, by medical and scientific training and professional experience, were qualified to evaluate the safety of substances such as amygdalin, and they recognized it as not only safe but as having some beneficial effects in the treatment of cancer. This has been recognized since prior to 1938.

15. Of my own personal knowledge, I know that both prior and subsequent to 1938 amygdalin was readily available to anyone who wanted it from United States suppliers of chemicals. Of my own personal knowledge, I know that before, during and after 1938, amygdalin was listed, and is still listed, as a purchasable item in various chemical catalogs published in the United States, e.g., Merck ~~Index~~ Catalog. Since the early 1900s, amygdalin has been commercially used and sold in the United States.

16. Among experts qualified by scientific training and experience to evaluate the safety of chemical substances and drugs, it is my information and belief that at least since

the early 1930s, pure amygdalin has been generally recognized as safe for use by human beings either by injection, intravenously or intramuscularly, or by oral intake. For example, pure amygdalin may be administered without adverse effects in amounts of 10 grams per day, orally or 3 grams intravenously, to a 150 pound man. It is my knowledge, based upon research and upon my own use of amygdalin at the University of California, that the conditions prescribed or recommended for its use then were appropriate on patients diagnosed as having malignant disease or cancer. Further, it is also my information that the conditions deemed appropriate for the use of amygdalin between 1934 and 1945 were also appropriate and were suggested, by proponents of amygdalin, as conditions for its administration on the day prior to October 10, 1962, as well as for a considerable time both prior and subsequent to that date through the present.

Charles Gurchot

CHARLES GURCHOT, Ph.D.

SUBSCRIBED AND SWORN to before me this 13 day of December, 1976.

Richard T. Knight

Notary Public in and for said County and State

OFFICIAL SEAL
RICHARD T. KNIGHT
NOTARY PUBLIC - CALIFORNIA
PRINCIPAL OFFICE IN
SAN FRANCISCO COUNTY
My Commission Expires February 20, 1979

MISTURA AMYGDALÆ.

℞ Confectionis Amygdalæ unciam;
Aquæ Destillatæ octarium dimidium.

Tere Confectionem cum Aquâ paulatim instillatâ, donec quam optimè misceantur; dein cola.

MISTURA ASSAFŒTIDÆ.

℞ Assafœtidæ drachmas duas;
Aquæ octarium dimidium.

Tere Assafœtidam cum Aquâ paulatim instillatâ, donec quàm optimè misceantur.

MISTURA CALCIS CARBONATIS.

℞ Calcis Carbonatis Præparati unciam dimidiam;
Sacchari,
Acaciæ Gummi in pulverem triti, singulorum, drachmas duas;
Aquæ Cinnamomi,
Aquæ, singulorum, fluiduncias quatuor.

Simul tere donec misceantur.

ALMOND MIXTURE.

Take of Almond Confection an ounce;
Distilled Water half a pint.

Rub the Confection with the Water gradually added, until they are thoroughly mixed; then strain.

ASSAFETIDA MIXTURE.

Take of Assafetida two drachms;
Water half a pint.

Rub the Assafetida with the Water gradually added, until they are thoroughly mixed.

MIXTURE OF CARBONATE OF LIME.

Take of Prepared Carbonate of Lime half an ounce;
Sugar,
Gum Arabic, in powder, each, two drachms;
Cinnamon Water,
Water, each, four fluidounces.

Rub them together till they are mixed.

OLEORESINA PIPERIS

Oleoresin of Pepper

Oleores. Piper.

PEPPER, in No. 40 powder, *five hundred grammes*..... 500 Gm.
ETHER, *a sufficient quantity.*

Place the pepper in a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle for volatile liquids. Pack the powder firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted. Recover the greater part of the ether from the percolate by distillation on a water bath, and, having transferred the residue to a dish, set this aside in a warm place until the remaining ether has evaporated, and the deposition of piperine has ceased. Lastly, separate the Oleoresin from the piperine by straining through purified cotton. Keep the Oleoresin in a well-stoppered bottle.

AVERAGE DOSE—Metric, 0.03 Gm.—Apothecaries, ½ grain.

OLEORESINA ZINGIBERIS

Oleoresin of Ginger

Oleores. Zingib.

GINGER, in No. 60 powder, *five hundred grammes*..... 500 Gm.
ETHER, *a sufficient quantity.*

Place the ginger in a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle suitable for volatile liquids. Pack the powder firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted. Recover the greater part of the ether from the percolate by distillation on a water bath, and, having transferred the residue to a dish, allow the remaining ether to evaporate spontaneously in a warm place. Keep the Oleoresin in a well-stoppered bottle.

AVERAGE DOSE—Metric, 0.03 Gm.—Apothecaries, ½ grain.

OLEUM AMYGDALÆ AMARÆ

Oil of Bitter Almond

Ol. Amygd. Amar.—Bitter Almond Oil

A volatile oil obtained by maceration and distillation from the ripe kernels of *Prunus Amygdalus amara* DeCandolle (Fam. *Rosaceæ*), and from other kernels containing amygdalin. It yields not less than 85 per cent. of benzaldehyde [C_7H_6O] and not less than 2 per cent. nor more than 4 per cent. of hydrocyanic acid [HCN]. The botanical

source from which it is derived must be stated on the label. Preserve it in small, well-stoppered, completely filled, amber-colored bottles protected from light and air. Oil showing crystals of benzoic acid must not be dispensed.

NOTE—This Oil is intended for medicinal use; it must not be used for flavoring foods.

Oil of Bitter Almond is a clear, colorless or yellow, strongly refractive liquid, having the characteristic odor and taste of benzaldehyde.

It is slightly soluble in water and soluble in all proportions in alcohol or ether. It dissolves, forming a clear solution, in 2 volumes of 70 per cent. alcohol.

Specific gravity: 1.038 to 1.060 at 25° C.

Refractive index: 1.5428 to 1.5439 at 20° C. (see Part II, Test No. 22).

It is optically inactive or dextrorotatory, not exceeding +0° 10′ in a 100 mm. tube at 25° C. (see Part II, Test No. 21).

When first prepared, the Oil is neutral to litmus paper, but afterwards develops an acid reaction due to the formation of benzoic acid.

It does not respond to the Test for heavy metals in volatile oils (see Part II, Test No. 3).

Hold the looped end of a piece of clean copper wire in a non-luminous flame until it glows without coloring the flame green, cool the wire, dip the loop into Oil of Bitter Almond, ignite the latter and hold it so that the liquid burns outside of the non-luminous flame. On slowly bringing the flame from the burning Oil of Bitter Almond on the loop in contact with the lower outer edge of the non-luminous flame, no green tinge is discernible (*chlorinated products*).

Add 10 drops of the Oil to a little alcohol, then add a small amount of zinc dust and 2 mils of acetic acid and boil the mixture for a short time; no odor of phenylisocyanide develops after rendering it strongly alkaline with potassium hydroxide T.S., adding a few drops of chloroform and heating (*nitrobenzene*).

Assay for benzaldehyde—Dissolve about 3 mils of freshly redistilled phenylhydrazine in 60 mils of alcohol and titrate 25 mils of this solution, which must always be freshly prepared, with half-normal hydrochloric acid V.S., using methyl orange T.S. as indicator. To about 1 Gm. of the Oil of Bitter Almond, accurately weighed, add 25 mils of the phenylhydrazine solution just prepared and allow it to stand for thirty minutes. Add a drop of methyl orange T.S., and acidify the mixture by adding a measured excess of half-normal hydrochloric acid V.S. Filter the mixture and wash the precipitate with small portions of distilled water until the washings cease to redden blue litmus paper. Then titrate the excess of hydrochloric acid in the filtrate with half-normal potassium hydroxide V.S. and subtract the number of mils of the half-normal hydrochloric acid V.S. consumed from the number of mils of the half-normal hydrochloric acid V.S. used in titrating the 25 mils of phenylhydrazine solution; the difference multiplied by 0.053 gives the weight of benzaldehyde.

Assay for hydrocyanic acid—Dissolve 15 Gm. of crystallized magnesium sulphate in enough distilled water to measure 100 mils, add 5 mils of this solution to 40 mils of distilled water, then add 5 mils of half-normal sodium hydroxide V.S. and two drops of potassium chromate T.S., and titrate the solution with tenth-normal silver nitrate V.S. to the production of a permanent reddish tint. Pour this mixture into a 100 mil flask containing about 1 Gm. of Oil of Bitter Almond, accurately weighed, mix well and titrate again with tenth-normal silver nitrate V.S. until a red tint, which does not disappear on shaking, is reproduced. Conduct this titration as rapidly as possible.

One mil of tenth-normal silver nitrate V.S. corresponds to 0.0027 Gm. of hydrocyanic acid. One gramme of the Oil corresponds to not less than 7.4 mils nor more than 14.8 mils of tenth-normal silver nitrate V.S.

Preparations—Aqua Amygdalæ Amaræ Amygdalæ Amaræ.

AVERAGE DOSE—Metric, 0.03 mil—Apothecaries, ½ minim.

— Exhibit "N" —

Health and Welfare Canada
Santé et Bien-être social Canada

Health Protection Branch
Direction générale de la protection de la santé

310 Federal Building
269 Main Street
Winnipeg, Manitoba
R3C 1B2

August 31, 1976

Mrs. Linda Miller
111 Balfour Avenue
Winnipeg, Manitoba
R3L 1N2

Your file Votre référence

Our file Notre référence

932-5

Dear Mrs. Miller:

This is to acknowledge your enquiry about importing medication from Mexico for your own personal use.

We do not issue permits in this regard, but see no reason to refuse entry of this proposed importation.

Products such as B-17, and Laetrile, cannot legally be sold in Canada because of insufficient evidence to establish their safety and effectiveness. However, at the present time, it is legal to bring medication into Canada for personal use, unless it is in a specific restricted category, such as narcotics or controlled drugs.

Yours truly,

V. F. Warkentin
Chief, Inspection Division

VFW/cd

— Exhibit "O" —

THE TROPHOBLAST THEORY OF CANCER

(JOHN BEARD, 1857-1924)

REVISITED

By CHARLES GURCHOT

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The Trophoblast Theory of Cancer (*John Beard,* 1857–1924) Revisited

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Key Words. Germ cell · Asexual generation – sexual generation · Trophoblast · Repression – derepression of genes · Phorozoon

Abstract. Beard's theory can be restated in a modified form in modern terms in the following way. Cancer represents primarily trophoblastic tissue derived either from an aberrant germ cell or from a somatic cell whose normally repressed 'asexual generation' genes are abnormally reactivated ('derepressed'). The variety of tumors, other than teratomas, may be due to a parallel chance derepression of some genes of somatic ('sexual generation') characters. This would be a defensive reaction against intramural parasitization by trophoblast and would result in the differentiation and hyperplasia of normally present more primitive somatic cells.

It is now more than 70 years since the Edinburgh zoologist and embryologist, *John Beard,* described his theory of cancer etiology from aberrant germ cells and trophoblast.

The theory has biochemical overtones and is only one aspect of his wide-ranging biological investigations. Whatever the theory's merits it deserves careful examination now in view of the directions cancer investigation has followed recently (92–94).

Beard's theory (1) was discussed in detail in 1911. As theories go, and whether right or wrong, it represents a successful effort of correlating many fields of biology as they apply to cancer. However, *Beard*'s investigations in cancer were meant to be only an interlude in his much more extensive studies in zoology and comparative embryology.

His conclusions in these fields were perhaps more revolutionary and at variance with accepted ideas than were his conclusions about the etiology of cancer. By many of his colleagues *Beard*'s work was regarded very highly, and they deplored his excursion into cancer because it shifted the focus of importance away from his remarkable work as a biologist. *Beard* himself considered his

cancer work a side issue. He pursued it as a humanitarian and because of the social implications of that disease.

Superficially *Beard*'s cancer theory may appear a complex variation of what he termed the Remak-Cohnheim theory of embryonic-rests. Since *Oberling*'s (87) discussion of it in 1946, the theory has been well-nigh forgotten. It deserves a brief restatement in *Oberling*'s words:

> 'As early as 1829, two French investigators, Lobstein and Recamier, attributed the origin of tumors to the proliferation of embryonal cells that had persisted into adulthood. Their suggestion, actually the first rational hypothesis on the origin of cancer, attracted enthusiastic support all through the 19th century. Johannes Müller, Paget, Remak, Durante, Cohnheim, and many others took it up and contributed original views and a formidable body of evidence that have done much to increase our knowledge of neoplasia. The idea of embryonal origin, though born of clinical observation, received from the very first the substantial support of pathologists. The microscopic appearance of cancer, with its multitude of cells and swarms of mitotic figures, is not without resemblance to that of embryonal tissue, and the likeness must have been particularly impressive in those early years when the technic of the microscope was so rudimentary as hardly to permit the recognition of minute structures.' 'But embryonic tissue in all stages of development have been inoculated into countless adult animals, and always with the same outcome; they never changed their character, but continued to act as they do in the embryo, growing for a time but ending as mature tissues' (87, p. 31).

Inspite of the disappointing negative outcome of the experimental tests the embryonic-rest theory remains provocative. In a sense, theoretically, it sidles rather close to cancer, but it leaves out the role of the germ cells and especially of what *Beard* called the asexual generation of the vertebrate life cycle. They apply to cancer, and are crucial to *Beard*'s theory as it will be explained later.

Unfortunately *Beard* appears, at first sight, to clash head on with verified conclusions at the cellular level and with biochemical observations, almost universally believed not to be accounted for in the trophoblast theory, in spite of those concepts in *Beard*'s theory which bear, in an important manner, upon phenomena associated with cancer. There is a general reluctance to attach the term trophoblast to pathological tissues which, although sharing properties with the trophoblast do not look like trophoblast and may be rather different from one another. However, these differences may be resolved. Moreover, the many similarities between cancer and trophoblast are striking and have been observed, enumerated and described on many occasions (2–12).

Presumptive, perhaps too simplistic, stereochemical similarities too were explored by *Beard* (1, pp. 143–165; 76) and described in a primitive experimental manner. His idea in this area was briefly described in 1940 (13) and briefly reviewed in that same year (14). However, the most extensive evidence to date of a possible relation between cancer and trophoblast is the close similarity of the endocrine profile, as well as the immunological properties of the two tissues (15, 93).

The endocrine profile, reported for unspecified hormones in 1936, 1938 and 1941 (88–91) was brought up to date by *Krebs* in 1973 (15). Human chorionic gonadotrophin (HCG) has been reported in cases of carcinoma of the lung (16, 17) and other cancers, as well as HCG-like reactions in large series (18). Adrenocorticotrophic hormone (ACTH) has been found in cancer of the thyroid (19), parathyroid (20), thymus (21, 22), lung (23–27), ovary (28), testicle (29), breast, prostate and pancreas (30, 31), in other cancers (32, 33), and in carcinoid tumors (34–39). Thyroid-stimulating hormone (HCT) was found in chorion (40, 41), in male choriocarcinoma (42), in a bronchial carcinoma (43), and in 1967 in eight females with choriocarcinoma (44). In 1967, HCT was immunologically and biologically identified in bronchial carcinoma (45) and found in association with HCG (46–48). In 1969, HCT was found to be antigenically distinct from pituitary thyrotropin (51). Growth hormone (GH) was reported in lung cancer (50). A melanocyte-stimulating hormone (MSH) was found in cancer of the pancreas along with ACTH (51) and again in another cancer (52). High titers of GH were found in the urine of cancer patients and pregnant women. The contention was made that properly performed studies would always reveal both ACTH and MSH (30).

In addition to the above review a recent detailed study by *Braunstein et al.* (53) of a heterogeneous series of 918 cases of testicular, gastrointestinal, hemopoietic, lymphomatous, sarcomatous, breast, bronchogenic, insulinomatous, mediastinal and melanomatous cancers revealed the presence of HCG in 113 cases. Tests for other hormones were not made.

In view of the properties of cancer tissues of all types, and their hormone profiles, it is difficult to avoid the conclusion of whether or not cancer is of trophoblastic origin – it doubtlessly behaves very much like trophoblast. Hence *Beard*'s generalization that *all* cancers are trophoblast is a remarkable statement especially since trophic hormone detection was virtually unknown in his day.

In the report of *Braunstein et al.* (53) the highest incidence of HCG secretion occurs in teratomatous and frankly trophoblastic cancers. This is to be expected where the trophoblast is morphologically recognizable, i.e. in cases where it is not permeated or mixed with somatic cells which could inhibit its hormone production either actively or simply by decreasing its relative mass. Scirrhus growths with their abundant fibrous tissue could be expected to be poor hormone producers. Lending additional support to the close similarity between cancer and trophoblast are the antiinflammatory effects of both cancer and trophoblast reported by *Fauve et al.* (93). These authors are aware that an analogy between cancer and trophoblast has been proposed before, including the implication that this analogy adds weight to the importance of their results. However, neither *Beard* nor reference to his work is mentioned. Another example of a similarity, less compelling because as yet it may not be exclusive, is

reported by *Currie and Bagshawe* (94) who state that '... a sialomucin similar to placental fibrinoid has been found on the surface of malignant cells ...' (94).

Furthermore, *Manes* (92) made the suggestion that a possible somatic resurgence of trophoblast by the activation of gene systems could explain malignant transformation. This view is somewhat similar to the conclusion offered in this paper. *Manes* also recognizes the suggestion made by *Beard* and refers to his work of 1902.

It is the purpose of this report to attempt to establish a reasonable argument that these and other analogies, including hormone profiles, are not simply coincidental, but suggest instead something approaching a biological imperative.

It must be kept in mind that *Beard* used in his cancer theory a rather unorthodox terminology derived from his equally unorthodox general biological concepts. This makes the understanding and acceptance of his views today somewhat difficult. Space does not permit even a general summary of the work of *Beard.* His work encompasses a complete reorientation in general zoology and comparative embryology. It includes the introduction of a logical order in biology approach similar to that of the physical sciences without specifically borrowing from them. But so far as only cancer and the use of *Beard*'s above-mentioned orientation in it is concerned, the following summary may suffice. The implications will be discussed later. A quotation from *Beard* may be inserted here since it epitomizes his views on epigenesis which are basic to everything he has proposed (1, pp. 54–55):

'In the higher animals – the Metazoa – what is termed "direct development" does not, and cannot exist. It has been found that the cycle of animal development, even of the highest forms, resembles very closely that of a fern or flowering plant (table I). In the line from egg to egg there are two generations – an asexual form, and one which, as it is the bearer of sexual organs, is spoken of as the sexual generation. Under prevailing views of development the line of ancestry from generation to generation is exceedingly simple – too simple, indeed, to explain the facts; so simple that Nature could not adopt it in practice, were she to make the trial. It may be represented thus: egg → embryo or sexual generation → egg → embryo, etc., the egg producing the embryo; the latter, when mature, forming from its own tissues new eggs. This is, undoubtedly, the most impossible conception which ever formed part of a science. The amended cycle of development and the course of heredity are as follows: egg → trophoblast (phorozoon or bearing animal, asexual generation) → primitive germ cell → primary germ cells → secondary germ cells → gametes, eggs or sperms → fertilized egg (fig. 1). In the line of ancestry, as given here, a line which apart from the asexual generation, is one of unicellular organisms, the embryo finds no place. It arises from one of the *primary* germ cells, whose number is always a definite one – 2, 4, 8, 16, 62, etc. – and the rest enter the embryonic body to form its sexual products ... The four important items in the cycle are: (1) The gametes, eggs and sperm, by whose union to form a zygote, a new cycle is initiated; (2) the first product of the zygote, the phorozoon, trophoblast or asexual generation; (3) the primary germ cells, destined for future generations, and (4), only important to enable the completion of the cycle, the embryo or sexual generation.'

Now a summary of *Beard*'s views regarding cancer can be given in these terms.

(1) All living embryonic and adult organisms are differentiated offshoots from an unending, potentially immortal stream of germ cells. The differentiated offshoot is a sheltering device for the life cycle.

(2) Within each life cycle, including the embryo, the germ cells are transferred from one generation (asexual) to the next generation (sexual).

(3) A considerable number of germ cells (primary and possibly some secondary, depending, upon the species) are lost or displaced from the unending stream during migration into an embryo. The displaced germ cells never reach the gonads which are the instruments of the sexual generation to propel and perpetuate the germ cell stream.

(4) With the exception of sponges and hydra all life cycles are composed of, or include, 2 alternating generations: an *asexual,* having no sex organs, followed by a *sexual* generation, possessing sex organs. The alternation occurs in mammals also.

(5) The asexual and sexual generations are mutually antithetic. In specific and normal circumstances each generation exists in toleration or at the expense of the other when the word antagonistic properly describes the relationship.

(6) The pregnancy trophoblast represents the mammalian asexual generation (table II).

(7) Cancer in man represents the activity of an 'irresponsible' trophoblast evoked from dispersed germ cells attempting, through gametogenesis, to repeat the life cycle in the wrong place, at the wrong time, and under circumstances disastrous to the life cycle as well as the host in which the attempt is made.

Point 7 of the above summary requires modification. This will constitute a departure from, or perhaps an addition to *Beard*'s postulates. The modification is necessary because we know that *all* cancers do not originate from germ cells. Points 1, 2 and 3 indicate what is in the process of being generally accepted, namely that teratomas originate from germ cells (54), not from 'budding'. The latter, sometimes a somewhat vague term, indicates an embryonic or somatic origin.

Budding has been perhaps most thoroughly studied in the armadillo, which regularly produces identical twins from buds that are clearly evoked from germ cells, not from embryonic cells (55–57). Benign teratomas too could develop from germ cells, but for some at least, if not all, there is a more logical explanation. To clarify the status of teratomas it is useful to examine the present status of the primitive, primary and secondary germ cells and their relation to the gametes.

By 1960, in spite of the ever increasing evidence favoring the precocious and somatically independent existence of the germ cells, and their exclusive role in the formation of gametes, some biologists still held that the issue was not settled. Since then the controversy has been fast eroding away, especially under the impact of very ingenious studies by *Mintz* (58), *Smith* (59), *Meyer* (60), and

Reynard (61). Of course no one will formally announce that the germ cells have been finally liberated from the long apotheosis of the soma. The issue more nearly resembles the fate of old soldiers who never die but simply fade away.

Not only have the germ cells regained their freedom but their vicissitudes as described by *Beard* (62, 63) have been and continue to be verified (54, 64, 65). Not only is every embryo produced by the unfolding of a primary germ cell (embryonic in destiny according to *Beard*), not only do we know now that the remainder of the *primary* germ cells migrate toward the mesodermal gonadal folds to become *secondary* germ cells and ultimately gametes, but that in many cases they multiply as they go (65) – except perhaps in birds in which the germ cells migrate through the bloodstream – so that their total number may increase many times. According to *Witschi* (65), 'during the migratory period they are ameboid and their number continues to increase by repeated mitoses. As migration ends they total 5,000 or more.'

According to *Beard*, 10–30 % do not reach the gonadal folds and are dispersed, depending upon the species, to come to rest finally at extragonadal sites where, interestingly enough, most teratomas and cancers occur.

Some of the displaced cells degenerate and some involute (62, 63). These aberrant germ cells should normally have no further function, but in man, evoke, some of them, all teratomas – certainly the malignant teratomas – and possibly some benign teratomas, and at least some cancers – how many is uncertain in view of an alternative origin of the asexual generation (the trophoblast) to be discussed later.

According to *Stevens* (54), 'Teratomas are derived from germ cells ... extragonadal teratomas are rare and they are thought to be derived from germ cells that became misplaced during their migration from the yolk sac to the genital ridge during the fetal life.'

Bresler (66) concludes that testicular teratomas are started by 'pathological cleavage of spermatogonia and formation of three germ layers ... and a trophoblast'. Only the trophoblast is invasive and metastasizes.

Bresler also reports the formation of teratomas from *adult* spermatogonia (67). This is important because it would indicate that an adult spermatogonium is still totipotent and capable of undergoing gametogenesis (growth and ripening) to produce an ovum rather than a spermatozoon to possess the capacity for evoking trophoblast if a malignant teratoma is to result (2, pp. 156–159). If the teratoma is benign, that is without evocation of trophoblast, the adult spermatogonium would have undergone embryogenesis such as a primary germ cell can achieve, without the development of that stage of gametogenesis, necessary for the evocation of a trophoblast. It is doubtful that *Beard* would have agreed with this for he believed that secondary germ cells lost their power of independent development. He would probably not have accepted the possibility of a spermatogonium reverting to a primary germ cell without first going through gametogenesis and cleavage as an egg. But like the question of a primary germ cell having to be 'embryonic in destiny' to evoke an embryo – about which more later – these are intricacies in the details of his deceptively simple theory of cancer from trophoblast and aberrant germ cells which he may not have lived long enough to clarify.

Table I. Revised comparison of animal and plant life-cycles (from *Beard:* 1, p. 127)

Animal	Plant
Asexual generation	
Zygote or fertilized egg (2 n)	Zygote or fertilized egg (2 n)
Phorozoon or trophoblast	Sporophyte or flowering plant (2 n)
Formation of primitive germ cell (2 n)	Formation of primitive spore mother cell (2 n)
Formation of primary germ cells (2 n)	Formation of spore mother cells (2 n); reduction and sex determination
'Apospory' (reduction postponed)	Spore formation
Sexual generation	
Primary germ cell (2 n)	Spore (1 n)
Origin of embryo by unfolding of a primary germ cell, inclusion of rest in the individual of the sexual generation (2 n)	Origin of sexual generation or gametophyte from one spore (1 n)
Ripening of germ cells; Reduction and sex determination	Ripening of germ-cells; Reduction previously effected.
Sperm Egg	Sperm Egg
Zygote	Zygote

1 n = Reduced number of chromosomes, and 1 n signifies the emancipated cell; 2 n = duplicated or conjugated cell, the 'conjugation' or joining together being carried out at fertilization. The 'reduction' is the undoing of the previous duplication effected at conjugation.

But evidently no trophoblast can be evoked from an *unchanged* primary germ cell, and that change can be nothing else than the change to a secondary germ cell followed by gametogenesis. Before a germ cell can produce a trophoblast (*as well as* an embryo later) it must develop to the stage of gametogenesis – but only growth and ripening, not necessarily meiosis also, and certainly not only meiosis (table I). In mammals gametogenesis and meiosis are closely related in time and space, but they are separate processes and serve different functions. Meiosis effects the redistribution and reduction of the chromosomes for eventual amphimixis with the chromosomes of the gamete of the opposite sex during fertilization if there is one. Meiosis plays no role in the preparation of the gametes for the purpose of evoking and separating during cleavage those blastomeres which will be the antecedents or *anlagen* of the trophoblast.

Normally the male gamete, *per se,* does not provide cellular *anlagen* that form trophoblast. This is evident in view of parthenogenesis. But in teratogenesis, in the testis for example, a spermatogonium still in a stage corresponding to that of a secondary germ cell, could evoke trophoblastic *anlagen* abnormally and produce a malignant teratoma parthenogenetically.

The distinctive places and functions that separate gametogenesis from meiosis are illustrated by the fact that in some plants reduction occurs *before* gametogenesis which is essentially growth and ripening (table I). In animals meiosis occurs *after* gametogenesis. *Beard* puts the matter succinctly:

'The formation of the primary germ cells in the skate – and in all probability in every other Metazoon – corresponds broadly to the genesis of spore-mother-cells on the asexual generation of a plant, the sporophyte. With this recognition it becomes possible to compare together, so as to show their essential similarity, the phenomena of the life-cycles of the Metazoa and Metaphyta' (95).

Another interesting conclusion, drawn by *Stevens* (54), is that 'the high degree of repeatability of experimental induction of teratomas in the mouse suggests that the neoplastic change is not the result of genetic mutation. It seems more reasonable that the activity of the genes has been changed in the environment provided by the adult testis.' This theme will be discussed in some detail later.

In spite of the major role played by the germ cells and trophoblast in *Beard*'s theory of cancer the hub of the matter is the existence, role and functioning of the asexual generation of the life-cycle.

While seeking an explanation of the properties of cancer cells we emphasize glycolysis, increased proliferation rate and invasiveness which are, after all, properties of normal cells too. The difference between cancer and normal cells is not simply quantitative but qualitative. The emphasis should be placed on the eroding, spreading, and destructive properties of cancer cells as well as the toxic and wasting effect of cancer upon its host.

These properties are not explained by those that cancer shares with normal cells. *Beard* expresses this in the following way:

'Reviewing matters, starting with the fertilized egg, this gives rise to an asexual generation – the trophoblast, upon which there arises an "apical cell" – the primitive germ cell. This latter divides a certain limited number of times, this number being a fixed one for the species; but while it is *n* in the male, it is *n* plus 1 in the female. The products are 2, 4, 8, 16, 32, 64, 128, 256, 512, etc. In the diagram (fig. 1) it is depicted as 128. These 128 germ cells are the primary germ cells. It is they which enter the embryonic body when this arises, and it is some of them which come to ocupy all sorts of abnormal positions. But all the line of primary germ cells are not destined for future generations. Some few of them, 1, 2, 4 or 8, are embryonic in destiny. At least one of these must unfold to form an embryo. If any of the others do so, the result is identical twins, triplets, etc. If any of these "embryonic" germ cells lie dormant within the developed embryo, they may become the seed of future tumors, as will appear later on. The line of heredity so far revealed, leads from fertilized egg to the primary germ cells, and thence through all the history of the germ cells, within the "reproductive glands" to new eggs and sperm; that is, all things considered, the cycle is one of unicellular organisms, the germ cells, in the history of which the sexual generation or individual is but an incident' (1, pp. 128–129).

'In animals and plants two modes of reproduction are recognized, the sexual one by means of germ cells, eggs and sperm, and the asexual by budding, which is really a process of continuous indefinite cell division, with no eggs or sperm. In an animal or plant a sexual generation is one which bears reproductive organs, in which eggs or sperm or both arise. On the other hand, an asexual generation of an animal or plant is one which never bears reproductive organs, eggs or sperm or both, but which reproduces in the way indicated above, really by cell division. In plants the asexual division is the flowering plant which is capable of indefinite unrestricted increase, as, for example, a hybrid rose or ... chrysanthemum. Originally there was but one plant of each of these. The sexual generation of a flowering plant is a small microscopic entity contained within the flower. In animals all the individuals which bear sexual organs belong to the sexual generation, while the asexual generations are represented in various ways. Thus in the sea polyps, the colony of polyps, while here the medusae or "jelly-fish" are sexual; in worms, starfish etc., by what are known as *larvae,* while here the worm, starfish, etc., are sexual; and lastly, in the highest animals or mammals the asexual generation is present only during uterine life, as what Hubrecht termed the trophoblast' (1, p. 13).

At this point we are aware of a discrepancy between *Beard*'s conclusion that the number of primary germ cells is a constant for the species and the observations of several investigators that migrating germ cells multiply as they go to total numbers in excess of the species-specific number postulated by *Beard* for the species of fishes he studied. The discrepancy can be explained. *Beard*'s highest species number of primary germ cells in elasmobranchs is written as 512 etc. – the product of eight cellular divisions of the primitive germ cell, or apical cell. Hence *Beard* does not exclude, generally, primary germ cell numbers higher than 512. If 512 cells were to undergo, in some animals, three more divisions their total would be 4,096 cells. This is nearly the number of dispersed germ cells (5,000 or more) counted by *Witschi* in human embryos (64). Also, *Beard* points out that, 'For the extremely large number of eggs produced by many

Table II. Life-cycles (from *Beard:* 1, p. 263)

Name	Asexual Generation	Sexual Generation
Nemertine	*Pilidium*	Nemertean worm
Sponge	Sponge-larva and adult	Absent
Sea urchin	*Pluteus*	Sea urchin
Hydra	*Hydra*	Absent
Hydroid polype *(Campanularia)*	Hydroid colony	*Medusa*
Raja batis	Blastoderm, transient nervous system, etc.	Skate
Mammal (e.g., man or rabbit.)	Trophoblast (chorion)	Mammal

invertebrates it would appear necessary not only for large numbers of secondary germ cells to exist but for commensurably large numbers of primary germ cells as well.' The secondary germ cells would be those normally formed from primary germ cells after reaching the gonadal folds. 'In the skate this formation of secondary germ cells precedes the announcement of the sex of the embryo and is possibly causally related to it (96).

We come now to the reciprocal relations between the asexual and sexual generations that reflect the spreading and destructive properties of cancer cells. What we are dealing with here is a peculiar phenomenon or, better, two phenomena: one is the enzymatic proteolysis of one live tissue by the enzymes of another live tissue. These two tissues represent two morphogenetically different organisms within the same life cycle (table I, II). Hence the importance of considering their behavior as that of two antithetic generations, as *Beard* described it, both very much alive and potentially agressive toward each other (1, pp. 54–55) even though they belong to the same life-cycle.

The second phenomenon is the unlimited power of growth best illustrated in plants by the sporophyte that can multiply indefinitely from cuttings and grafts; and also by the trophoblast's potentially unlimited growth capacity as well as a normal permeating invasive tendency directed into the maternal organism during a normal pregnancy.

Since the asexual generation in all forms shelters the germ cells before the embryo is evoked to serve as the second lap for the unending stream, the early nutrition of the embryo must be provided for. This early nutrition has to be provided by the asexual generation, the first in the life-cycle to develop. For this nutritive function the asexual generation has special properties. The embryonic organism, appearing later than the asexual generation, cannot actively feed itself in its early stage; hence the asexual generation's embryo-nursing function.

All young or immature invertebrate organisms are generally called larvae. From *Beard*'s viewpoint this is confusing and imprecise because some are asexual and others are sexual generation organisms. This obviously would lead to confusion. *Beard* cuts the Gordian knot by coining the word 'phorozoon' (Greek for 'bearing animal') to describe the asexual generation 'larvae', reserving the word embryo for the immature sexual generation. The mammalian phorozoon is the trophoblast. Phorozoa in invertebrates, trophoblast in mammals, chorioallantois in other forms, provide the pantry for the early embryos developing upon or within phorozoa from primary germ cells, resulting from the multiplication of that apical primitive germ cell that *reappeared* (or came again into existence) at the end of cleavage (1, pp. 128–129).

That the phorozoon and the embryo are distinct and virtually separate organisms is shown by the fact that in invertebrates, where this is easily observed, (for example Echinoderms) the body axis of the phorozoon is *perpendicular* to the body axis of the embryo (69); and as both developments are traced the embryo is observed to grow at the expense of the phorozoon which is eventually absorbed (69).

As *Beard* described the process, the disposal of the phorozoon by the embryo is not a 'substitution of organs' as one biologist suggested, but a substitution of *organisms.* Since an early embryo has neither prehensile nor killing devices it, in effect, preserves the phorozoon while gradually digesting and absorbing it.

In this type of proteolytic digestion of and by live tissues *Beard* detected an enantiomorphic stereochemical relationship, based on the work of *Pasteur.* In view of the complex character of modern stereochemistry *Beard*'s conclusions in this area are weak or simplistic at the moment. They are not essential to our present discussion (1, pp. 255–264).

Since the trophoblast represents the mammalian asexual generation it would follow logically that: 'During the first week of implantation (it) literally eats its way into the maternal stroma' (70, 72, pp. 37–48). The antithesis – the digestion operating in the reverse direction, which normally should occur in the later stages of pregnancy is not as clear-cut, but the phenomenon is there. *Hertig* states: 'Another thing to remember about invasive moles, as about trophoblast in general, is their inherent tendency to undergo spontaneous involution' (72). And, according to *Patten* (71): 'From the standpoint of functional significance in the development of the embryo one would stress the exuberant development of the trophoblast during the period of invasion, followed by the gradual reduction of the epithelial layers of the villi after their invasive role has been carried out, and the thinning thereby of the amount of tissue for which the interchanges between the fetal and maternal blood takes place.'

In analogy, but more actively, the living *pluteus* (the asexual generation of sea urchins); the *pilidium* of nemertine worms; or the *trochophore* of *Nereis,* are

gradually digested live and absorbed by their respective embryos developing from primary germ cells within their asexual generation precursors, until nothing remains of the *phorozoa* (1, pp. 255–264; 69, 73, 74). Similar phenomena occur in vertebrates (68, 75).

During pedogenesis, in the fly genus *Miastor* for example, the normal embryo, a normal guest in the body tissues of its mother – which is also an embryo but in a later stage – and surrounded by its chorion deep within the embryonic tissues of the mother insect, digests its way through and out of the live body of the mother embryo which is left to die (77).

An analogous phenomenon occurs in the case of the small tapeworm *Tenia echinococcus.* Here the inner cystic envelope formed by the worm's asexual generation occasionally proliferates into the *alveolaris* modification to erode and spread throughout the human host's tissues, while usually, it is kept in check as a hydatid cyst by a tough fibrous membrane formed by the parasitized soma which covers and invests, and limits the inner cystic envelope of the parasite.

So much like cancer is the *alveolaris* modification that it was at one time diagnosed as colloid cancer until *Virchow* recognized its true nature (78). Another peculiar situation of this type is occasionally encountered in incubating eggs of birds (79), fishes (80) and insects (81) in the event that there is no noticeable or normal embryonic development within the blastoderm. In such eggs, a peculiar mass grows, a development of chorioallantoic tissue and other equivalents of the mammalian trophoblast, at the expense of a destroyed or abnormal embryo.

The above are a few examples – there are many more – of the normal and also of the accidental antithetic relations manifested by the two generations of the life-cycle in different animals. According to *Beard,* asexual-sexual antithesis is a universal phenomenon of which cancer is but a special case.

If, apart from choriomas and teratomas, cancer in mammals is usually a mixture of masked trophoblastic and somatic tissues – the ambient somatic tissues proliferating either as a result of stimulation by or as attempted protection against the trophoblast, or for other reasons – where does the trophoblast come from if not from germ cells?

If *Beard* is right, at least some nonteratomatous cancers may originate from aberrant germ cells. However, since it is now well established experimentally that cancer can be induced *in vitro* physically (radiation), chemically (carcinogens) or biologically (viruses) from virtually any somatic cell we can assume that such induction can occur *in vivo* also. In fact we know it does. The morphological character and clinical manifestations of animal and accidental, chemically induced, human cancers are so similar that a basic identity between a formal etiology of *in vitro* and *in vivo* cancer is justified. The results of experimentally induced cancer are so extensive and so well known that no summary will be attempted at this time (97, 98).

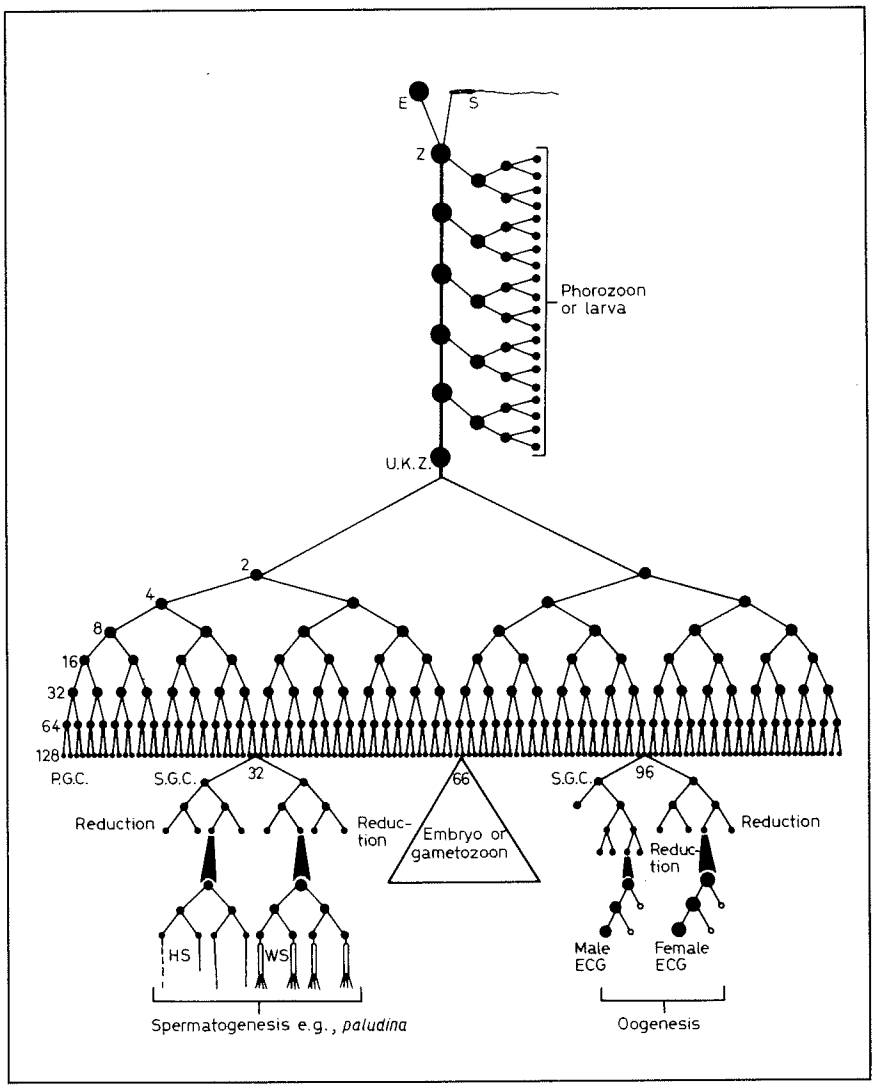

Fig. 1. Beard's original diagram to explain his concept of two alternating generations in the life-cycle of animals (1, p. 124). The original legend is the following: 'Diagram of the life cycle of a backboned animal, such as a fish or a mammal, illustrating the union of egg and sperm, E and S, to form the zygote, Z, the origin of the phorozoon or asexual generation (trophoblast), the germinal track from Z to U.K.Z, the latter being the primitive germ cell. The divisions of the latter are carried to seven mitoses or cell-divisions, as in some male dog-fish (in a potential female embryo there would be an additional division, giving 256 primary germ cells). Diagrammatically, the unfolding of one primary germ-cell, the 66th, is depicted as forming an embryo or sexual generation. To complete the track of heredity

Since *Beard*'s explanation of malignant tumor formation based on germ cell origin alone will not suffice, a more inclusive explanation is required. In view of the progress of chemical genetics such an explanation can be formulated. Although it represents a correction of *Beard*'s general thesis it also tends to validate his principal conclusion, namely the role of trophoblast in cancer.

The basis for a more inclusive explanation than *Beard*'s obligatory germ cell origin of cancer is the experimentally derived generalization that 'all cells have a fund of genetic information which they do not use or express' (82). In other words the function of any cell represents the result of the greater or lesser expression of the 'information' contained in the cell's complete genetic potential and the repression of the remainder in a physiological or pathological manner. From this a correction of *Beard*'s theory follows logically. The source of the genetic information remains intact because 'the whole blueprint is faithfully copied at each cell division, from that of the fertilized ovum to those (divisions) taking place in the mature adult organism' (82).

Thus in a gamete or zygote, the portion of the genetic potential representing the sexual generation is repressed. If there are dynamic degrees of repression of genes – which is probable as we will see – the repressors of the sexual generation must be firmly held at this stage. On the other hand the repressors of the asexual generation's genetic potential are loosely held as a result of gametogenesis. This appears to be necessary to allow for the actual evocation of the asexual generation during cleavage. In a gamete, or zygote before cleavage, the still unexpressed asexual generation potentiality would be on its mark as it were, ready to be evoked or completely derepressed at the onset of cleavage. Cleavage would therefore represent the number of divisions required to evoke the cellular *anlagen* that would unfold or differentiate into asexual generation tissues. At the end of cleavage, all asexual potentialities having been evoked, *Beard*'s 'apical cell' will appear, known as the primitive germ cell, in which the asexual generation repressors are in full force again. At this point the blastocyst would be fully formed; but not resting. The primitive germ cell would begin the series of divisions to form the species-specific number of primary germ cells (fig. 1). These would collect at first in, and make up part of, the inner cell mass. It is very improbable that the number of primary germ cells in the inner cell mass can ever

from generation to generation through the morphological continuity of the germ-cells a diagram of oogenesis or egg formation has been appended to the 96th germ-cell, and one of spermatogenesis or sperm-formation to the 32nd. In the former the formation of a male egg and of a female egg is shown, in the latter the two forms of sperms (as in the fresh-water snail, *Paludina*, after the statements of F. Meves), i.e. the hair-like or functional, and the worm-like or functionless sperm. The additional division in the formation of functional male eggs should be noted. It accords with the additional division to form primary germ-cells in the development of a female.'

be the total species-specific number *Beard* observed, for example, in elasmobranchs (1, pp. 54–55; 62). But it is probable that the germ cells in the inner cell mass are those that are 'embryonic in destiny' since the inner cell mass stage is immediately followed by the formation of an embryonic disk.

Although the primary germ cells have been observed, so far, to migrate only from the yolk sac, it is reasonable to assume that the species-specific number is being developed before the yolk sac stage. In any case the primary germ cells very likely lose no time migrating into the developing embryo to multiply as they go before they reach the gonadal folds (65). They will develop eventually into gametes by way of secondary germ cells (1, pp. 54–55) or they might develop as embryo-forming cells if the proper – probably very proper – environment is available. This could occur in a blastocyst, less likely in a later embryo except in pedogenesis, and, very unlikely, in an adult organism. This may appear contradictory, but more about it later. Development in a blastocyst would be the usual, normal embryogenesis. Except for pedogenesis which normally occurs in the fly genus *Miastor,* and without the lethal result, in some axolotl *(Ambystoma),* embryogenesis might occur from a primary germ cell within an embryo or adult to produce a benign teratoma – really an abnormal misplaced identical twin. More likely, and probably much more so in an adult than in an embryo, a dispersed germ cell would go through gametogenesis within the soma and produce a malignant teratoma. The reason for this is the presence of gonadal hormones everywhere in an adult; but less likely to be present throughout an embryo. Embryogenesis would require derepression of sexual generation genes. The asexual generation repressors would remain in force. As a result of gametogenesis the reverse would occur, the derepression of the genetic endowment of the asexual generation. It it is justified to describe a primary germ cell as a pivotal cell, especially the primitive apical cell, it might be represented as an internally compensated cell in terms of those genes that represent two antithetic generations. By contrast how would the secondary germ cells be described?

The *primitive* germ cell appears at the end of cleavage according to *Beard* (fig. 1). In some forms the number of cleavage divisions is small – two or three. In others, there may be as many as eight, as in the frog. At the end of cleavage all derepressed genes of the asexual generation would have completed their function, at least for the time being, leaving a compensated *primitive* germ cell – let us assume a 'firmly' compensated germ cell.

The ensuing divisions of that apical primitive germ cell into *primary* germ cells might, in one sense, be analogous to cleavage. But in the primary germ cells it would be the genes of the sexual generation that would be candidates for derepression to make embryogenesis possible. Thus in general only primary germ cells could be forerunners of embryos. But a primary germ cell, 'embryonic in destiny', would normally have to be one in a blastocyst at a certain time. The secondary germ cells on the other hand would be, in a sense, compensated again

and await the specific chemical influences of gametogenesis to derepress the asexual generation genes once more so that the asexual generation could be evoked should the gamete undergo cleavage.

This brings up the difference between the primitive germ cell and the secondary germ cells before the latter undergo gametogenesis assuming both to be compensated. Here we may have to borrow from ecology. There is little doubt that the blastocystic environment – presumably surrounding the primitive germ cell, and also its progeny – of those few primary germ cells embryonic in destiny is very different from the future somatic environment of the primary and secondary germ cells.

For one thing, the environment of the inner cell mass is the only one during the life-cycle when germ cells are *normally* in close contact with asexual generation or trophoblast cells. If it is true that in a fairly well differentiated neoplasm for example, the somatic cells in that neoplasm are stimulated to proliferate because of the proximity of cancer cells – assuming these to be trophoblast cells – we may understand the possible reason why germ cells in the inner cell mass are spurred, as it were, to be embryonic in destiny; but that *per se* they are not after they have migrated into the embryo.

There is probably no comparison between the environment of the inner cell mass and the environment of the gonads, or, assuming that the primitive germ cell may be in a sense comparable *per se* to the secondary germ cells, between the primitive germ cell-blastocyst system and the secondary germ cell-gonad system. No matter what kind of cell, if all the genes are always there, the change or vicissitudes of the environment of the cell and the genes will determine which genes or combination of genes will operate.

Although derepression of genes of the asexual generation occurs normally during gametogenesis, the possibility remains that it can occur at any time in somatic cells – since the genetic information is there – provided requirements are met even when such derepression is no longer a normal occurrence. However, there must be differences between, let us say, the repression dynamics in a germ cell, a gamete and a somatic cell.

Since a primary germ cell has to undergo derepression of the genes of the sexual generation, such as in twinning in armadillos, for example (55–57), the genetic information representing the asexual generation must be firmly repressed. It would be, therefore, a main function of gametogenesis to derepress the genes of the asexual generation so that it can be evoked easily during cleavage. The repression of genetic information representing the asexual generation in a somatic cell continues the process begun in the primary germ cell. Repression may become progressively tighter as cellular differentiation progresses until derepression of genes necessary to bring about simple mitosis may become difficult or impossible. This could be another reason why only germ cells and not somatic cells can become gametes in the gonads. Also it would tend to explain

why chemical carcinogenesis, oncogenesis by artificial influences or hormones, or protracted exposure to unphysiological environments would be necessary to derepress the genetic endowment of the asexual generation in the differentiated soma and why it is statistically unlikely to occur, except in chemical carcinogenesis.

Moreover, in view of the orderly and controlled sequence of cellular differentiation we can assume that the progressive derepression of genetic information repressors is itself genetically determined just as it must be during gametogenesis. If for an adult somatic cell we postulate the possible derepression of asexual generation genes, it would be as a possible or small chance event out of other chance derepressions. Also a gene-controlled derepression such as would occur in normal gametogenesis would not occur at this time.

If, too, we assume an oncogenic virus, for example, to have a predilection for repressors rather than for genes etc., it would tend to explain its status – oncogenic rather than cell-destroying. Then too, along with predilection for repressors an oncogenic virus might at the same time derepress, again by chance, other cell growth capacities, such as derepressing the melanocyte-producing mechanism and endow a tumor with the character of a melanoma.

An adenocarcinoma or a sarcoma might be explained in a similar way. A rhabdomyosarcoma, on the other hand, might just as well originate from an aberrant germ cell as from a somatic cell whose genes for 'asexual generation' characters were derepressed. Leukemia might logically result in the environment of a similarly 'derepressed' undifferentiated potential mesenchyme, and so on. A trophoblast, evoked from an aberrant germ cell might be, as part of a teratoma, associated with a cluster of embryonic tissues quite different from cells associated with a trophoblast evoked by derepression of the 'asexual generation' genes of a differentiated, more nearly adult cell. This might explain the difference between the morphology of teratomas on the one hand and carcinomas and sarcomas on the other hand. In the case of anaplastic tumors we might have to assume that little if anything else than the trophoblast undergoes the type of gene derepression which is here envisaged.

It is conceivable that all overgrowths: hyperplasias, benign tumors, cysts, keloids, etc., are expressions of derepressions of 'sexual generation' genes in somatic cells on the pathologic level. Bone calluses, temporary scarring, leucocytosis, might all be physiologically controlled gene derepressions. In cancer, derepression of the 'asexual generation' (trophoblast) genes in somatic cells could come into play and give a tumor its varietal character by derepressing certain genes in neighboring cells resulting in differentiation and also proliferation. But whatever gene derepressions occurred, the proliferating somatic tissue could not be cancerous unless there occurred at the same time in somatic cells derepression of the cluster of genes producing asexual generation characters with the capacity for destructive invasion, unlimited reproduction, and production of

trophoblastic hormones, simulating those of the pituitary and the ovaries, as in pregnancy.

Gene derepression may not, by itself, account in every way for the appearance of the asexual generation in the soma. The precise mechanism of derepression of asexual generation genes in somatic cells still would have to be clarified.

The trophoblast, if not infected by virus and having its normal origin, as in pregnancy (and even in the unphysiological cases of tubal pregnancy), will proliferate and invade other tissues until checked by a resumption of physiological control. The organs of gestation are geared to this kind of performance. Would a virus-free trophoblast survive within the rest of the soma? Or would its survival require the presence of an oncogenic virus? Probably not, if everything else is equal.

In chemical carcinogenesis the carcinogen is not reproduced and tends to be detoxified and eventually excreted. Furthermore, once the genome of the asexual generation characters is derepressed and a trophoblast is evoked its growth tendency would probably continue regardless *how* the repressor was derepressed (93). Finally, if continued virus infection were required to produce other cancer cells, virus carcinogenesis might be self-limiting since any specific gene derepression caused by virus can be a chance occurrence only.

Hence a malignant tumor probably *need not* contain any oncogenic virus beyond the time and stage of the initial presumed effect on gene derepression. If this is true the search for oncogenic viruses in cancer growth would be fruitless, or at least inconclusive even if the malignant process were virus-induced at the beginning. Repeated tests for virus might yield widely different quantitative or even negative results. All this is quite different from phenomena attached to the expression of somatic mutation.

Mutations are an affair of the abrupt modification of one or more genes during meiosis. And meiosis is an affair of germ cells, so far as we know.

Meiosis has been often observed in the soma. This is perhaps another indication that the adult soma contains aberrant germ cells. If a mutant is to be quasi normal and viable, a helter-skelter genetic disturbance by virus invasion would be the worst sort of mechanism to change the orderly framework of a species that reproduces and differentiates with precision. Most likely an oncogenic virus does not effect anything permanent in the genes; but there is little doubt that it removes or changes something in the cell. If it removes or changes too much, the cell dies.

Prolonged artificial cell culture with its slow development of a respiration-restricting metabolism is in effect a special type of chemical carcinogenesis. The influence of glass or plastic is mediated probably through adsorption or preferential wetting of the vessel by the surface of cells with diminished respiration at the adsorbed areas. Metabolites could combine with gene repressors to inhibit or neutralize them. Chemical carcinogenesis could effect a more vigorous and more

rapid derepression following chemical reaction with repressors. A more rapid development of malignancy could occur.

Viruses derive their sustenance in a nuclear environment by attacking its components and may do so without destroying the cell by preying on repressors to evoke potentialities out of their normal ontogenic order. Apparently oncogenic viruses do not usually attack the genetic apparatus itself, by creating lethal mutations or destroying the cell, as other infective viruses do. They may do so in special circumstances.

The gametogenic hormones induce malignant teratomas by evoking gametogenesis of germ cells in the manner in which the hormones function in the gonads. This may involve gene derepression. Hence all teratomas show important similarities regardless of their disorder or degree of development. Benign teratomas, judging from *Ewing*'s observations (7, pp. 1046–1047), are those which, like the normal embryo, have brought about destruction or degeneration of their trophoblast. It may be that there is seldom, if ever, a teratoma benign from the onset of its development. This means that every human being begins development as a potentially malignant teratoma.

There is one area in cancer development in which trophoblast betrays its presence unmistakably. This is seen in primary extragenital chorionepitheliomas which turn imperceptibly into carcinoma and sarcoma (83–85). Since we are dealing in either case with one and the same tumor, now chorioma, now carcinoma or sarcoma, the gradation probably should not be attributed to derepression of asexual generation genes in somatic cells because if a trophoblast tumor reveals a semblance of chorionic villi it is teratomatous and originates from an aberrant germ cell. Hence the carcinomatous or sarcomatous development may be a degree of protective somatic response that succeeds only in influencing the trophoblast's typical morphology.

This is not an unusual phenomenon (see *Maximov,* 86) nor is it unexpected if we can, in addition, postulate that the carcinomatous character represents a growth stimulus directed toward undifferentiated epithelial cells in the soma which normally replace spent parenchymal cells.

Normal uterine nidations, pedogenesis, invertebrate phorozoon development or replacement, to use *Beard*'s terminology, *Tenia echinococcus alveolaris,* anidians or chorioallantoic monstrous growths in eggs, are all normal and abnormal invasive and destructive processes that involve trophoblast cells or their extra-embryonic equivalents in different species.

Fortunately, abnormal gene derepression would be no less fortuitous *in vivo* than *in vitro* – not dependable and therefore improbable. For this we can be thankful.

In conclusion, a malignant tumor may represent primarily trophoblastic tissue, derived either from a germ cell, or from a somatic cell whose normally repressed asexual generation potentiality is accidentally derepressed. Further-

more, the varietal character of tumors, other than teratomas, may be due to a parallel, simultaneous, chance derepression of some other genes, controlling somatic characters as a possible defensive reaction against an intramural parasitization. This results in the differentiation and hyperplasia of normally present more primitive somatic cells.

Finally, to quote *Oberling* (87, p. 9): 'Some day, perhaps it will turn out to be one of the ironies of nature that cancer, responsible for so many deaths, should be so indissolubly connected with life.'

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— Exhibit "P" —

Physician's Handbook

of

VITAMIN B-17 THERAPY

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PHYSICIAN'S HANDBOOK

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PREFACE

Cancer, like many diseases, is an expression of conflict between the living organism and hostile factors in the total environment.

The mind, through the nervous system, can influence this conflict constructively or destructively.

Hence to a varying degree Cancer is something which the mind is permitting to happen to the body.

From contact with more than 5000 Cancer patients over the past 15 years it is apparent that for many of them Cancer was a form of socially acceptable suicide.

For best results under Vitamin B-17 therapy the patient must co-operate mentally and physically, positively and actively in his treatment.

More often than not: Quitters die, Fighters live.

Andrew R. L. McNaughton

CONTENTS

Second Edition

INTRODUCTION

Excerpts from the writings of Dr E. T. Krebs, Jr., 1973

Our present state of knowledge accepts that Cancer is a chronic metabolic disease[1] in which the host resistance is diminished. All metabolic diseases now prevented or cured are, without exception, prevented or cured by vitamins, minerals, and other factors normal to the diet and to the animal economy. By contrast, no chronic or metabolic disease — or any other disease *of the host* has ever been prevented or cured by toxic chemicals or by radiation or by anything else foreign to the natural experience of the organism.

We have characterized the totality of the pancreatic enzymes as the "intrinsic surveillant antineoplastic factor", in contrast to the extrinsic antineoplastic factor comprising the nitrilosides or Vitamin B-17*. The immunological system in its lymphocytic function is looked upon as a secondary intrinsic anti-neoplastic mechanism. The denudement of the trophoblast or neoplast cell of the shell[2,3] that confers upon it immunological privilege opens the cell to not only immunological attack but to further digestion by the "deshielding" enzymes themselves.

The control of the trophoblast external to gestation is not only under the surveillance of the totality of intrinsic enzymes and the immunological resources of the host as exemplified in the behavior of lymphocytes,[4] but it is also undoubtedly (in my opinion) under the naturally selected surveillance of dietary or extrinsic enzymes brought into the organism.

This is, then, the tentative rationale for the heavy reliance upon fresh and raw plant material as contrasted to cooked foods (with total and irreversible enzyme inactivation) even when supplemented with all the known vitamins and required minerals.

Dietary deprivation of enzymes or vitamins or minerals may be decisive in the proper functioning of the immunological forces of the body.[5,6]

*A vitamin is an organic substance essential to biological transformations in the animal organism, in this case a water-soluble accessory food factor.

With the failure of the immunological mechanism for one reason or another,[5,7,8] a prolonged and fulminating deficiency of Vitamin B-17 is determinative of the clinical emergence and persistence of neoplastic cells that are otherwise checked and destroyed by the intrinsic surveillant mechanism.

A major thrust in the prevention and control of cancer is held to rest in the adequacy of this extrinsic or dietary factor, with the intrinsic surveillant antineoplastic resources playing a less critical, albeit important, role.

As such these extrinsic and intrinsic factors are mechanisms natural to the experience of the organism consistent with the physiological management of the metabolic disease cancer.

THE MODE OF ACTION OF VITAMIN B-17

The antineoplastic effect of Vitamin B-17 is based upon the toxicity of cyanide to mammalian cells. The closeness of the lethal and therapeutic dosages of pure cyanide makes its use impractical.

In Vitamin B-17 therapy the cyanide is liberated under safe conditions. Thus adequate dosage is possible without the occurence of toxic effects. Detoxification of cyanide occurs in normal mammalian tissue through the action of the enzyme rhodanese in the presence of sulfur-bearing compounds, converting free cyanide to thiocyanate.[20,21] Cancer cell deficiency of rhodanese may be a determining factor in the effect of the cyanide upon neoplasms.

Hydrolysis of amygdalin (Vitamin B-17) releases hydrocyanic acid, benzaldehyde, and two sugar molecules. Dean Burk[9] has demonstrated a synergistic increase in antitumoral activity between the released HCN and the benzaldehyde.

ROUTES OF ADMINISTRATION

ORAL

Oral administration of Vitamin B-17 is the most convenient and frequently the most effective route. The tablet sizes are from 100 to 500 milligrams. For patients unable to swallow, the tablets may be broken up and added to soft food.

For some patients in whom gastric acidity is deficient,* side reactions of weakness or headache following oral administration may be avoided by taking citrus juices or grape juice, or hydrochloric acid tablets such as betaine hydrochloride to prevent these unpleasant reactions.

INTRAVENOUS

When higher dosages are desired, the intravenous route is recommended. This route provides a relatively high concentration in the blood as compared with the oral route. The 3-gram vial of Vitamin B-17 solution is injected slowly into a vein. When the veins are undetectable, B-17 may be injected intramuscularly *(see below)*. Intra-

*see page 17 re: calcium di-orotate and gastric acidity.

venous dosage may range from 3 grams to 9 grams or even 12 grams per day, and is administered, preferably, between meals.

INTRAMUSCULAR

Intramuscular injections may be used when the intravenous route is impracticable. The content of one 3-gram (lyophilized) vial is dissolved in 6 cc of sterile distilled water and injected into large muscles such as the gluteus, vastus, deltoid, or triceps.

Intramuscularly the absorption of Vitamin B-17 is slower than intravenous, and the available concentration of active material is less. There is loss of the B-17 draining away through the lymphatic circulation. Also the depot of high osmotic pressure fluid may cause pain at the site of the injection. However, intramuscular injection is convenient for use when a physician is not available.

INTRATUMORAL

Intratumoral injection is not advised. In place of intratumoral injection employ the arterial route up-stream of the tumor in accordance with table II (page 11) to produce peak concentrations within the tumor.

DIRECT APPLICATION

Water solutions of Vitamin B-17 may be applied to open wounds by saturating several layers of gauze to cover the raw area.

Vitamin B-17 water solution may be used as an overnight retention enema also, or instilled directly into the intestine via a colostomy, following a cleansing irrigation.

Vitamin B-17 in solutions may be made into a water-soluble salve and applied to localized skin lesions.

Vitamin B-17 in a solution of 1 gram/cc of DMSO has also been successfully used for direct application.

OTHER ROUTES

Vitamin B-17 can be administered via intrapleural and intrauterine injection. Intra-arterial administration should be carried out only in a hospital. *(see table II following:)*

GUIDELINES FOR TREATMENT

CRITERIA FOR EVALUATION OF CLINICAL PROGRESS[10]

TABLE I

1) Decrease of pain, indicated by a decrease in the amount or frequency of the use of narcotics or sedatives.
2) Increase in the sense of well-being.
3) Increased appetite.
4) Disappearance of fetor from lesions.
5) Increased energy or endurance.
6) Increase in weight.
7) Increase in muscle strength.
8) Improvement in blood and urine chemistry.
9) Increased tissue repair.
10) Decrease of tumefaction.
11) Decrease in the output of presumptive chorionic gonadotrophin in the serum or urine as measured by the pregnancy test (see page 23).
12) Return of symptoms following the use of placebos or interruption of treatment.
13) Remission of symptoms following the reinstatement of therapy.

TABLE II — SUGGESTED ARTERIAL ROUTES:

site of the tumor	artery to be injected
brain, eye	Internal Carotid Artery
face, jaw, tongue	External Carotid Artery
thyroid	External Carotid & Superior Thyroid Arteries
breast	Subclavian at the Internal Mammary Artery
abdomen	Descending Aorta at the Coeliac Axis
pelvis	Descending Aorta at the Internal Iliac Artery
leg	Femoral Artery (see page 15)
arm	Brachial Artery
lung	Brachial Vein

GENERAL CLINICAL ROUTINE

Current treatment at the clinics in Germany, North America, and the Philippines centers around a dosage of 3 grams of Vitamin B-17 per day, with a range of one gram to twelve grams per day, with a total dosage in the initial course of approximately 100 grams.

While the laboratory work* is being carried out, over the first four days the patient receives a three-gram injection each day. After receipt of the laboratory studies the patient is reviewed with the data collected. If no response *(table I)* has been noted by the fifth day of injections, the dosage should be doubled. Under this general procedure positive responses may be observed to develop within three weeks if not sooner.

When patients are unable to receive intravenous or intramuscular injections every day they should take Vitamin B-17 orally on the days when they are not receiving the injections.

CLINICAL FACTORS THAT DETERMINE THE ADJUSTMENT OF DOSAGE

During the course of treatment with vitamin B-17 it is sometimes advisable to change the dosage. The sense of well-being of a patient is probably the best practical guide to decide if a change in dosage is indicated. The sense of well-being is influenced by the patient's capacity to dispose of the toxic products that result from tumor breakdown.

For example when drainage from a cancer area is inadequate or detoxification and excretion are impaired, toxins released by lysed cancer cells may result in an occasional episode of weakness, dizziness, or increased body temperature, or other evidence of toxemia such as nausea, vomiting, diarrhea, fever, mental confusion. High dosage could be followed by a higher rate of tumor destruction and toxemia than a patient can tolerate. Such toxemia is usually temporary lasting from a few hours to one day and subsiding as detoxification and elimination adjust to the rate of tumor breakdown. Should the patient's impaired sense of well-being continue, however, the dosage level should be decreased accordingly, and perhaps raised once again as well being is restored.

Where extensive radiation has taken place, or where chemotherapeutic drugs have been used, their toxic effect may mask the evidence of toxemia from cancer cell destruction. Under such conditions the physician's judgment will determine the need for possible dosage change.

*Appendix A, page 26.

With Vitamin B-17 therapy in Leukemia the destruction of the cancerous process does not immediately lead to a reduction in quantity or quality of circulating "leukemic" cells, but may show an initial moderate increase. Here again the useful criterion of adequate dosage is the patient's sense of well being over a period of many months and possibly years, during which the gradual decrease of circulating white cells may be followed clinically.

On the whole, should detoxification and elimination be adequate, higher dosages are well tolerated by patients receiving up to 20 grams daily of combined oral and intravenous administration *(see page 15)*. Where the response is very good and higher dosages are used, progress against the cancerous process may be rapid. Good results, however, are usually obtained using the standard 3 grams per day.

TYPICAL DOSAGE SCHEDULES

In adjusting dosage schedules it is desirable that administration of Vitamin B-17 and enzymes should be kept separate. For example the Contreras Hospital Del Mar routine prescribes B-17 one hour before meals, Pangamic Acid (Vitamin B-15) at the end of each meal, and the pancreatic enzyme mixture prescribed at mid-morning and at 10 p.m. *(see page 16)*.

In a few patients Vitamin B-17 has been given at the rate of 2 grams orally every two hours, 12 grams per day.

EXAMPLES OF DAILY SCHEDULES

1) *The Contreras Clinic Schedule:* The average dosage is 3 grams I.V. daily (6 day week) for two to three weeks, followed by 3 grams injected every other day, with 1.5 to 2.0 grams orally on alternate days for several weeks, followed by injection of 3 grams of B-17 twice a week, eventually decreasing the injection to once a week, oral B-17 given on alternate days.
2) *Conservative Schedule:* This starts with injections three times a week, oral B-17 tablets every other day to bring a cancer crisis under control*. Under this schedule 3 grams of Vitamin B-17 are given intravenously every other day and 1 gram orally on the alternate days.

*A cancer crisis is defined as: "active and progressive disease".

3) *High Dosage Schedule:* This is used after an initial trial of several days with 3 grams intravenous of Vitamin B-17. The Higher Dosage Schedule is 6 grams intravenous daily for five days, followed by 9 grams intravenous every other day for fourteen days. On those days when the injections are not given, oral Vitamin B-17 is administered in one-gram doses followed five hours later with a half gram. Following the increased I.V. series proceed with 1.5 grams oral B-17 for the next 21 days.
4) *The Nieper Schedule:* This schedule requires the taking of 100 to 200 mg of bromelin enzyme about an hour before each meal; followed by 1 gram of Vitamin B-17 a half hour later. The dosages of Vitamin B-17 may vary from a half gram to 1½ grams or higher (orally).

RATE OF ADMINISTRATION

The rate of administration of Vitamin B-17 has been found to be more important than overall quantity, peak concentration being better than continuous low concentration. Thus a set amount of 1.5 grams daily is preferably given at least 1 gram at a time and a half gram five or six hours later. (Note that a steady concentration of high dosage and rate is described under Typical Dosage Schedules above.)

Intravenous administration may be carried out by the drip method in saline or by means of a needle and syringe. A number of factors influence the decision, and the technique used is left to the judgment of the physician.

DOSAGE RANGE[10]

Recommended dosage ranges of Vitamin B-17, either oral or injected, are non-toxic. The usual dosage ranges are well below the following calculations:

For the calculation of the upper limits of dosage use this procedure:

300 mg Vitamin B-17 per kilogram of body weight
(one kilogram equals 2.2 pounds).
approximately equal to 140 mg Vitamin B-17 per pound;

Examples:
for a 154 pound adult (70 Kilograms) the upper limit of dosage is about 21 grams a day.
for a 100 pound person the upper limit is 14 grams per day.

As a rule successful control of cancer crises occurs at considerably smaller dosages than is indicated in the above calculations. Dosages higher than the usual routine *(see page 13)* have occasionally been administered without toxemia.[16] For example: 1) 19 grams per day for a thirty-day series of combined oral and intravenous Vitamin B-17; 2) a single approximately 40-gram intra-arterial dose followed by a daily maintenance of 3 grams I.A. and I.V.; 3) a daily 12-gram intravenous drip alternating weekly with a 9 and 12 gram intravenous injection daily.

DOSAGES IN ANIMALS[10]

Dosage ranges of Vitamin B-17 based on animal toxicity studies indicate no acute or cumulative toxicity nor antigenicity, teratogenicity, or other toxic reactions in dosages in excess of 100 times the maximum intravenous dose used in human therapy. The rate of 100 mg per kilogram administered per minute is safe in canine experiments. Oral doses of up to 2500 mg/kilogram of body weight have been safely administered to dogs. In animal experiments with rats, mice, rabbits and dogs the minimum LD_{50} via the oral route was found to be 295 mg/kg of body weight (in rats).

MAINTENANCE DOSAGE IN HUMANS

Over a period of time a total dosage in excess of 300 grams is the average in controlling a moderate cancer crisis. The time needed to develop the maximum response is four months to over a year. If good response *(see page 10, Criteria of Clinical Progress)* is obtained within the first three weeks, the dosage may be reduced or the clinical schedule changed to suit the convenience of the patient.

A severe cancer crisis brought under control may be maintained in a quiescent state by the oral administration of 1 gram of Vitamin B-17 daily. However some patients claim to feel "better" or "safer" with a 1.5 to 2.0 grams of B-17 daily. Such dosage is determined by the patient's sense of well-being, gain in strength, increased appetite, weight gain, and psychological improvement with reduction of anxiety and nervousness, with exhibition of a more nearly normal degree of optimism and interest in his environment.

Abnormal situations, stress or ill health of any kind have been known to be followed by a renewed outbreak or progression of the cancer process in some patients. The attending physician should be aware of these possibilities in patients in whom the cancer is under control. The patient's sense of well-being may not be a reliable guide in connection with such an apparently unrelated stress. During such

stress the physician's own observations should be relied upon in judging whether the patient might be over-extending his physiological resources in his rising physical response to the occasion. The physician is cautioned not to be misled by the patient's own optimistic statements made in the heat of a stress crisis but to be aware of the possibility of the patient "running on nerves" with observable nervousness from over-extension and exhaustion of physical resources. Increase of dosage during such periods of apparently unrelated stress may even control the rate of nervous energy expenditure.

When a cancer crisis has been successfully controlled for more than two years, with patient showing good objective responses in weight gain, increased strength, return to a more nearly normal state of activity and vigor, with negative CGH urine tests *(see page 24)*, and with an improvement in x-rays or other objective evidence, the maintenance dose may be reduced to dietary levels of nitriloside of at least 500 milligrams of Vitamin B-17 per day.

ACCESSORY THERAPY

(see Appendix B for listing of available compounds)

1) ROUTINELY PRESCRIBED

PANCREATIC ENZYME PREPARATIONS containing trypsin and chymo-trypsin are included as an essential part of Vitamin B-17 therapy.

Oral dose of pancreatic enzyme preparations is usually two tablets (4x NF) 3 times daily between meals for a total of six tablets each day. They may also be administered as 3 tablets in the mid-afternoon and 3 tablets just before retiring, or given at the same time with bromelin *(see below)*.

The enzymes and Vitamin B-17 should be scheduled at a different time.

BROMELIN is included in the therapeutic regimen for its proteolytic effect, and for a possible synergistic effect suggested by Dr Nieper as occuring with Vitamin B-17. The oral dosage is 100 to 200 mg three times a day, a total of 300 to 600 milligrams per day.
Bromelin may be given with the pancreatic enzymes as stated above, but is usually prescribed an hour before each meal.

CALCIUM SUPPLEMENTS are prescribed to reduce pain and in an attempt to correct calcium deficiencies.

CALCIUM DI-OROTATE in tablets or capsules is sometimes included in routine therapy as an aid in the utilization of conventional calcium compounds.[31] Calcium di-orotate is believed to bring about good pain relief in connection with metastatic bone lesion and recalcification.[11]

Patients with normal or above normal stomach acid should ingest calcium di-orotate in acid-resistant coated granules. On the other hand achlorhydric patients seem to absorb the calcium di-orotate without special coating.

The usual oral dosage is 3 capsules or tablets with meals, for a total of 1½ grams per day. Capsules or tablets may also be administered in the form of a rectal suppository in cases of extensive bone involvement (a dosage of 500 to 1000 mgs).

2) ACCESSORY THERAPY NOT ROUTINELY PRESCRIBED BUT RECOMMENDED

VITAMIN B-15 (Pangamic Acid)[12] prescribed as 50 mg tablets is probably useful in increasing the cellular uptake of oxygen. Dosage is one tablet with each meal, or three per day taken at the end of each meal.

VITAMIN C is useful as a possible control of undesirable oxidations,[13] and for its presumed effect on adrenal hormone production and increased liver function. It may also be useful in detoxification of free radicals and in acidifying the mucoid coat of the neoplastic cells. The dosage is up to 6 grams daily, 2 grams with each meal.

VITAMIN E may augment the anti-oxident effect of Vitamin C and aid in the conservation of oxygen in tissues. Patients with elevated blood pressure should be started on small doses gradually increased as blood pressure adaptation occurs.[14] The dosage range is from 300 to 2400 I.U. per day.

VITAMIN A in large doses* may improve the integrity of the epithelial tissues. A useful variation is "Carotene with Oil", in which a glass of fresh carrot juice with a tablespoon of vegetable oil is given three times a day. Another objective of Vitamin A administration is the possible effect of stimulation of the thymus gland to increase the sensitization of the T-Lymphocytes.[4]

ELIMINATION

A history of chronic constipation may be a factor in the etiology of some cancers. In any case constipation is to be avoided. Generally laxatives or cathartics should be avoided through increasing dietary roughage.

*25,000 units three times a day[15]

COMBINED MODALITIES OF TREATMENT[32a]

There are no contraindications to the use of Vitamin B-17 and/or the proteolytic enzymes along with surgery, radiation, and the cytotoxins.

All forms of radiation can in one degree or another shrink benign as well as neoplastic tumors. Many of the cancer chemotherapeutic agents are similarly capable of shrinking tumors, malignant or benign. Unfortunately any shrinkage is gained at cost of destroying somatic cells, especially the primitive repair cells. Although many benign tumors are radio-sensitive, and while the trophoblastic growths of the chorionepitheliomas and similarly highly malignant undifferentiated cells are radio-resistant, the radiation may increase the proportion of neoplastic cells in the tumor,[17] making the index of tumefaction a misleading and unreliable criterion of anti-neoplastic therapeutic response.

However surgery is often live-saving in cancer by correcting blockages, repairing fistulas, correcting hemorrhage, reconstructing plastic damage, and the like.

If surgery can remove a tumor completely, as in early non-metastatic cancer of the uterus, it may conserve the health and life of the patient. The same applies to the use of surgery in pre-neoplastic hyperplasias, and polyps, papillomata, skin lesions, leukoplakia, senile keratoses, etc. Where rational surgery is used, B-17 and proteolytic enzyme therapy is not contra-indicated in any way, and is indicated even before surgery.

Since pulmonary neoplasms appear to be especially responsive to the use of Vitamin B-17 and proteolytic enzymes, such an approach is the preferred method of treatment.

Except for lesions in or close to the skin, radiation or the radiomimetic cytotoxins are to be avoided because of their highly immunosuppressive and other destructive effects.[18]

LIGHT

Researches on the effect of various kinds and sources of light[30] point to the use of artificial illumination as increasing the growth rate of tumors in animals, and the possible stimulation of existing cancer in humans. Patients should avoid constant artificial lighting except full spectrum fluorescent lights, and be out of doors in the sunlight several hours every day without glasses.

Life span of test animals with tumors, and apparently human cancer patients also seems to be increased significantly by utilizing the full spectrum light source of sunlight not filtered by window glass, auto windshield glass, clear eyeglasses, tinted (dark) glasses, or contact lenses. (The ultraviolet range is especially beneficial but is filtered out by ordinary glass and plastics.)[30]

HYGIENE AND DIET

The following principles of hygiene and diet recommended for cancer patients are more extensively described in the PATIENT'S HANDBOOK OF VITAMIN B-17 THERAPY.*

HYGIENE

1) Do not smoke or remain in a room with a smoker.
2) Do not drink alcoholic beverages or sugary beverages.
3) Avoid permanent wave lotions, toxic hair sprays, synthetic cosmetics, lipsticks made out of coal-tar dyes, anti-perspirants.
4) Television: as little as possible *(see Appendix D)*.
5) An adequate amount of sleep is recommended.
6) Increase the oxygen intake *(see page 17, B-15)* with exercise in the open air and sunlight away from freeways and other sources of air pollution. When out in the sunlight remove eye-glasses and do not wear dark glasses.
7) The bowels should be evacuated at least once a day.
8) A daily warm bath is recommended to stimulate the circulation.

DIET

The following dietary regime is usually strictly followed for the first three or four months of therapy, and may be gradually relaxed following improvement.

The diet should be based almost exclusively upon fresh fruits and vegetables and/or their *fresh* juices. Food from the animal kingdom should be limited to the frequent use of fresh fish, and the occasional use of poultry† cooked without the addition of fat or salt. The patient should memorize the following dietary formula:

*Science Press International

†Be careful to obtain poultry that has not been treated with hormones and is free from viral and bacterial infection[32]

PLANT FOODS: All edible fruits and plants are recommended. These are preferably eaten raw and as fresh as possible. Some may have to be cooked just enough to make them edible. Brief and judicious cooking for short periods and at low heat (as done in Chinese restaurants) will not appreciably destroy enzymes in foods. All plant food should be free of added chemicals of any kind, such as in sprays, preservatives and the like. Whole grains are to be preferred to refined flour. All sprouted grains are even more desirable as foods.

ANIMAL FOODS: Fish and poultry should be baked, boiled or broiled (never fried), and prepared without salt or animal fat. Any animal food of any kind that is not fish or poultry is to be avoided.

Tea and coffee without any sweeteners or honey or dairy products, may be used moderately, although their avoidance is preferred. Herb teas may be used as substitute. Tobacco is strictly to be avoided.

The average persons eats his own weight in sugar every year. Sweeteners should never be added to any food. The avoidance of sugar and products containing sugar is essential.†[32b]

Moderate vitamin and mineral supplementation is advised. The supplements used must include *all* vitamins and *all* nutritional minerals.[6]

Though the fruit and vegetable diet should supply a substantial quantity of fiber or indigestible cellulose, it may be advisable in many cases to augment the fiber content of the diet by adding 2 to 4 tablespoonsful of 100% All Bran each day. This may be taken in fruit or vegetable juices or mixed with the food.

Specific foods to which the patient is sensitive are to be avoided, and the addition of bran is to be made with the consent of the physician or nutritional advisor.

Our biological commonsense impels us to the insistence upon fresh, raw and uncooked fruits and vegetables as well as their juices for all dietary purposes in general, but impellingly so for the cancer victim.

THE ROLE OF POSITIVE THINKING

The Physical Aspect

The effect of a positive attitude in increasing the body's immunological response in overcoming disease can be observed in alterations in serum proteins, antibody production, and the total immune response of the organism.[19] Patients should be advised that their bodies need the help and stimulation of positive attitudes and optimistic thoughts.

†Dr. John Yudkin, M.D., Ph.D., Professor of Nutrition and Dietetics, Queen Elizabeth College of London University.[32b]

The patient's co-operative effort in taking responsibility for his diet and hygiene, for taking the Vitamin B-17 tablets and the enzymes, for follow-up diagnostic tests, and for acting positively on his own behalf is essential to the most complete controlling possible of his cancer. If the patient's attitude is uncooperative or negative with the continued use of tobacco, cigarettes, or exposure to known occupational carcinogenic environment, the patient should be dealt with in a forth-right manner. Negative attitudes should be thoroughly discouraged.

The negativism associated with the majority of cancer patients prior to Vitamin B-17 therapy is one of the corrections which may be brought about in the course of this therapy. Persistent negative attitude and failure to improve may indicate that the dosage is too small or too infrequent.

The Psychological Aspect

"The mind, the emotions, and the attitude of a patient play a role in both the development of a disease, cancer included, and the response that a patient has to any form of treatment." (Air Force Major O. Carl Simonton, M.D.)*[33]

The onset of cancer may be correlated with major crises previously occuring at both social levels and deep personal levels of life experience, characteristically the loss of personal orientation or ego diminishment brought on by major disruptions such as occupational or social reversals, bereavement or deprivation, divorce. As such, cancer may appear in the self-defeating patient as "a form of socially acceptable suicide."

Self-defeating attitudes should be recognized by the physician, who may indicate to the patient that he is using his illness to further his personal psychological objectives, and this is why his thinking and behavior remains negative in spite of objective gains of the therapy.

Patients (and their families) should also be encouraged to carry on or develop interests outside of their illness as indeed the majority of successful patients do, since with Vitamin B-17 therapy many are relieved of the continual reminder of cancer by the relief of pain and the reduction of other symptoms.

*In the treatment of cancer Dr Simonton uses meditative techniques in addition to conventional therapies for his patients (see Appendix A), advising both patients and their close family members to participate in group meditation sessions several times a week.

SUGGESTED MECHANISMS OF ACTION OF VITAMIN B-17

Charles Gurchot, PhD

Oral doses of Vitamin B-17 seem not to be much affected by the action of the acid medium of the stomach, but pass into the intestine where the substance is acted upon by bacterial enzymes.

In the intestine the enzyme complex Emulsin containing the enzymes β-glucosidase, Benzocyanase, and others, degrades the Amygdalin into four components: Hydrocyanic acid, Benzaldehyde, Prunasin, and Mandelonitrile, which are absorbed into the lymph and portal circulations.

Cyanide is converted to thiocyanate probably in the blood circulation, and certainly in the liver by the enzyme rhodanese in the presence of sulfur-bearing compounds.[20,21] The circulating thiocyanate exerts certain physiological effects on blood pressure and thyroid action, and is not excreted rapidly. (In the absence of the enzyme or sulfur, the cyanide may form cyano-hemoglobin.)

In cancer patients some thiocyanate finds its way to the site of the cancer lesion.

The benzaldehyde formed in the intestine probably has no important function, but in the circulation forms benzoic acid and is excreted as benzaldehyde hippurate.

Prunasin (the mono-glucoside of Mandelonitrile) can circulate in the body and reach the malignant lesion, and as such hydrolyse to liberate hydrocyanic acid, benzaldehyde, and one glucose molecule.

Prunasin may also be changed in the liver to Mandelonitrile glucuronoside. This conversion to the glucuronoside may take place in two different ways: 1) by combining with glucuronic acid, which would remove one sugar molecule; 2) by oxidation of the terminal alcohol group of the prunasin glucose molecule.

The mandelonitrile is absorbed from the intestine, going directly to the liver where it is converted by the detoxification mechanism of joining it to glucuronic acid. It may then be excreted as the glucuronide or find its way to the site of a malignant lesion.

Glucosidic enzymes at the lesion may hydrolyse prunasin into its components cyanide, benzaldehyde, and a glucose molecule, to interfere with tissue respiration. In the process of enzyme hydrolysis pure mandelonitrile, as an intermediate step, may be released.

Mandelonitrile of itself may undergo spontaneous hydrolysis to HCN and benzaldehyde or enzymatic decomposition by benzocyanase present in the emulsin complex.

Mandelonitrile glucuronide may be hydrolysed at the tumor site by β-glucuronidase to yield HCN, benzaldehyde and glucuronic acid.

Benzaldehyde released through these processes at the site of the malignant lesion may be reduced to benzyl alcohol, and combine with the thiocyanate to form benzo thiocyanate. This compound is further reduced to a thio-alcohol, benzo mercaptain, and hydrocyanic acid. In this manner HCN reappears and may continue to do so in a cyclic manner until the intracellular conditions that permit the reaction involved in the cycle are no longer operative.

These phenomena would explain the synergistic effect of benzaldehyde and cyanide in depressing the metabolism of mouse tumor slices in the Warburg apparatus (Dean Burk[9]).

In the absence of rhodanese the cyanide probably exerts its lethal effects on cell respiration, which is relatively small in cancer cells, by interference with the cytochrome oxidase enzymes.

Cyanide, either as such, or as mandelonitrile, may combine with glucose to form cyanoglucose, which, on hydrolysis forms a glucuronide heptose analogous to gluconic acid, which would be excreted, or dehydrogenated to heptose, which also would be excreted. The conditions for this transformation exist in cancer tissue and would constitute anti-gluconeogenesis.

EARLY DETECTION OF CANCER

Manuel D. Navarro, M.D., F.P.C.P.

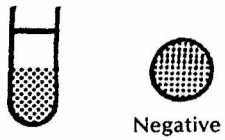
Early detection of cancer is the crux of the problem of protecting and salvaging cancer sufferers.

In 1930 Engle[22] observed the presence of chorionic gonadotrophins in the urine of cancer patients which others [23] confirmed later. Indeed, detection of choriocarcinoma is demonstrated by a high titer of human CGH which gradually diminishes upon regression of the tumor following effective chemotherapy.[24] Similar cancers have been reported among males,[25] so that it is not surprising to find positive pregnancy tests in males due to high titers of urinary CGH. The isolation of HGC from the urine of males suffering also from extra-genital cancers was described by Krebs and Gurchot[26] in 1946. Using modern radio-immunoassay techniques for examining serum, Braunstein and his associates in 1973[27] reported the presence of CGH in a substantial number of patients with a wide variety of cancers.

In 1960 Wide and Gemzell[29] introduced an immunological test for pregnancy, testing for HCG in the urine. The test is an inhibition of an antigen-antibody reaction, utilizing an anti-HCG-like serum as the antibody and sheep red cells sensitized to HCG as the antigen. (Commercial test kits available include Orgonon's Pregnostocon, and Gravindex, etc.)

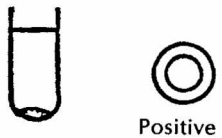
The anti-HCG-like serum:

add Sensitized RBC:



Negative

To anti-HCG-like serum:
Add Pregnancy or cancer urine:
Add sensitized RBC:



Positive

The presence of HCG in the urine — in pregnancy or the malignant state — will inhibit the reaction between the anti-HCG serum and the sensitized RBC, causing the latter to settle down and form a reddish-brown ring at the bottom because the end of the tube is rounded.

Studies begun in 1963[29] illustrated a better than 99% accuracy in detecting or confirming cancer in males and non-pregnant females using these types of tests for a urinary HCG-like hormone.

CASES FOUND POSITIVE WITH THE CANCER IMMUNOLOGICAL TEST (CIT)

number of cases:		+	—	confirmed +	confirmed —	being followed up	accuracy
cancer	300	300	0	300	0	67 (recurrences)	100.0%
†other diseases	181	27	154	26	1	1 (undergoing x-ray therapy)	99.5%
†normal	130	2	128	?	?	2	98.6%

Overall tentative accuracy 99.3%

†*Cancers detected from these latter groups were confirmed histologically.*

The application of this type of test has special value in the detection of unsuspected cancers from among supposedly healthy individuals and ailing patients clinically diagnosed as non-cancerous. Also post-operative detection of recurrences as early as 15 months before the tumor reappears is extremely significant in that such recurrent cancers may be subjected to suitable preventive measures notwithstanding the absence of palpable or visible tumor.

APPENDIX A: LABORATORY DATA (check list)

Blood: Complete blood count, Hemoglobin and Hematocrit.

Liver: SGOT, SGPT,
Bilirubin.
Alkaline Phosphatase
B.S.P.
Prothrombin,
L.D.H.

Kidney: Urinalysis, Proteinuria, Hematuria, BUN

Specific Cancer tests, HCG, may be done in addition to X-rays (lungs, G.I.), biopsy, or scans of specific organs.

APPENDIX B: MATERIALS

Amygdalin, available in 100, 250, 500 milligram tablets; in solution ready for injection, or in 2 gram and 3 gram vials crystalline (Lyophilized) for dissolving in 6 to 10 cc of sterile distilled water for injection.

Pancreatic Enzymes: 4 NF and 20 NF tablets available as well in different combinations and strengths. General Research Labs.*; Viobin Co.**; Eli Lilly.

Bromelin Enzymes: Bromalain (General Research Labs.) 100 mg
Ananase (Rohrer) 100 mg, or 50 mg tablets.
Trauminase (European) 100 mg tablets.

Calcium Di-Orotate, 500 mg tablets (General Res. Labs.)

Vitamin B-15 (Pangamic Acid) 50 mg tablets

*6925 Hayvenhurst Ave., Van Nuys, Calif. 91406
**Monticello, Ill. 61856

APPENDIX C

The MEDITATION TECHNIQUE of Dr O. Carl Simonton, M.D.*

(Chief of Radiation Therapy, Travis Air Force Base, California)

This meditative technique is a combination of relaxation and visualization. Patients are asked to meditate on a regular schedule, in the morning at first rising, at noon, and before retiring at night, for 15 minutes each time. The first few minutes are used for going into a state of complete relaxation while sitting comfortably. Then the patient visualizes a pleasant and peaceful scene.

Then he is asked to proceed to visualize his cancer lesion.

Whatever visual information or understanding is necessary for the patient to visualize his cancer is provided beforehand with pictures, x-rays, or verbal descriptions of the lesion. He is also shown by means of diagrams and photographs how his own white blood cells work in his body to destroy the cancer. He may also be shown pictures of patients with visible cancers that illustrate the gradual response to treatment such as getting smaller and disappearing. He is informed that the methods really work and is given corroborating evidence.

During his meditation the patient is asked to visualize the tumor cells as dead or dying, the white blood cells swarming into the area of the tumor, destroying the tumor cells and carrying them off, the debris to be eliminated elsewhere in the body.

At the end of the meditation the patient is to visualize himself as being well, and in such good health that he sees himself actively and usefully occupied and enjoying life perhaps in new ways and by means of new activities.

*from the Seminars on Healing, June, 1973, The Academy of Parapsychology and Medicine.

APPENDIX D

RADIATION

Small doses of X-irradiation cause abnormal activity in plant and animal cells (and later, exhaustion as shown by markedly decreased activity.[30]) Repeated X-ray doses, no matter how small, should be avoided by cancer patients.

Although official levels of 0.5 milliroentgens per hour are permitted, such dosages are cumulative, and adverse effects of such repeated dosages of X-rays from television sets may occur at distances of up to 15 feet from a normally functioning set and through two thicknesses of wall in between. Fully shielded television sets are not yet manufactured, partially shielded ones emit most of their extra radiation through the bottom of the set. But the effects of even small dosages are cumulative.

The radiation of color sets proceeds also out through the picture tube through three color-rendering cathodes operating in higher voltage ranges (for color rendition), in contrast to the one cathode operating in black and white sets. Such X-radiation goes in all directions and through solid walls, but not through lead shielding.[30]

Microwave ovens are also a source of low but cumulative radiation.

APPENDIX E

Notes on the BEHAVIOR OF TUMORS under Vitamin B-17 Therapy

BONE METASTASES appearing on X-ray as thinned areas with blurred edges are observed to develop a slightly larger but clearly discrete outline within the first few months of combined Vitamin B-17 Therapy and adjunctive calcium (as calcium di-orotate). Increasing definition of the edges of the lesion is interpreted as re-calcification, which may be followed on X-ray as the defect gradually closes. Complete filling of the defect may take from five to eight months. (Nieper, Lanpar Conference, 5/73)

SILENT LESIONS IN THE LUNGS may become visible to diagnostic X-ray within the first eight weeks of Vitamin B-17 Therapy. Concurrent signs (Table I, page 11) such as weight gain, and increased strength and well being are indications that the visibility of the infiltration is often actually the result of fibroplasia rather than new tumor extension and that successful corrections of the disease are taking place.

APPENDIX F

SUBSTANCES INCREASING THE METABOLIC SUPPORT

Cancer patients frequently exhibit a derangement of basal metabolic rate which may temporarily improve under the challenge of the toxic therapies, radiation, surgery and chemotherapy. Following recovery from these destructive programs patients and their physicians may observe the seeming metabolic improvement and share optimism that such therapy was successful in halting the cancer process. With internal, metastasized cancer the frequency of recurrence (93%) attests to the temporary nature of this metabolic pseudo-stimulation. As the metabolic rate gradually returns to its former (lower) level, cancer symptomatology increases until the recurrence of tumor masses confirms the continued presence of active disease.

Clinicians report that in addition to increased susceptability to bacterial and viral infection, low metabolic rate detracts from the best effect of Vitamin B-17 Therapy (Drs. E. T. Krebs, Senior, Nieper and Contreras). While adequate iodine and protein intake and/or absorption are important,[39] the following metabolic support substances are given to increase resistance to infection and to improve the immunological responses of the patients.

THYROID extracts or supplementation are given in small amounts just sufficient to bring the basal temperature into the normal range. The most satisfactory method of monitoring the status of the patient is the axillary skin temperature measured for 10 minutes before rising three consecutive mornings. Pre-menopausal women take the temperature during the second to fourth day of the menses. The normal range is 97.8 to 98.2f. It is recommended that an adult dosage of 2-3 grains daily be observed over a period of at least two months in order that the basal rate be raised only gradually.[40]

THIAMIN chloride (or hydrochloride) is used by Dr. Nieper and others to increase the susceptibility of cancer cells to correction by Vitamin B-17 Therapy by increasing cell respiration. It may be given as 100 mg, p.o. 3 times daily, or as a component of injectible solutions of Vitamin B-17 (amygdalin) as 100 mg per vial.

ZINC.[41] In addition to anti-viral activity the application of zinc compounds to increase the healing of tissues is a recognized adjunct to metabolic therapy. Zinc orotate, 80 to 120 mg per day p.o., or zinc gluconate up to 150 mg is recommended.

VITAMIN C.[42] For acutely ill and cachectic patients massive doses may be given, 20 or more grams daily (Rx Cetane, Fellows Pharmaceutical) as part of the intravenous administration of Vitamin B-17

and or calcium supplements (such as Rx Calphosan, Carlton Pharmaceutical). For ordinary routine the daily amount varies from 5 to 10 grams of Vitamin C injected intravenously with the B-17.

APPENDIX G

VITAMIN B-17 and SICKLE CELL ANEMIA

The successful use of cyanates in the control of sickle cell crisis has been indicated clinically[34,35] and experimentally.[36,37] Thiocyanate, an intermediate product of the metabolism of Vitamin B-17 (see page 22) is thought to be the active component. The recommended daily supplementation of Vitamin B-17 is 50 to 100 mg for small children and 250 to 500 mg per day for the adult sickler.[38]

APPENDIX H

FLUORIDATION-LINKED CANCER

*Studies based upon the U.S. Vital Statistics for fluoridated versus non-fluoridated U.S. cities indicate a significant (greater than 99% confidence level) increase in cancer death rates occuring within the first two years of artificial fluoridation. The nine organ sites affected and their increase above the normal are:

Mouth, 15%; Esophagus, 48%; Stomach, 22%; Large Intestine, 31%; Rectum, 51%; Kidney, 10%; Bladder and other urinary organs 22%; other organs specifically female: Breast 15%; Ovary and Fallopian Tube, 15%.

Patients having cancers of these organ sites should be advised that they should not continue to drink or cook with fluoridated city water but should substitute bottled spring water or distilled water.

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*by Dr. Dean Burk formerly chief of CytoChemistry, The National Cancer Institute, and Dr. John Yiamouyiannis, Science Director of The National Health Federation, formerly an editor of Chemical Abstracts.

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Dr Ernest T. Krebs, jr. Ph.D., D.Sc.
Dr Ernest T. Krebs, sr. M.D.
Dr N. R. Bouziane, M.D.
Dr Dean Burk, Ph.D.
Dr Ernesto Contreras, M.D.
Dr Christian Deckers, M.D.
Dr Ettore Guidetti, M.D.
Dr Charles Gurchot, Ph.D.
Dr J. D. Hamilton, M.D.
Dr Maurice Kowan, M.D.
Dr J. Maisin, jr. M.D.
Dr J. Maisin, sr. M.D.
Dr Leon Lewis, M.D.
Dr John A. Morrone, M.D.
Dr Manuel Navarro, M.D.
Dr Hans A. Nieper, M.D.
Edward Spicer, esq.
Dr Emory Thurston, Ph.D., D.Sc.
Dr Prof. Manfred Von Ardenne
Dr. John A. Richardson, M.D.

and many other physicians and scientists whose contributions from the early 1920's laid the groundwork for the present state of the art of physiological management of the metabolic disease of cancer with Vitamin B-17.

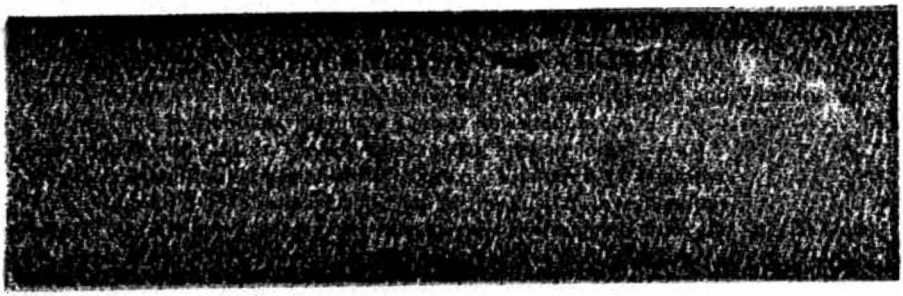


Exhibit "Q"

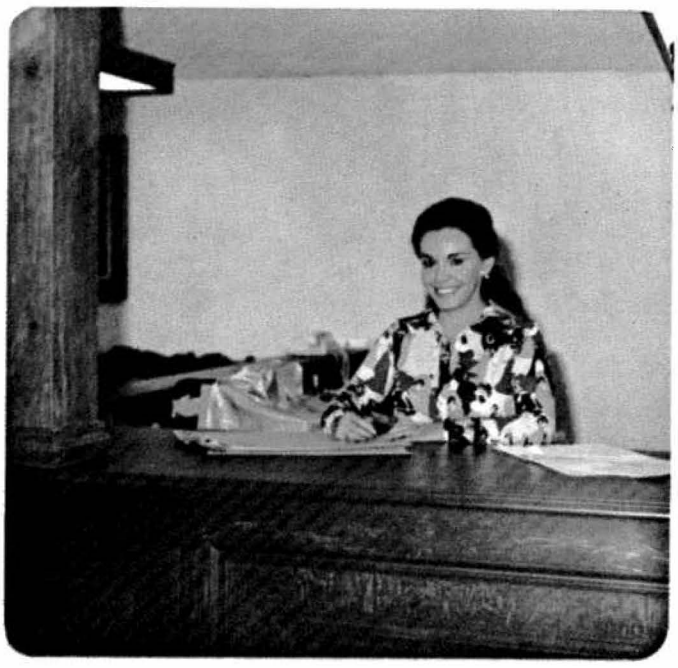
Clinica Cydel

Tijuana, Mexico

. . . a bright new hope for the control of cancer through total metabolic and non-toxic therapies, including Laetrile (Vitamin B17).

OFFERING:

- **Reasonable rates**
- **Reception and attention in English**
- **Limited waiting period**
- **Expertly trained and dedicated staff**
- **The most modern, innovative diagnostic and patient profile techniques and a full range of laboratory services**
- **Specialty restaurant and pharmacy**
- **Modern, tastefully furnished apartments for patients**
- **Limousine service to San Diego International Airport**



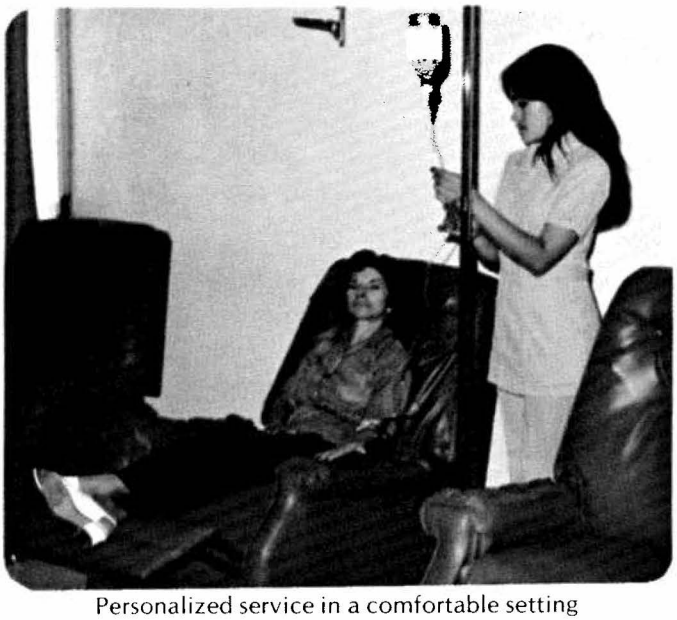
CENTRO DE DETECCION Y TRATAMIENTO

MEDICO CYDEL, S.A.

Apartado Postal 3437, Tijuana, B.C., Mexico
P.O. Box 4290, San Ysidro CA 92073

U.S. telephones: (714) 426-7000 and 426-7803
Mexican telephones: (903) 387-1502
and (903) 387-1503

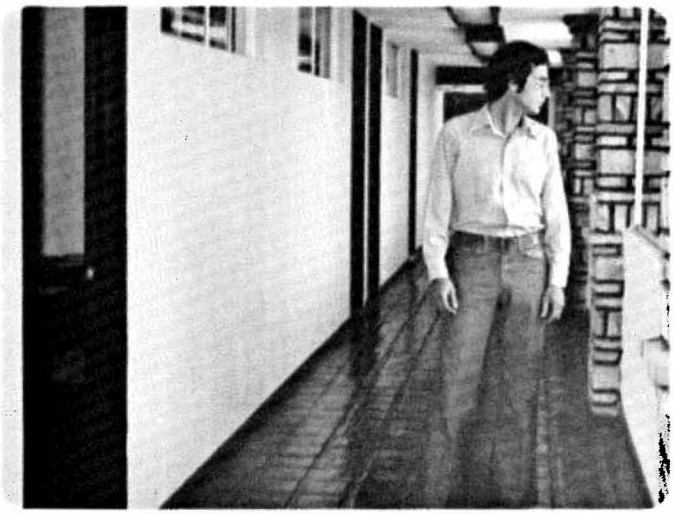
Clinica Cydel *realization of an idea –*



Personalized service in a comfortable setting

The finest center in the world for the treatment of cancer through total metabolic and non-toxic therapies in which Laetrile [Vitamin B17] plays a central role is open just over the California-Mexico border in Tijuana.

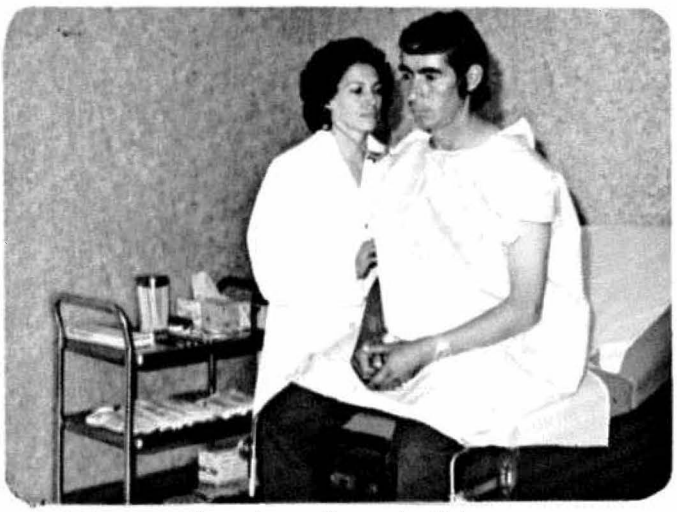
In a beautiful, Spanish Mediterranean-style setting, the gleaming new Clinica Cydel offers to cancer patients from throughout the world the most modern and innovative methods of diagnosis, a dynamic and dedicated medical team, a fusion of metabolic disciplines and an up-to-date grouping of facilities and services — all at a reasonable price.



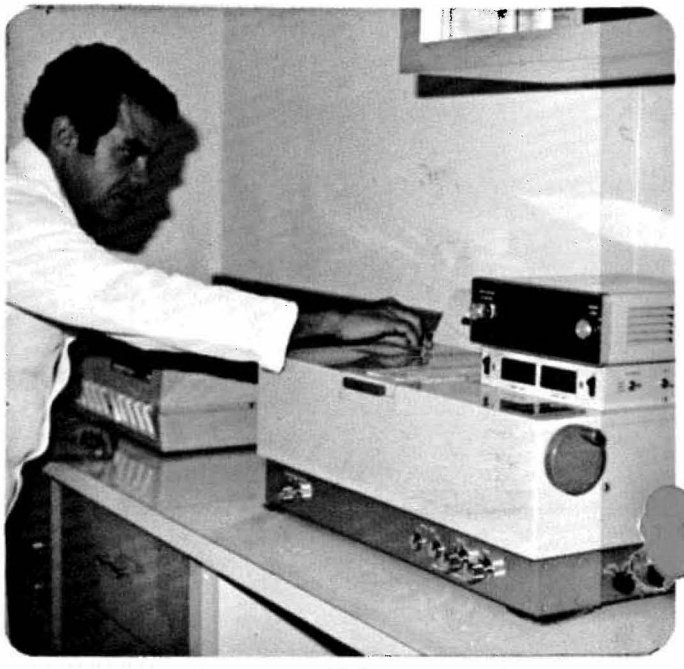
Warm and hospitable surroundings

Available for patients, too, are modern, tastefully furnished apartments, restaurants specializing in regular, Laetrile and other special regimens, and a pharmacy, all part of the Cydel complex, where treatment programs not ordinarily available in the United States are readily accessible.

Reception and attention in English, a minimal waiting time, a limousine service to nearby San Diego International Airport and availabil-



All-modern, all-new facilities



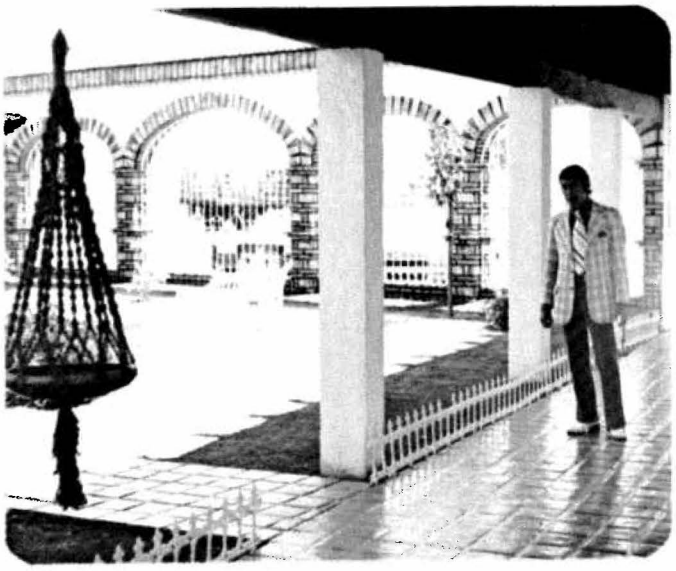
A complete range of laboratory services

total metabolic treatment, non-toxic therapies.

ity of emergency hospital facilities are part of the package of services offered by Clinica Cydel. The world's top-grade and quality-controlled Laetrile [amygdalin, Vitamin B17] is provided by CytoPharma de Mexico, whose owner-operators, the Del Rio brothers, also operate Clinica Cydel.

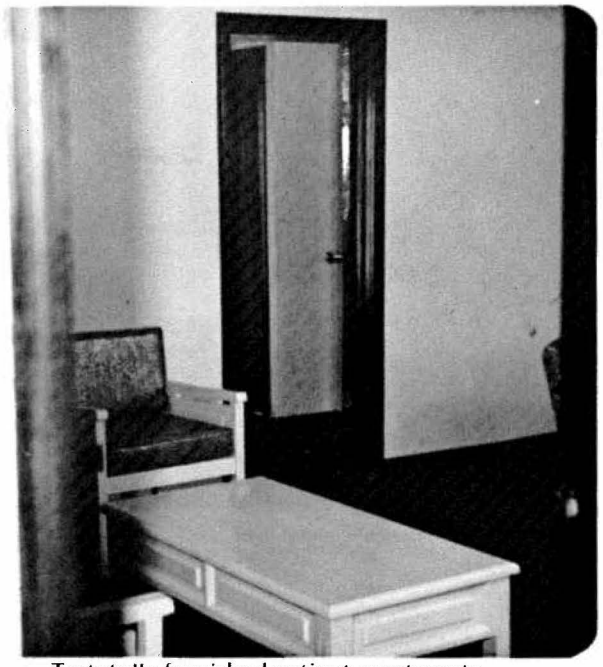
Extensive laboratory services and facilities include blood chemistry, routine urinalysis, body mineral analysis, computerized patient medical history and diagnostic profiles, tests for HCG hormone detection and other hormone assays, diagnostic X-ray equipment, nuclear medicine, electrolyte assay, serum analysis and dental survey.

The Clinica staff, fully trained and growing, consists of an oncologist [expert in cancer], internist, dental-oral specialist, two general practitioners, trained nurses and nurses aides and qualified laboratory analysis experts. Within a few months of Clinica Cydel's opening in 1975 this dedicated team claimed a positive response rate of more than 90 per cent in cancer therapy.



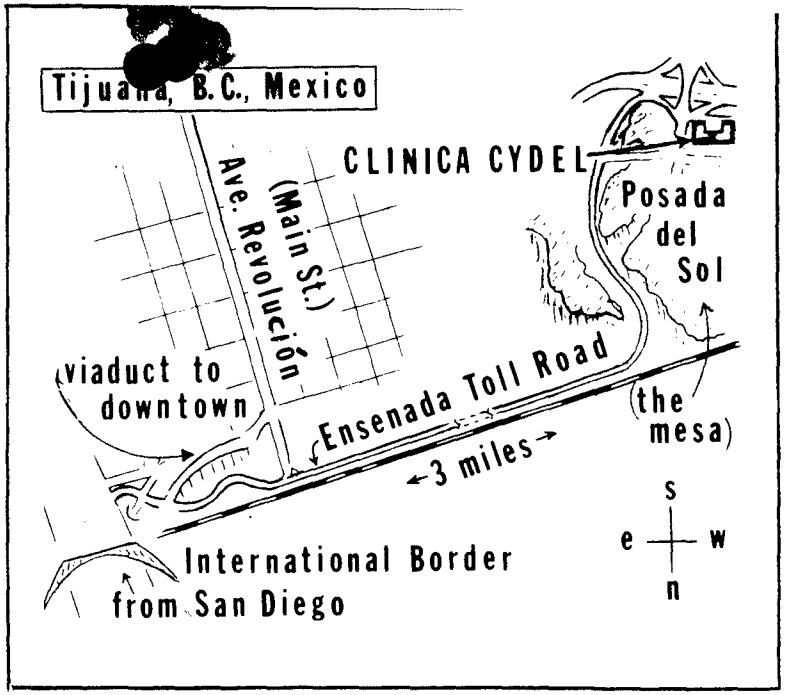
Sunny courtyard in a Mediterranean setting

Professional guidance from the first consultation



Tastefully furnished patient apartments

Spacious reception area, limited waiting period



CLINICA CYDEL:
offering hope for cancer control through metabolic therapy, including Laetrile (Vitamin B17)

HOW TO BECOME A PATIENT AT CLINICA CYDEL:

- Telephone ahead for reservations through the Chula Vista, California, numbers (see TELEPHONES).
- Prospective patients will be mailed complete medical history forms to be filled out and hair-analysis kits for probing body mineral levels. The forms and analyses will be processed before patients arrive.
- Patients should bring with them as much data (X-rays, prior medical records, etc.) as possible.

FEE SCHEDULE

1. First consultation, with complete physical examination including teeth and oral examination ..... $ 50.00
2. Initial diagnostic-medical history profile including mineral analysis ..... $ 40.00
3. Computerized patient diagnostic work-up ..... $ 40.00

$130.00

(Costs thereafter vary from patient to patient)

CLINIC APARTMENT FEE (all 20 units are doubles)

One person, $18 per day; two persons, $20 per day; three (with extra bed), $22 per day.

PAYMENT

Payment is in U.S. dollars, American Express travellers checks, bank drafts for money orders. Personal checks not accepted due to clearance problems in Mexican banks.

TELEPHONES

Clinica Cydel's answering service is available through Chula Vista, California, telephone numbers from 8 a.m. to 5 p.m. Monday through Friday and from 8 a.m. till noon Saturdays. The Chula Vista numbers are: (714) 426-7000 and (714) 426-7803. Direct telephone line service to Clinica Cydel in event of emergencies is available by calling either (903) 387-1502 or (903) 387-1503.

MAIL

Patients at Clinica Cydel may be written via P.O. Box 4290, San Ysidro CA 92073. The mail pickup there is twice daily.

EMERGENCY HOSPITALIZATION

Available nearby at about $35 per day.

ABOUT TIJUANA

Tijuana, B.C., Mexico, enjoys a year round temperate climate, though winter visitors are advised to bring raincoats and fall clothes. The rapidly growing border city (estimated population: 750,000) has all modern conveniences and facilities and is a shopper's paradise, particularly for those articles, arts and crafts manufactured in Mexico. Excellent jai-alai and bullfight arenas add to the color of this busy border city.

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(415) 948-9475
official U.S. representative of
CLINICA CYDEL

— Exhibit "R" —

IN THE UNITED STATES DISTRICT COURT FOR THE

WESTERN DISTRICT OF OKLAHOMA

GLEN L. RUTHERFORD, Et Al,

Plaintiffs,

vs.

UNITED STATES OF AMERICA, Et Al,

Defendants.

No. CIV-75-0218-B

DONALD BOHON,
JoANN HARDIE,
SHEILA ALTSHULER,
LUCAS BREUKER,
LLOYD V. GRANT,
SPENCER R. SMART,
MARIE SILVA,
MARY A. NEFFINGER,
ROSALINE GRUBERG,
MARY LOUISE COLLINS,
DONALD W. JONES,
MARSHA COLLER,
LEONARD C. RITZLER,
LILLIAN VREHOTA,
JUNE E. JOHANSEN,
SALLY ELLIS,
BARBARA P. HARDIN,
JOHN WALTER BUCZKOWICZ,
KENNETH W. McHAM,
FLORENCE E. FULLER,
MRS. CHARLES W. SELLERS,
WESLEY J. CARNEGIE,
STEVE J. GADLER,
RUTH E. TAMPLIN,

CERTIFIED CLASS MEMBERS.

FILED

MAR 9 1977

REX B. HAWKS
CLERK, U. S. DISTRICT COURT
By Irene H. [illegible]
Deputy

ORDER

The Court having read the Application for Certification as Class Members of the captioned individuals, and the affidavit in support thereof, hereby orders that as the above listed Applicants are cancer patients; they are proper members of the class of Plaintiffs in the above entitled action; and are hereby certified as Plaintiffs in this action and are subject to all provisions of this Court's orders pertaining to Plaintiffs in this action, including, but not limited to the provisions of this Court's Order dated January 4, 1977.

On January 4, 1977, this Court enjoined and restrained the Food and Drug Administration (FDA) from preventing Plaintiffs' importation or interstate transportation of Laetrile for purposes of their own consumption under the terms of the Food and Drug Act, including Section 505 (a) of the Act, 21 U.S.C. Section 355 (a).

Under the terms of the Order referred to above, Defendant, FDA, is enjoined from preventing the importation or interstate transportation by the above listed Plaintiffs or their appointed agent, Andrew Robert Leslie McNaughton, of Laetrile for purposes of their own consumption under the terms of the Food and Drug Act referred to above.

DATED this 9th of March, 1977.

LUTHER BOHANON

UNITED STATES DISTRICT JUDGE

3-9-77

APPROVED AS TO
FORM ONLY:

UNITED STATES DISTRICT ATTORNEY

/s/ William S. Price
WILLIAM S. PRICE
Assistant U.S. Attorney

CLERK

By Ann Hyphantis
Deputy

APPROVED AS TO
FORM AND CONTENT:

LOONEY, NICHOLS, JOHNSON & HAYES

By /s/ Kenneth Coe
KENNETH COE

Attorneys for Applicants