Chapter 6

Immuno-Augmentative Therapy

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INTRODUCTION

This chapter is devoted to a single treatment, Immuno-Augmentative Therapy (IAT). IAT is covered more extensively than other treatments in this report because, in addition to being asked to produce an overall report on the topic of unconventional cancer treatments, OTA was asked to seek a way to gather valid information on the effectiveness and safety of IAT. The request concerning IAT was initiated by then-Congressman Guy Molinari of New York, and cosigned by about 40 other Members of Congress. The request arose because the IAT Clinic, located in the Bahamas, had been closed by the Bahamian Government at the recommendation of the Pan American Health Organization (PAHO), after contamination of IAT treatment materials with hepatitis B and the AIDS virus was reported. Congressman Molinari acted in the interest of constituents who were patients at the clinic. In response to the request, OTA attempted to develop a clinical trial protocol for IAT as a case study under the umbrella of the larger study. IAT is popular among unconventional treatments, but no evidence existed when OTA began this study in 1987, nor does it exist 3 years later, to suggest that IAT is more or less "promising" than many of the other treatments discussed in this report.

The development and current use of IAT and background on its developer and practitioner, Lawrence Burton, Ph.D., are covered in the first part of this chapter. OTA's unsuccessful attempt to develop a clinical trial protocol in agreement with Burton is discussed in the latter part.

BACKGROUND ON IAT

IAT is one of the most widely known unconventional cancer treatments. Treatment consists of daily self-injections of processed blood products, continuing for the life of the patient. IAT patient literature states that IAT acts as an immunologic control that causes most types of cancer to either stabilize or regress (430). Biologist Lawrence Burton, Ph. D., developed IAT and first offered it to cancer patients in the 1970s at an office in New York State. Burton left there in 1977 to start the Immunology Researching Centre, Inc. (IRC) in the Bahamas. A second clinic under his direction was opened in 1987 in West Germany, and a third opened in Mexico in 1989.

Various State and Federal legislators have, in recent years, sought to broaden the availability of IAT. In 1980, a bill was introduced in Congress (though not passed) to exempt the "blood fractions" used in IAT from the requirements of the Federal Food, Drug, and Cosmetic Act (FDCA) for 5 years.[1] The Florida and Oklahoma Legislatures enacted laws (since repealed) in the early 1980s to permit the prescribing and administering of IAT in those States (32). In 1986, U.S. Congressman Guy Molinari of New York held a special public hearing on IAT. Subsequently, he and 41 other Congressmen and Senators signed letters to OTA requesting an evaluation of IAT.

In July 1986, the Food and Drug Administration (FDA) imposed an import ban, prohibiting bringing IAT into the United States, "due to the direct hazards that have been associated with IAT agents" (888). Although the circumstances under which IAT is manufactured and offered have reportedly been improved (115,553), the ban remains in effect and IAT products may be confiscated by U.S. Customs or Postal officials. The ban is generally not enforced, however, and there have been no reports of IAT seizures or of IAT patients without access to treatment materials (426).

Burton's cancer treatment, his controversial career, and the circumstances under which he manufactures and offers IAT have intrigued the press and public for many years. IAT has been described in several books that are widely read by U.S. cancer patients (341,510,531,648) and was the subject of a 1980 segment of the television program 60 Miinutes *(782). Magazines such as* Penthouse *(685) and New York (49), and journals that advocate unconventional medical treatments (20,496) have also carried stories on IAT.*

[1]House of Representatives Bills 7936 (Aug. 18, 1980) and 8341 (Nov. 13, 1980), introduced by Representative McDonald.

Several organizations, including the American Cancer Society (ACS) (27), the National Cancer Institute (NCI) (246,901), FDA (679,888), and the Centers for Disease Control (CDC) (882,883), have published statements warning U.S. cancer patients against using IAT. Some of these statements are based on possible viral contamination of IAT. Since IAT materials are not tested regularly by any independent laboratory, it is not known whether the claimed improvement in manufacturing and viral testing procedures since 1986 effectively mitigates the risk of biologic contamination identified at that time.

Burton's Theory of Cancer Control Through Augmentation of the Immune System

The IAT patient brochure describes a specific anti-cancer immune system in mammals and states that "it works optimally when a balanced proportion of activated components are present. Burton adopted this theory early in his career and he continues to cite it (114). However, despite the fact that laboratory technology to do so has existed for many years, Burton has never directly demonstrated that the factors he describes actually exist in IAT, nor shown that IAT has activity to alter the course of human cancers.

Burton asserts that IAT is based on restoring optimal function to the native immune system, one function of which "is to recognize and destroy neoplastic cells and thus to serve as a natural mechanism for the control of carcinogenesis' (430). Burton maintains that "an immune defense against cancer antigens is at least initiated in most, if not all, persons who contract cancer." The IAT brochure states that "some patients' immune systems are initially impaired by cancer itself, or were previously impaired to allow the disease, and are then further weakened in patients treated by radiation or chemotherapy." This allows "mutant cells that otherwise would have been neutralized or destroyed . . . to proliferate, invade nearby tissues, and migrate to other parts of the body' (430). Burton claims that "immune augmentation' with IAT will "destroy the cells and metastatic or local recurrence of cancer" (430).

John Clement, M. D., a physician at the IRC, describes the theory behind IAT as follows:

> ***In the normal healthy person any mutant cancer cells are recognized and antibodies attempt to destroy them; this reaction is promoted by Tumour Complement (TC), which is produced by cancer cells, and is the effective signal to the antibodies to destroy that cell. These necrotic tumour cells are then passed to the liver to be "sanitized." If tumour cell necrosis occurs too rapidly the liver can be overloaded, leading to production of Blocking Proteins which shield tumour cells and slows down the antibody reaction to those cells. Patients with cancer may have very high levels of this Blocking Protein. Deblocking Proteins neutralize this blocking action and so enable antibodies to access the tumour cells. Patients with cancer tend to have a deficiency of Deblocking Protein.***
>
> ***. . . in order to effect this control you need Tumor Complement produced by the cancer cell to alert and activate the Antibodies and you also need sufficient Deblocking Protein to neutralize the Blocking Protein and allow the antibodies access to the cancer cells. (200)***

At least four IAT products maybe prescribed to treat human cancer patients. The IAT brochure states that some of these are manufactured from the pooled blood of cancer patients and others from the pooled blood of human donors who do not have cancer. The brochure (430) describes IAT products as:

> *Deblocking Protein* ***(DP)—an alpha 2 macroglobulin[2] derived from the pooled sera of healthy donors.***
>
> *Tumor Antibody 1 (TA1)-a* ***combination of alpha 2 macroglobulin, IgG, IgM, and IgA[3] derived from the pooled sera of healthy donors.***
>
> *Tumor Antibody 2* ***(TA2)-differs from TA1 in potency and possibly composition of immunoglobulins; also derived from pooled sera of healthy donors.***
>
> *Tumor Complement (TC)-a* ***substance isolated from blood clots of IRC patients with many types of cancer. Described as complement C3[4] that is uniquely active in activating TA1 and TM.***

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[2]In usual scientific use, alpha 2 macroglobulin would refer to anantibodybelonging to one of the five major classes of bloodborne immunoglobulin, the Ig M group. Although Burton describes DP as an alpha 2 macroglobulin, to OTA's knowledge he has produced no analytical results to confirm that. No alpha 2 macroglobulin that has been identified by mainstream researchers has the properties Burton ascribes to DP.

31@, IgM, and IgA are three of the five classes of bloodborne immunoglobulins. IgM molecules are also called macroglobulins.

[4]In usual scientific use, C3 refers t. one of a group of plasma proteins that are activated to various immunologic functions by antibody-antigen complexes.

There is no record of Burton's carrying out biochemical analyses of these materials to identify their components, and his patents describing their manufacture prescribe no tests for verifying identity. Nor has independent analysis of IAT materials been reported from samples provided directly by Burton. Reference to analysis is made in a popular article (982) on IAT, which says that it has not been classified "down to the last molecule," but that there were "some limited chemical and immunochemical analyses run by an outside chemist several years ago." The article goes on to say that Burton and his former partner Friedman were told that the substances contained " alpha^{2}macroglobulin, "immunoglobulin A" and traces of "complement C'3." There is no indication of who did these analyses and no actual record of the results.

NCI analyzed IAT treatment materials provided by the family of a deceased IAT patient in 1984. According to the NCI analysis, all the treatment materials were dilute blood proteins, in which the major component was albumin, and all were reported to be devoid of the components described in the IRC brochure (246).

The IAT Cancer Treatment Regimen

Burton states that treatment regimens are based on his determination of the patient's initial immunocompetence and the responses of past patients with similar status, which have been compiled in a computer program. As treatment proceeds, Burton tests patients' blood daily or twice-daily for the relative concentrations of four basic factors: Tumor Antibody (TA1 and TA2), Tumor Complement (TC), Blocking Protein Factor (BPF), and Deblocking Protein Factor (DPF). BPF "blocks" the claimed antitumor effects of TA1 and TA2, and is not administered as part of the IAT regimen. Burton adjusts the daily prescription of TA1, TA2, TC, and DPF in light of his blood tests during patients' initial 6-to 8-week course (430). Patients inject themselves subcutaneously or intramuscularly with the prescribed amounts. Other medications (e.g., prednisone, a corticosteroid) are also prescribed for many patients (199).

After the initial treatment period at the IAT clinic, patients generally return home with supplies of IAT to continue self-injections according to a schedule provided by Burton, based on his proprietary computer program (115). At regular several-month intervals, or if patients have acute illnesses unrelated to their cancer or the treatment, they are encouraged to return to the IAT clinic for further assessment and adjustment of their treatment regimens (199). Burton advocates surgical removal of cancerous tissue before beginning IAT, to the extent possible, but discourages chemotherapy or radiotherapy (1 15).

Burton's Pre-Clinical Research

Burton asserts that the basis for IAT, as it is currently offered, is the pre-clinical research that he and his colleagues conducted at U.S. research institutions (114,430). Burton and various colleagues published about 20 papers dealing with biological factors affecting turners in fruitflies and mice in scientific journals between 1954 and 1963, and brief abstracts of additional work with mice and humans through 1969. One or two articles on human research were reportedly submitted for publication through 1972 but were never published.

Research on Fruitflies

As graduate students in biology at New York University, Burton and his colleague Frank Friedman studied the inheritance of various traits in fruitflies. Though many researchers were studying fruitflies at the time, Burton and Friedman were apparently alone in postulating that tumor-bearing fiuitflies contained a transmissible, biologic factor that could be isolated, injected into, and cause tumors in other fruitflies (113,117,123,380).

Burton and Friedman received their doctoral degrees from New York University in 1955 and, in 1957, went to the California Institute of Technology (Caltech) for post-doctoral training. In the course of their research at Caltech, Professor Herschel Mitchell advised Burton and Friedman on developing a method to purify the tumor factor they had reportedly identified in fruitflies (618). They later reported that purified tumor induction factor, "TIF," had interspecies activity (between fruitflies and mice), while the crude extract did not (315). After a series of experiments (122,312,313), Burton and his coinvestigators concluded that TIF, the presumed active component in the purified fruitfly extracts, contained protein, nucleic acid, and lipid (312), and was most likely a tumor-inducing virus (122).

Burton and his colleagues hypothesized that the variable tumor-inducing potential of TIF that they observed in different stages of its purification was explained by other substances that motified its

activity or had independent tumor-inducing or inhibiting properties (121,309,310,312,313). However, these conclusions are also consistent with an assumption that the fruitfly bioassay was valid, and neglecting to consider the inherent variability of the test as an alternative explanation for their results.

Burton and Friedman's research was questioned at Caltech when it was noted that the control fruitflies in their experiments had no injection scars while their experimental animals did, although the research protocol called for injecting controls with an inert material (618a). After this was reported, Renato Dulbecco, Ph. D., then Professor of Virology (later a Nobel laureate), became skeptical about the results already published, and Burton and Friedman were asked to participate in a validation of their assay. Mitchell reported on this experiment and his own attempt to reproduce Burton and Friedman's findings in *Science (618).* Using Burton and Friedman's own materials and reported purification methods, George Beadle (another advisor) and Dulbecco presented Burton and Friedman with "coded samples containing only buffer solution or buffer plus various concentrations of 'purified TIF.' " Mitchell reported that, "using their own fruitfly assay, Burton and Friedman could not distinguish buffer solution from TIF solution."

To rule out possible explanations for the failure of the blind experiment, Mitchell himself repeated Burton's tumor transmission experiments on more than 2,000 fruitflies. The percentage developing melanotic inclusions (which Burton and Friedman identified as "tumors") varied from experiment to experiment (from 2 to 80 percent), but the percentage of controls with these inclusions was always similar to the percentage of experimental, when injected at the same time, suggesting no effect of TIF. Burton and Friedman left Caltech shortly after this series of events.

In his report in *Science,* Mitchell stated that he "would be pleased to be forgotten as a collaborator' in Burton and Friedman's work (618). In a letter to OTA, Mitchell concluded that 'none of the work on the so-called tumor factor in Drosophila is valid and this fact raises serious doubts about the validity of subsequent claims. '

Research on Mice

In 1958, Burton and Friedman began work as Research Assistants in the Department of Pathology at St. Vincent's Hospital in New York. Later they were promoted to Associates, and then Senior Associates in Oncology in St. Vincent Hospital's Hodgkins Laboratories. As members of a small research staff, Burton and Friedman worked with Robert Kassel, Ph.D., and Antonio Rottino, M.D., a pathologist and Director of St. Vincent's Laboratories. They began to investigate biologic substances that might affect tumors in mammals.

They injected purified extracts from leukemic mice into both fruitflies and newborn mice with a low natural incidence of cancer and reported the surprising induction of cancers other than leukemias in the mice (469), and speculated that the substance was similar or identical to the TIF previously discovered in fruitflies. Burton and colleagues asserted that identification of the factor was less important than defining its mode of action (120), and assumed that similar activity correlates with similar identity. Biochemical tests of identity were never carried out to confirm the similarity to the fruitfly material.

Burton and his colleagues subsequently reported that they had isolated substances similar to TIF from several other species of animal, including a human patient with lymphoma (120,311). They stated that since TIF from human sources induced tumors in test mice, this suggested that TIF was not species-specific and that "the purification procedure apparently removed substances responsible for the maintenance of the. species specificity barrier."

Burton's published work in the early 1960s concerned TIF's interaction with various modifying agents in mammalian cancer. A brief abstract by Burton and Friedman on tumor remission in mice (injected with extracts of mouse and human origin) stated that tissues of leukemic mice contain two oncolytic (anticancer) substances, "V' and "I" (118). While "I" was stated to produce a 50 to 100 percent reduction in mouse lymph node and spleen size within 24 hours, "deleterious side effects' were produced. Lesser amounts of "I" were needed to reduce organ size when given with "V," and in this situation, the side effects did not occur. The abstract also stated that daily administration of combined "I" and "V" to mice with early leukemia for 4 weeks eliminated palpable disease in 26 of 50

treated animals, and that the treated group survived longer than did the untreated controls. What appears to be the same experiment was included in the 1963 presentation and paper discussed below.

Burton and his colleagues presented three papers about tumor induction and inhibition in mice at the New York Academy of Sciences in 1%2 (119,311,470). They described an elaborate system of bloodborne tumor-inducing and inhibiting factors that was stated to exist in mammals. The effects of injecting different combinations of purified extracts were described, some of which reportedly reduced measurable tumors in mice. In these presentations, Burton's group first speculated that injection of carefully balanced doses of these factors could be used therapeutically to control mammalian cancers. They reported on six experiments with leukemic mice, including the results that, in five of the experiments:

> *. . . 37 of 68 experimental animals survived for an average of 131 days without any evidence of leukemia. The leukemia had gradually regressed, as evidenced by reduction of palpable nodes and spleen, until it was eliminated by the end of the fourth week of treatment.*

They reported that average survival of untreated mice was 12 days.

In 1963, the team presented a summary of their research on tumor-inducing complexes in mammals to the New York Academy of Sciences (subsequently published in the Annals of the New York Academy of Sciences (468)) *describing the response of cancerous mice to various combinations of purified fractions. In leukemic mice, they reported that the untreated controls died after an average of about 13 days. About half of the treated mice died after an average of about 37 days, and the other survived much longer. In mice with mammary tumors, they reported significant decreases in tumor volume in the treated groups and significantly increased volume in the controls.*

The authors concluded:

> *The study of the biological action and interaction of these components in mice bearing spontaneous neoplasms has suggested the existence of an inhibitory system involved in the genesis of tumors and capable of causing specific tumor cell breakdown.*

This talk met with a mixed reception among researchers in attendance. Of particular concern was the fruitfly assay that they were still using as part of the mouse experiments. During the discussion, Kassel indicated that they were in fact using a new assay, based on blackening and death of fruitflies, that was "much less complicated than identifying a tumor and also bypasses this question. " Burton stated that the new assay correlated completely with their old assays and they had given them up.

At about this time, Kassel left St. Vincent's to pursue research elsewhere and was involved in the discovery of tumor necrosis factor (170). In 1966, Burton and Friedman presented a demonstration of their extracts' ability to shrink tumors in mice to the Science Writers Seminar sponsored by the American Cancer Society. They injected four mice with hard mammary tumors with their serum fractions, and, one observer wrote, within 45 minutes the tumors had become soft and shrunk by half their original size (982).

Some observers were amazed and others were skeptical. Some journalists quickly sensationalized Burton and Friedman's demonstration. One newspaper headline read, "15 Minute Cancer Cure for Mice: Humans Next?" (565). An oncologist who examined the mice following the demonstration later stated that "it was obvious that he had massaged the tumors until they had become fluid and then aspirated out the tumor and necrotic material. ' He stated further that a "fresh puncture wound was found at each tumor site' (638). Although his colleagues apparently took this mixed response in stride, Burton was reportedly infuriated (982). After the science writers' seminar, the ACS offered to fund Burton and Friedman's research, on the condition that it proceed in collaboration with a team of clinical research oncologists. The ACS offer was refused. The mouse demonstration was repeated before oncologists and pathologists at the New York Academy of Medicine in September 1965, but there was apparently skepticism and little interest in pursuing their research.

A brief abstract in 1965 reported an experiment in which 48 tumor-bearing mice were injected with "I" and "V" extracts derived from leukemic mice and from cows with lymphosarcoma (314). The abstract states in part:

Small tumors disappeared in 2 hours. Larger ones softened-liquefied in 24 hours and in many instances, resorbed in 2 to 4 days. Many of the mice died, the cause of death being associated with *massive hemorrhage into the tumor.... Conditions necessary to obtain survival after tumor liquefaction included a precise ratio mixture of V and I and the precise dose.*

Treatment of Human Cancer Patients With IAT

Burton described the use of IAT in cancer patients at the hearing held by Congressman Molinari in 1986 (see above) (114). Burton recounted that Antonio Rottino, M.D., then Director of Laboratories at St. Vincent's Hospital, administered some of the purified blood fractions prepared by Burton and Friedman to a few terminal cancer patients during the mid to late 1960s. Burton recalls some encouraging results in this undocumented initial human trial.

An early goal of Burton and Friedman's human research was to develop a blood test to measure the effects of their injections. Burton testified that a paper submitted in 1972 to the Society for Experimental Biology and Medicine reported the isolation of "Blocking Protein" (BP), which Burton described as a titratible substance that reflected tumor status and could be used to monitor changes. Burton stated at the Molinari hearing that this paper was rejected for publication because it included insufficient information on the substance's identity. This was one of his last attempts to publish his work in the scientific literature.

Burton and Friedman left St. Vincent's in the mid 1970s. With the support of clergy, businessmen, and several physicians, the Immunology Research Foundation (IRF) of Great Neck, New York was established on their behalf in 1973. It was there that significant numbers of cancer patients were first treated with IA" By the late 1970s, more than 100 cancer patients had been treated at IRF. Also during that period, Burton and Friedman obtained five U.S. patents for four IAT-like products and the methods by which they are produced (432,433,434,435,436). They also took initial steps with FDA toward obtaining Investigational New Drug (IND) status for MT. The FDA did not allow the IND to proceed because it lacked specific information that they required (889), and eventually, Burton and Friedman withdrew the IND. The Great Neck facility closed in 1977, and Friedman ended his affiliation with both Burton and IAT (308).

Later in 1977, Burton's New York sponsors helped him to establish the Immunology Researching Centre, Ltd. (IRC) in Freeport, Grand Bahamas (958). It was intended by the sponsors as a research institute, with investigational treatment to be provided to cancer patients. The initial plan was to treat 3,000 to 5,000 cancer patients according to a specific study protocol submitted by IRF to the Bahamian Ministry of Health (957). In practice, IAT has not been provided according to a formal study protocol, and clinical data have not been collected systematically, beyond patient history and encounter records.

In 1978, the Bahamian Ministry of Health asked the Pan American Health Organization (PAHO) to participate with them in a joint site visit to IRC after its first year of operation (852). Based on this visit, PAHO recommended to the Ministry that IRC be closed in large part on grounds that IRC was not carrying out its stated intent, part of its agreement with the Government of the Bahamas to operate there, to evaluate IAT as a cancer treatment. The site visit report concluded that "the present procedures of the Center do not permit any meaningful evaluation,' and further that "it is highly unlikely that any change in procedures will make the treatment evaluable. They observed in addition that "no consistent treatment effect has been achieved when assessed by objective criteria. "

Commenting on IAT treatment materials, the report states:

> *The material being used to treat patients is similarly a totally unknown quantity. Although the various fractions are referred to by Dr. Burton as "antibody fractions' and 'complement fractions,' there is in fact no evidence that any of these fractions do contain antibody of any relevance to the tumor involved or that in fact there are any active or even inactive complement components.*

The Bahamian Government did not close the clinic after the PAHO report was issued.

As scientific knowledge about the human immunodeficiency virus (HIV, the AIDS virus) and technologies for detecting it emerged in the mid-1980s, the safety of all biologics derived from human blood and blood products, including IAT, began to be questioned. In 1985, two patients in Washington State brought vials of various IAT products to the health

department for testing. Using ELISA (enzyme-linked immunosorbent assay) screening tests, all tested vials were reportedly positive for hepatitis B surface antigen, and 8 of the 18 were reported positive for HIV antibody (diagnostic for the presence of the viruses themselves) (883).

The set of IAT vials and accumulated test data were then sent from Washington State to CDC for additional testing. At CDC, repeat testing by ELISA identified 6 vials positive for HIV antibody, and all 18 positive for hepatitis B surface antigen. Results of more definitive Western Blot testing on all 18 vials were uninterpretable. The final test, the "gold standard' for establishing the presence of HIV, is to grow it in lymphocyte culture in the laboratory. A sample from one of the IAT vials did contain live HIV which was grown and isolated by this method. Thirteen of the vials were also positive for hepatitis B antigen (883).

As a result of these tests (all had been completed except the HIV culture), the Bahamian Ministry of Health asked CDC and PAHO to send a scientific team to IRC, to determine whether a public health hazard existed. On July 2, 1985, the scientists toured the facility and met with Burton and his staff concerning sterility practices and precautions.

Burton told the site visitors that he did not acknowledge the association of hepatitis B surface antigen with the potential for infection, nor the association of HIV (then called HTLV-III or LAV) or HIV antibody with AIDS. Burton said he relied on micropore filtration and heating during processing of the products to eliminate biological contaminants and product infectivity. He stated also that the sterility of the serum is checked by injecting it into laboratory mice and monitoring for sickness (89). In his trip report, the PAHO Chief of Epidemiology, who led the site visit, concluded that the clinic should be closed for several reasons, beginning with:

> *First and foremost, the clinic is producing an unsafe biological product with procedures and methods which appear to be unsafe for the staff involved. There are no indications of real interest in establishing accepted quality control measures. (830)*

Later that month, the Bahamian Government closed the IRC.

During the period the clinic was closed, Congressman Guy Molinari visited IRC, and in January 1986 in New York, held a "congressional public hearing on the Immuno-Augmentative Therapy of Lawrence Burton" (114). At that time, the patients formed the IAT Patients' Association (LATPA), and reportedly shared the IAT treatment materials that they had among them.

The clinic reopened in March 1986, after IRC agreed to conditions set forth by the Bahamian Government, including the acquisition of equipment to screen blood sources for HIV and hepatitis B; regular reporting of all viral test results to the Ministry of Health; compliance with standard blood donor screening and collection practices; treating only non-Bahamian cancer patients; requiring that patients who begin IAT have a confirmed outside diagnosis of cancer; and requiring review by the Ministry of full medical records for all new patients.

Scientific Review of Burton's Patents

The IAT patient brochure states that the methods of isolation and extraction for the IAT fractions given to patients at IRC and for blocking protein are described in five U.S. patents (two patents pertain to "Blocking Protein' issued to Burton between 1978 and 1980 (430). The findings reported here come largely from a contract report to OTA (725) and comments on it by outside reviewers.

The patents describe substantially different substances and processes than those described in Burton's pre-clinical research. The relationship to his previous work is not direct. The extent to which the patents describe the process actually used at the clinic also is unknown, as there are no available eyewitness accounts of its preparation.[5]

The patents are confusing and complicated, without being particularly complex or sophisticated scientifically, and all contain directions that would make it impossible to assure that the end products would be similar from batch to batch. These directions include ranges of settings on analytic instruments, ranges of processing times, and the necessity of taking precise readings that go well beyond the reliability of the laboratory equipment specified. In addition, the methods described to

[5]OTA has been criticized, in review comments by Robert Houston, for assuming that the patented procedures accurately represent the production of IAT at the Clinic, as is stated in the brochure. Mr. Houston asserts that "patents often omit key elements and blur important details as a safeguard against infringement."

establish the identity and potency of the products are often convoluted; many steps are repeated with no clear purpose, after which the process returns to a previous step.

The essential method of isolating the specified fraction in each of the patents is by differential centrifugation-spinning at high speeds—many different times. Centrifugation alone is an ineffectual technique for isolating specific proteins, contrary to what is claimed in the patents (725). For example, "Prol A Fraction" (corresponding to Tumor Antibody in the IAT patient brochure) is described as an antibody, meaning that it belongs to a particular class of protein with distinct immunologic activity. Using the patented Prol A Fraction recovery technique, however, it would not be possible to isolate an active antibody.

In the Tumor Complement Fraction patent, ammonium hydroxide (a strong base in the acid-base system) is used to adjust the pH of the material. This will damage or inactivate most components of the immune system, including all elements currently thought by mainstream researchers to be active against cancer. The procedures for Blocking Protein Fractions I and II could not specifically produce anything except clarified blood serum. While substances present in the original donor serum (except the active immunologic molecules which would be inactivated by a heating step) might remain in the final product, these would vary from batch to batch, depending on what was initially present.

It is possible that immunologically active substances, such as lymphokines, tumor necrosis factor (TNF), etc., could be present at various stages of the IAT manufacturing process, but it appears likely that they would be inactivated by the process, and if present at all, could be in only trace amounts.

The "MetPath contract"

60 Minutes, in its May 1980 episode about Lawrence Burton (782), Glassman's book, *The Cancer Survivors* (341), and Lerner's *Integral Cancer Therapy* (531) (citing Glassman) all report that a major U.S. manufacturer of diagnostic technology, MetPath, had been interested in Burton's blood test for detecting cancer. According to *60 Minutes*, MetPath entered into a contract with Dr. Burton in July 1979, in the frost phase, to "verify the existence and determine the measurability of the substance in serum said by Dr. Burton to be related to the presence or absence of cancer.' They reported further that MetPath setup a laboratory in Freeport to "see if there really was a protein in the blood of patients who have malignant disease," and to ascertain if their scientists could measure "what Dr. Burton said he was measuring." MetPath was reportedly able to find a "strange protein in the blood of certain of the specimens." According to a 1981 letter from Paul Brown, M.D., Chairman of the Board of MetPath at the time of the interaction with Burton (105a), MetPath was unable to develop a reliable test based on Burton's information and "extensive laboratory testing." There were 25 percent false positives in patients without cancer, and 25 percent false negatives in patients with cancer.

Glassman reported that MetPath sent 193 coded vials of blood samples, four from cancer patients, to Burton for testing. She states that Burton identified the cancer patients correctly, but also identified six other samples as positive. While MetPath initially considered them 'false positives,' Glassman states that within a year, all six had been diagnosed with cancer. Brown stated:

> MetPath did, in fact, send a certain number of vials of blood samples to Dr. Burton in the Bahamas for testing. The results obtained by Dr. Burton were substantially delayed and were not received by MetPath until well after the original specimens had been destroyed. Accordingly, no conclusion can be drawn from the results of this testing trial. We are not aware of the basis for the assertion that the results were "spectacular" or that the "tests proved to be 100% accurate and identfied the blood specimens of patients known to have cancer."
>
> We are quite distressed at the assertions being made by Dr. Burton and hope that this letter will put any misconceptions to rest. (105a)

OTA could find no other documentation of the relationship between Burton and MetPath, and no specific references were given in the books cited or by *60 Minutes*. We contacted MetPath to see if the original test results were available for independent analysis. They replied that they no longer have the records. The medical personnel with a memory of this event hold the general view that the assay did not work (486), as reported in 1981 by Paul Brown.

Information on Safety

No formal studies have been done to identify possible adverse effects of treatment with IAT. The information presented here includes past reports of safety problems (documented and suspected) and indicates potential areas of concern.

Risk of Inherent Treatment Toxicities[6]-The IAT patient brochure states that earlier animal research has shown IAT to be non-toxic; however, no systematically collected data are available to support this statement, particularly as it applies to human beings. Early publications suggested that the materials Burton was studying in mice may have had some liver toxicity, however, these papers did not contain detailed physiologic data. In support of Burton's application to open the Bahamas facility in 1977, the Immunology Research Foundation of New York reportedly submitted unpublished data on 100 human beings injected with one IAT product, among whom no toxicity was noted (852); but OTA was unable to obtain these data.

Potential Side-Effects—Based on the anecdotal reports of patients, in most cases the short-term side-effects of IAT appear minor (426). John Clement, an IRC physician, states that IAT is generally non-toxic, and the few side-effects reported have been minor (e.g., fatigue, malaise, pain at the site of injection or at bony metastasis, flu-like symptoms, somnolence) (199).

Risk of Exposure to Infectious Agents—As with any treatment material produced from human blood, IAT poses some risk of infection to patients, which could be minimized with appropriate manufacturing practices and product testing. Donor screening practices, the exact precautions taken during manufacture, whether standard "good laboratory and manufacturing practices' are followed, and the infection rate in IAT patients all are unknown.

The most serious safety concern is the possible contamination of IAT with viruses, including HIV and hepatitis B. Equipment to test for hepatitis B antibody, which has been required of U.S. blood centers since 1972, and for HIV antibody, which has been used voluntarily by manufacturers of biologics and by blood banks since 1985, was brought to IRC as a condition set by the Bahamian Government for the clinic to reopen in 1986. The IAT production processes themselves, as judged from Burton's patents and statements he has made about the processes, are not likely to be sufficient to inactivate these viruses.

Contamination of IAT products with Nocardia, a bacterium, was reported in the early 1980s, and was linked to nocardial skin infections and abscesses in IAT patients (850). By 1984, CDC had reports of 16 IAT patients with abscesses at injection sites, most of those cultured due to Nocardia, but other organisms (Staphylococcus aureus, Escherichia coli, an Actinomyces-like organism) were cultured from some patients. Four vials of IAT serum analyzed by CDC at that time were contaminated with a number of disease-producing organisms (882). NCI also studied treatment materials provided by five IAT patients in 1984, and reported that all were contaminated with bacteria (246). Burton has attributed the Nocardia problem to an air-conditioning vent from an adjacent animal laboratory, a problem he states was corrected by separating animal laboratories and manufacturing laboratories in a new IRC building (199). The poor laboratory practices and the potential for transmission of bloodborne infectious agents was the main reason PAHO gave for recommending that the clinic be closed in 1985, as discussed earlier (830).

Cassileth and colleagues surveyed IAT patients by telephone to find out the results of any tests for HIV or hepatitis B that they had. Fifty-four IAT patients and 25 next-of-kin of deceased patients were interviewed. Of 23 who had been tested for hepatitis B antibody, 4 tested positive, and 1 of 24 patients tested for HIV antibody reported a positive result. Although these data provide no information about the source of infection, the authors conclude that the findings suggest a need for "more careful, controlled testing of the immune serums and their preparation by its proponent." They noted also that the patients were convinced of IAT's medical safety and were generally unwilling to be tested for infection with viruses (178).

The IAT Patients' Association (IATPA), formed shortly after the clinic was closed in 1985, sent questionaires to about 500 IAT patients, in which they asked about possible infection with hepatitis B

[6]Toxicities are defined as unintended or adverse physiological effects of treatment, such as decline in cardiac, renal, or hepatic function. "Sterility" is defined as the absence of biological contaminants or infectious agents (e.g., viruses, bacteria, fungi, mycoplasma).

and HTLV-III (now called HIV). About 50 of the 150 IAT patients who responded reported negative blood tests for HTLV-III antibody or virus, and none reported a positive test. About 6.5 percent indicated that they had confirmed diagnoses of hepatitis B, though the questionaire did not ask how the diagnosis had been made or when it occurred in relation to the timing of IAT treatment (552).

U.S. oncologists responding to a 1987 survey by NCI and the American Society of Clinical Oncology (ASCO) reported their observations of 95 IAT patients seen in the course of their practices. These reports included 1 patient positive for HIV antibody; 1 case of adenopathy (enlarged lymph nodes); 3 cases of fever of unknown origin; 7 cases of hepatitis; 13 cases of infection (abscesses or sepsis, mainly Nocardia); and 1 case of rash or arthralgia. The Nocardia infections were acknowledged by Burton as originating at the Clinic (see above). For the other problems, it cannot be concluded that IAT was or was not the source (898).

Because some IAT products are made from the pooled blood of cancer patients, there is an additional theoretical concern about transmission of cancer-causing viruses (111), however no data exist on which to judge the likelihood of this happening with IAT. The potential infectious and oncogenic risks posed by IAT increase with the number of donors used in product manufacture.

Recently, the AMA's Diagnostic and Therapeutic Technology Assessment (DATTA) program attempted an assessment of the safety and efficacy of IAT. DATTA provided a panel of medical experts with published and unpublished information on IAT and asked for their evaluation of the treatment. Of 26 panelists, none rated IAT safetyas"established"; 6 rated it as "investigational"; 19 rated it as "unacceptable"; and 1 rated IAT safety as "indeterminate" (467).

Information About Effectiveness

There are currently no reliable data about IAT's efficacy as a cancer treatment. A number of anecdotal reports exist, however. One hundred forty-two testimonials of cancer patients treated at IRC were submitted to the Florida State Legislature in the early 1980s. Despite discrepancies noted later, an analysis of these submissions showed patient reports of subjective improvement (986). A few oncologists have reported on terminal cancer patients who benefited psychologically from seeking and undergoing IAT. During the 1978 PAHO site visit, 49 charts, selected by IRC staff, of patients who had "encouraging results,' were reviewed. The site visit report concluded that, "In the majority of cases, the best thing that could be said is that there was insufficient information to reach any kind of judgment" (852).

The IAT Patient Brochure contains a detailed two-page table that lists a large number of human malignancies for which "at least 50% of patients have responded to immuno-augmentative therapy with long-term regression of tumors and/or remission of symptoms" (428). The major types are: cancers of the breast, colon, lung, ovary, pancreas, prostate, head and neck, stomach, cervix, liver, bladder, and kidney; Hodgkins disease; leukemias; mesotheliomas; lymphomas; melanomas; and brain tumors. These include patients with metastatic disease. A few subgroups are identified for which fewer than 50 percent of patients have responded. OTA requested the data or calculations on which this table is based, but IRC was unable to provide them or to support the claims with other data (199).

In the 1987 survey of IAT patients by Cassileth and colleagues referred to above (178), an attempt was made to look at two standard measures of treatment efficacy. The study was designed originally to compare survival and quality of life between matched pairs of patients with metastatic cancer (a patient from the Pennsylvania Cancer Center files was to be matched to each IAT patient), but because too few IAT patients met the eligibility requirements (only 29 had available biopsy reports and metastatic disease at diagnosis), the authors did not carry out a matched analysis. In addition, the authors found that at the time they first went to the IRC, the IAT patients in the survey were more likely to be ambulatory, were younger, better educated, and of higher socioeconomic status than are cancer patients in general.

About a third of the patients reported improvement in appetite following the first visit to the clinic, and about a third reported becoming more ambulatory (although 86 percent reported being ambulatory before starting treatment). About half the patients reported no change in their performance status.

Cassileth and colleagues also reported on the survival of the 79 IAT patients. The patients in the study began IAT an average of 17 months after

diagnosis, and 50 patients were alive an average of 65 months after diagnosis. The 29 deceased patients survived an average of 59 months. The authors cautioned against inappropriate interpretation of these data, later writing that "it is not possible to determine the extent to which patient sampling biases contributed to these results, especially the observed survival distribution' (175). In a review of Cassileth's study done at OTA's request, John Bailar (a biostatistician) agreed with Cassileth's conclusion, adding that the quality of life questionnaire used may have been seriously flawed and inadequate for obtaining accurate information from these patients. Bailar emphasized that the information Cassileth reported on survival time is unusable in the absence of some appropriate comparison (64). Accordingly, valid inferences about the efficacy of IAT in controlling cancer cannot be drawn from this study. Nonetheless, IAT supporters continue to point to this study as strong evidence of the efficacy of IAT (see, e.g., (416)).

Clement, Burton, and Lampe compiled the records of 11 peritoneal mesothelioma patients treated with IAT between May 1980 and February 1987 (202). They reported the following survival information:

> *The total subject population represents a mean survival of 35 months and a median survival of 30 months; with a range for all cases from seven months to 80 months.*

Comparing survival to average survival of mesothelioma patients reported in other published series, the authors conclude that survival in these IAT-treated patients is two to three times greater than that reported for mesothelioma patients otherwise treated. They apparently did not consider the IAT patients' prior treatment regimens, however, nor the selection factors that rendered patients well enough to go to the Bahamas clinic even before IAT treatment began. The authors also failed to note that the ranges of survival times observed are actually quite similar to the ranges of survival times noted in other reported series of mesothelioma patients. They reported a survival range of 7 to 80 months for IAT-treated mesothelioma patients, while the literature reports they cite give survival times ranging from 1 to 60 months.

No valid statistical analysis can be performed on such a group of cases. They are not analogous to the usual case series presented in the literature, which comprises all patients who present at diagnosis in some identifiable catchment area (though this cannot always be defined precisely, on a population basis). The experience of the series, if large enough, should approximate the survival experience of the larger population of patients with that type of cancer. If some patients, in particular those who die in the first few months after diagnosis, are excluded, the statistics of the group would be skewed toward longer survival times. During a site visit to IRC in September 1987, OTA staff were asked to examine the IRC medical charts of the 11 peritoneal mesothelioma patients included in this study. The mean survival of the 11 patients was 9 months before they began treatment with IAT. One of the comparisons made in the paper by Clement, Burton, and Lampe *is with a series of 45 patients whose mean survival was 6 months. It is clear that many patients with this type of cancer die very soon after diagnosis. For the most part, Burton's patients had already survived a critical period before beginning IAT"*

As described above, a survey was conducted by NCI and ASCO in 1987 to ask U.S. oncologists about their experiences with IAT patients. Responding to a series of questions concerning IAT's potential efficacy, oncologists treating 78 cancer patients reported: 2 patients alive with objective response; 9 alive with no objective response; 12 alive with evidence of disease progression; 1 dead despite objective evidence of response; 63 dead with objective evidence of progression; 4 dead with evidence of IAT-related toxicities; and 3 unevaluable patients. The researchers concluded that this survey cannot be used to draw valid inferences about the effectiveness of IAT (898).

The AMA's recent DATTA report on IAT included a rating of efficacy (in addition to safety, discussed earlier). Of the 27 DATTA panelists, none rated the efficacy of IAT as "established"; 6 rated it as "investigational," 16 rated it as "unacceptable' and 5 rated it as ''indeterminate. ' The DATTA report concluded that IAT is "of no proved value as a treatment for cancer' (467). Because the information base on which to judge efficacy is inadequate, this DATTA opinion cannot be regarded as evidence that IAT is or is not efficacious.

After more than 10 years of IAT use in human cancer patients, and despite several attempts to plan a prospective clinical trial, no reliable data are available on which to base a determination of IAT's

efficacy as a cancer treatment. IRF and various New York physicians attempted unsuccessfully to arrange a clinical trial for IAT in the 1970s. NCI directly attempted to arrange a clinical trial again in the early 1980s, but negotiations finally broke down with Burton's representative. The process was aborted due to poor communication between NCI and Burton, complicated by reported findings of product contamination (244). In all of these attempts, as with OTA's, Burton himself was, for the most part, involved only indirectly; the people he designated as representatives, who were devoted patients or other supporters, did not have authority to speak for him, nor did they have intimate knowledge of the details of IAT treatment. OTA's attempt to develop a clinical trial protocol in collaboration with Burton, described below, also ended in failure.

DESIGN OF A CLINICAL TRIAL FOR IAT

Congressman Molinari and his cosigners asked OTA to develop "the first comprehensive protocol to be used in an evaluation of IAT," and to perform a "statistical analysis on IAT's efficacy, utilizing existing clinical data. ' OTA enlisted the assistance of academically based experts in clinical trials, an oncologist from NCI and one from FDA, and asked Burton for his participation. Burton appointed a resident patient who was active in the IATPA, to represent him on this "IAT Working Group." Burton himself would not participate except at interim and final decision points. As is turned out, this was a significant handicap.

There were pluses and minuses to having IAT as the object of this task. On the plus side, IAT presented many of the challenges likely to arise in attempting to evaluate other unconventional treatments for cancer+. g., "secret' components to the treatment, significant concerns about safety, treatment taking place outside the country. Another advantage was that the claimed effects of IAT were no different from those made for most mainstream cancer pharmaceuticals, and should, therefore, have been amenable to testing and measurement using standard study designs. On the minus side, it was not Burton but Congress, speaking for Burton's patients, who initiated the request for evaluation; and previous attempts on the part of NCI to work with Burton on an evaluation of IAT had ended in failure, with Burton finally refusing to provide what NCI considered crucial information about IAT, and then claiming bad faith on NCI's part (762).

The First IAT Working Group Meeting

OTA's IAT Working Group first met on March 31,1987, to discuss possible approaches to a fair and competent evaluation of IAT. A specific proposal prepared by IRC was considered as were other approaches. At the meeting, three major issues were discussed at length: 1) the potential for obtaining information from IRC patient records that might be useful in an overall evaluation of IAT; 2) the patient safety issues raised by a clinical trial of IAT; and 3) possible approaches to clinical trials of IAT.

Obtaining Information From IRC Patient Records

A proposal by IRC and suggestions from the Working Group for use of existing patient records were considered. The IRC proposal asked for a "statistical analysis" of the records of 11 patients with peritoneal mesothelioma who had been treated at the clinic. These 11 patients are discussed in the paper by Clement, Burton, and Lampe (201), which was reviewed earlier in this chapter. For the reasons given earlier, there appears to be no valid means to analyze this group of patients for the possible effect of IAT on length of survival, which was the suggestion made in the IRC proposal.

The Working Group considered two other approaches to using existing patient records. A "best case' approach similar to that carried out by NCI for laetrile (discussed in ch. 5), relying on documented evidence of tumor regression, was considered. OTA considers the best case approach potentially useful as a formal way to present evidence that could be useful to support carrying out appropriate clinical trials of unconventional treatments. In the case of IAT, however, the goals of such an exercise were unclear. Since the decision to evaluate IAT had already been made on political grounds, it did not appear that presenting best cases would accomplish anything, except to delay the beginning of a clinical trial, if it were to take place.[7] This is somewhat analogous to the laetrile review, which ended with

[7]The mesothelioma cases did not meet the standards of a best case review; because the analysis was based only on length of survival and nOt tumor regression it did not appear that those eases would be appropriate for a best case review.

very little evidence in support of the treatment. With laetrile, a decision was made to proceed with a clinical trial anyway, because of the public health importance of doing so. (At the time, laetrile had been legalized in more than 20 States, and was in widespread use, which was not the case with IAT.)

An "informal" examination of patient records was also considered by the Working Group. It was thought that there might be some value in simply looking at typical patient records to get an idea of the type of patient treated at IRC and to see how records were generally kept. This activity would have no specific endpoint. It was decided that the time and money needed to carry out such a review, given the lack of clear goals, would not have been justified.

Issues Related to Patient Safety in a Trial of IAT

IAT materials are made from pooled blood samples from people with and without cancer. As such, the potential for infection must be assessed and minimized before such mater-ids are given to patients in a clinical trial. At the time of the first Working Group meeting, it was assumed that treatment with IAT would take place in the Bahamas, so the treatment materials would be made there. What was contemplated was that quality assurance procedures would be developed to be put in place at the clinic and that testing of fmished materials would take place on some regular schedule at an independent laboratory in the United States. At the time of the meeting, it was left that OTA would ask IRC for information about the processing of IAT materials and would gather information from FDA and elsewhere concerning probable testing requirements. This issue was left in an unfinished state at the first meeting.

Planning a Clinical Trial

The IRC proposed a clinical trial in patients with peritoneal mesothelioma who did not have advanced disease. According to the proposal, patients would have to be diagnosed in the United States and "given a definitive prognosis by the evaluating oncologist." Patients would be treated at IRC under Burton's direction. After treatment, 'Patients would be re-examined at a period after their prognosis date thought to have statistical significance and possibly again near the end of the study period. " Serious problems with this proposal, discussed below, relate to the patient population and the basic study design.

Peritoneal mesothelioma is an exceedingly rare cancer; about 200 cases per year are diagnosed in the United States (894). This may be contrasted with 149,000 cancers of the lung, 98,000 cancers of the colon, 42,000 cancers of the rectum, and 90,000 cancers of the prostate (25). Under the best of circumstances, even if patients with more advanced disease were included, it would take years to accrue sufficient numbers of patients for even a modest clinical trial in this disease. If IAT were a treatment used exclusively on patients with peritoneal mesothelioma, then there would be no choice, but since it is used widely, and is reported successful by Burton for patients with a wide range of cancers, the preferable choice is a commonly occurring cancer.

A more fundamental concern with the IRC proposal is the concept of comparing actual survival with a "definitive prognosis' given to the patient on entering the study. Except in rare circumstances, prognosis for individual cancer patients cannot be determined accurately enough to form the basis for such analysis, which is why it is necessary in attempting to determine effects of treatment on survival to have a randomized control group. Based on the 11 cases presented by Clement, Burton, and Lampe, if IAT is effective, its effect is not so extreme as to be evaluable in this way.

Regression of disease was the other major endpoint proposed by IRC, and it would be possible to measure this in a clinical trial without a control group. "Phase II" clinical trials in cancer, designed to detect tumor regression, are often of this type. According to members of the Working Group, however, mesothelioma can be a difficult disease to follow in terms of disease progression or regression. Other solid turners are more easily followed and assessed.

The Working Group went on to consider other approaches to an IAT clinical trial and cancers other than mesothelioma. According to IRC literature, patients with virtually all types of cancer are treated and for most types, IRC reports that more than 50 percent benefit from treatment (430). The Working Group stressed the need to study patients with common cancers who have measurable and followable disease (e.g., primary or metastatic lung cancer, colon cancer with followable lung, liver, or intra-abdominal masses, or primary renal carcinoma).

Two possible phase II clinical trial designs were discussed: uncontrolled (all patients treated with IAT), similar in some ways to the IRC proposal, and a trial with randomized controls (one group treated with IAT and the other receiving other standard or supportive treatment, whichever is appropriate). OTA and the Working Group assumed at the time that IAT-treated patients, regardless of the study design, would have to be treated at the IRC in the Bahamas.

In an uncontrolled phase II study, patients who met study criteria (type and stage of disease, previous treatment, general condition or "performance status," etc.) would be offered participation. Those who agreed would be evaluated for tumor status and other possible outcome measures (e.g., "quality of life" measures) and sent to IRC for treatment. The number of patients needed for the study would be determined in part on the basis of the predicted effectiveness of the treatment (this would have to be supplied by Burton). Patients would be reevaluated at specified intervals (determined on the basis of how quickly Burton predicted the treatment would work), the number of responses (complete and partial remissions) counted, and the proportion responding compared with prespecified measures of success. For instance, a sample size of 20 to 30 would give a good chance to detect a benefit in 20 to 30 percent of patients (399).

It was envisioned that, in a randomized study of IAT, a principal investigator in the United States would share overall responsibility for the clinical trial with Burton. Physicians agreeing to collaborate at various institutions would offer enrollment to patients meeting specified entry criteria. The design would be explained to patients, so that they understood that they had an equal chance of getting IAT or supportive treatment. As each patient agreed to participate, random assignment would be made to one or the other arm (this could be done by an independent center). After patients were fully evaluated, those randomized to receive IAT would go to the Bahamas for treatment. Patients in the control group would receive their specified care. All patients would be reevaluated at appropriate intervals. The endpoints would be standard, objective measures of disease regression or progression. The results would be analyzed by comparing the percentage of patients with positive responses who had been randomized to the IAT arm with the percentage responding in the control arm. In addition, measures of the quality of life of the two groups would be compared.

A reasonable size for a study of this type assuming, for instance, that about 25 percent of patients would benefit (a more modest goal than what is claimed for IAT), would be a total of about 80 patients, 40 in each arm.

The advantages and disadvantages of each study design were discussed at length. The main advantages of a small uncontrolled study, compared with the randomized design, would be its lower cost, somewhat shorter duration, and the fact that it is a standard design. As used in mainstream research, small phase II studies are often used to help identify which specific cancers should be included in further phase II studies. With IAT, however, Burton would specify, based on his experience, which cancers would and would not be appropriate.

The main disadvantage of the small uncontrolled study would be the difficulty in interpreting the results. A "patient selection bias," which would not affect trials of new mainstream treatments to the same degree, could work either for or against finding an effect. On one side, for instance, physicians enrolling patients in the study may have a conscious or unconscious bias for or against the treatment, and may choose to offer enrollment in the trial as an alternative selectively, based on a preconceived notion of IAT's value and on the patient's prognosis. Patients themselves may also have preconceptions about IAT and may "select themselves" into the study differentially on that basis. With no control group, there is no way to assess the effects of this possible "enrollment bias," which could be large, on the outcome. This would not be a concern in a randomized design.

Other factors may also show some variability that would be impossible to account for adequately without a randomized control group. These include variations in tumor size due to measurement variability, real short-term fluctuations (but not long-term shrinkage) in tumor size, and other influences on the size of the tumor (e.g., effects of previous treatment). Any small or moderate response in an uncontrolled study would be inconclusive and likely to lead to controversy. While this could happen in a randomized study as well, it is much less likely, given the direct comparison with controls. Another advantage of the randomized design is that evaluation of serial tumor images would be conducted by individuals

blinded as to which treatment group patients were in, eliminating a potential source of bias.

overall, a clear-cut result would be much more likely in a randomized trial than in an uncontrolled one. Even a negative result in the proposed randomized study would be more informative and would allow better estimation of the upper limit of potential effectiveness of IAT than would the uncontrolled design, should further studies be planned. Of the options considered, OTA adopted the randomized phase 11 trial as the best first step toward the fair and unbiased evaluation of IAT called for by Members of Congress.

A summary of the meeting was circulated to all participants afterward, and some important points emerged in their comments. Some of these, particularly concerns of NCI and FDA, had to do with whether Burton would be willing to supply Suffi cient information about the treatment materials for their safety to be assessed and assured, to the degree possible. NCI stated that the study should take place at a research institution in the United States. Other comments expanded on the types of cancer that might be considered. In general, the Working Group members were supportive of proceeding in the direction spelled out in the draft summary paper.

The response from Burton's representative (425), who had offered little guidance during the meeting, was received 2 months after the draft was sent. It was a long and legalistic discourse on the OTA process for the study, with general discussion about evaluating unconventional treatments and the need for "innovative evaluative techniques," but with no comments specifically on the plan set out for consideration. The response also said that Burton himself had been advised by his representative not to read the draft.

OTA responded to Burton's representative in detail, and wrote to Burton (397) to inform him that his "lack of representation by an appropriately skilled person' on the Working Group appeared to be making progress difficult. In the letter, Burton was asked to replace his representative with someone with technical experience in appropriate areas, and to become more involved himself in the process.

Burton responded that he believed the situation would improve with the participation of his attorney, who was very familiar with IAT and with Burton's views. Contact was made between OTA and the attorney, and subsequently the attorney, acting on Burton's behalf, asked that OTA staff visit the clinic in the Bahamas. Specifically, Burton wanted OTA staff to tour the clinic, examine the records of his patients with peritoneal mesothelioma, and meet some patients. OTA agreed to travel to the clinic and to follow an agenda set by Burton, with the understanding that progress on the protocol, as reported in the draft OTA report, would be discussed as well. An OTA Assistant Director (Herdman), Project Director (Gelband), and Analyst (Solan) planned a 3-day trip to Freeport in early September 1987, in accord with Burton's proposed agenda.

The First Bahamas Meeting

In addition to OTA staff and Burton, Burton's original representative, his lawyer, a consultant statistician, and a member of then-Congressman Molinari's staff were present. The outcome of the meeting, which actually ended after 2 days, was a review by OTA of the peritoneal mesothelioma records (discussed earlier in this chapter) and a "memorandum of understanding" (see Addendum to this chapter), signed by Burton and Herdman, covering some key points in the design of a clinical trial. OTA staff were present on the second morning to observe the process of drawing and testing patients' blood according to Burton's specifications. There was no preparation of the treatment materials going on, however, and OTA requests for more information about how the products were made were not fulfilled.

Burton's participation in the discussion was limited mainly to the first morning. At that time, he characterized the OTA draft as "childish and inane. At the conclusion of the meeting, OTA agreed to continue exploring the feasibility of studying peritoneal mesothelioma and to try to further develop a protocol based on the memorandum of understanding.

Key provisions of the memorandum of understanding included: that the design would be a randomized trial; that the trial would be conducted in the United States; that recruitment of patients should be possible within a span of about 1 year; and that appropriate measures would be taken to assure the safety and sterility of materials that would be given to patients.

Further Development by OTA

The two issues requiring the greatest attention after the first meeting in Freeport were: 1) whether peritoneal mesothelioma was a feasible choice for tumor type, and if not, what types of cancer could be studied; and 2) further development of information relating to assuring the biological safety of IAT for patients in a clinical trial. OTA looked into these areas and began planning another meeting with the IAT Working Group.

Burton and his attorney agreed, based on further documentation gathered by OTA, that it would not be possible to accrue sufficient patients within 1 year for a trial of peritoneal mesothelioma, because it is such a rare cancer. Burton subsequently requested that various types of non-Hodgkin's lymphoma (NHL) be considered (116). OTA gathered information about the incidence, current treatment and prognosis for the types and stages of NHL, and about current clinical trials enrolling patients with these cancers. In addition, two NHL experts, one in the pathology of NHL and the other in clinical management, were consulted and asked to attend the planned second meeting of the Working Group.

The issue of the biological safety of IAT continued to be difficult to deal with satisfactorily. OTA consulted with biologics experts within and outside the government, and developed some general guidelines and some minimum testing requirements. However, because the preparation methods for IAT fractions were not known to OTA and would not be divulged at that time by Burton, it was impossible to develop any specific recommendations. (Testing and preparation requirement for biologics are determined very much on a case-by-case basis, because the compounds in the class are so varied and requirements not amenable to complete standardization.) OTA also arranged for an expert in biologics from the FDA to be present at the second Working Group meeting.

The Second IAT Working Group Meeting

The Working Group met in May 1988, supplemented by two experts in NHL, a biologics expert from FDA, and an oncologist who had looked into methods that might be used to gather information about possible toxicities associated with IAT before a clinical trial began. Burton was represented by his attorney only, as his patient representative was unable to attend at the last minute.

It was concluded that it might be possible to study NHL patients with particular types of tumor (i.e., tumors consisting of predominantly certain cell types) and particular stages. There was little enthusiasm for this, however, as these can be difficult cancers to follow and patients often receive considerable palliative treatment during the course of their illness, which would complicate following them over the relatively long period of time (on the order of 6 months to 1 year) needed on treatment with IAT for a fair evaluation of its effect. The Working Group expressed the strong opinion that a solid tumor (e.g., colon cancer) be included in the study as well, if a trial in patients with NHL were to be planned.

Further consultation after the meeting led OTA to the conclusion that NHL would actually be a poor choice because, although not as rare as mesothelioma, the number of eligible patients would probably be too small for the trial to be conducted within a reasonable time period. A common type of cancer, one of the many treated with reported success at IRC, still appeared to be a more appropriate target.

The issue of biologic safety of IAT was again discussed at length at the meeting, but with little real progress because of the lack of detail concerning how the products are made. The Working Group considered several mechanisms for gathering information about possible IAT toxicities before a trial would begin. The information would serve two main purposes: first, to anticipate testing requirements for possible adverse effects during the actual clinical trial, and to inform potential trial participants of what they might expect were they to take IAT. Unless dire problems arose, the information would not be used to attempt to cancel plans for the clinical trial.

One pre-trial mechanism emerged as the best possibility for determining short-term effects. Under this plan, patients just beginning IAT treatment in the Bahamas would be asked to have blood drawn in the United States before going to the clinic, to establish baseline measurements, after returning from their initial course of treatment (usually 6 to 8 weeks), and at intervals thereafter (e.g., monthly). Standard measurements (e.g., liver function tests, hematologic profiles) would be recorded. Patients could also be interviewed to gather information about subjective effects.

The most significant issue relating to patient safety, however, was whether the clinical trial would be carried with official Investigational New Drug (IND) status from FDA. For all practical purposes, if the trial were to be carried out as envisioned in the United States, an IND would be necessary. The IND application would entail Burton's disclosing the details of how IAT treatment materials are made and how much of each material patients generally receive. This information would allow FDA to consider possible risks, ways of reducing them without interfering with the basic IAT regimen, and appropriate quality control tests to be carried out during the clinical trial. (Information provided to FDA in an IND or a Drug Master File (DMF), on which an IND may be based, remains entirely confidential with FDA.)

It was possible that Burton could maintain as confidential the algorithm used to determine the exact dosages, which is the one part of the treatment that he maintains exclusively proprietary, but it was not assured that FDA could agree to this. The materials themselves are prepared in both the Mexican and German IAT clinics, but Burton provides dosage information for all clinics based on transmitted laboratory values. Burton would have the same relationship to the U.S. trial as to his clinics in other locations.

All of this information was communicated to Burton in a letter in June 1989 (397). In concluding, the letter stated:

> At this point in our process, I now need your assurance that we all understand where we are. We still must select a type of tumor that will make for a feasible, meaningful trial of IAT. We need to know any conditions you would place on NCI as a trial sponsor, the role you expect to play in the trial, and we especially need to know that you can provide the type of information that I've described [regarding an IND], which is absolutely essential to getting a trial going.

OTA proposed a meeting with Burtor$_A$ to discuss these issues, with the added participation of an expert in biologics and an oncologist of Burton's choice, or suggested by OTA. In further telephone conversations, OTA requested also that the visit include an opportunity to observe IAT materials being produced.

The Second Bahamas Meeting

OTA representatives (Herdman and Gelband), accompanied by an FDA oncologist who is an expert in biologics, traveled to the clinic in August 1989. The objectives for the meeting were to come to agreement on an appropriate type of cancer to be studied, and to allow Burton and his representatives to begin a dialog with FDA so that the IND process could be started.

It was OTA's belief that the first of these objectives was met: an agreement was reached that patients with advanced colon cancer with measurable disease would be studied. The entire meeting with Burton, planned for 2 days, lasted only a few hours. There was no opportunity to observe the IAT production process. The FDA biologics expert discussed the general requirements for an IND and explained what is done with the information fried with FDA. Burton and his then-current representative (the original representative to the IAT Working Group had died by this time) did not pursue this discussion in detail.

Burton expressed his wish to have a "pre-test," in which patients with advanced colon cancer with measurable disease (the same criteria as for the clinical trial) would be treated at the clinic in the Bahamas and their progress monitored in the United States. Burton stated that this would require patients to be recruited in the United States by NCI or another clinical trial sponsor and sent to the clinic. OTA made it clear that this would not be considered part of the clinical trial and that NCI was unlikely to cooperate in such a venture.

OTA prepared a draft summary of the second Bahamas meeting, covering mainly the choice of cancer type to be studied, the requirements for an ~-D, and-Burton's responsibilities during the trial. It reiterated OTA's position that a pre-test in the Bahamas, as described by Burton, could not be the basis for an acceptable evaluation of IAT, and therefore the idea could not be supported by OTA. The draft report was sent to the IAT Working Group and Burton for comments.

The Clinical Trial Described by OTA

The clinical trial design developed by OTA, in consultation with the IAT Working Group, expert consultants, and Burton and his representatives, would be a test primarily of whether treatment with IAT leads to shrinkage of tumors, as reported by

Burton. It would also gather information on quality of life, adverse effects, and survival (though it probably would not be large enough to definitively detect possible improved survival due to IAT).

The clinical trial would take place at an accredited U.S. medical center acceptable to both the trial sponsor (possibly NCI) and Burton, in accordance with the current regulations of the Department of Health and Human Services concerning IND and Institutional Review Board requirements. All patients would be treated in the United States. Patients agreeing to participate after giving informed consent would be allocated by random assignment to IAT or supportive treatment.

Patients with metastatic cancer of the colon with measurable disease would be eligible, specifically a diagnosis of "Dukes' D colorectal carcinoma.' This is a relatively common cancer, and one for which treatment options are limited. To the extent possible, patients would have had no previous chemotherapy or radiotherapy, a condition set by Burton to preclude the possibility that responses during the trial could be attributed to the previous treatment rather than IAT. However, response to prior treatment would not be a problem because the control group would provide a check on late responders to previous treatment.

Patients would spend the necessary 6 to 8 weeks initially at the treatment center, having blood drawn each day and receiving IAT. They would return home with treatment materials and a schedule for self-administering them for periods of time specified by Burton (about every 3 months, according to treatment regimens at the clinic in the Bahamas).

Burton (personally or through a representative) would be responsible for providing instructions for making the various IAT fractions and for carrying out necessary laboratory measurements at the U.S. treatment site. He would be asked to test materials made at the site to ensure that they met his standards. Measurements would be transmitted to Burton daily during initial treatment and thereafter at intervals specified by Burton, and he would transmit back the dosage schedules for each patient.

All patients would be examined at regular intervals, including appropriate scans and tumor measurements, and aspects of quality of life assessed. All review of patient data to assess response would be done in a blinded fashion, that is, the reviewers would not know which treatment group patients were in. Blinding is used to assure that the groups are assessed without bias. In this trial, the assessment would involve review of initial pathology and assessing the regression or progression of tumors.

Standard, accepted, statistical techniques would be applied in the analysis. Whatever the result of the study, Burton and the trial investigators would agree to publish the results for scrutiny by the scientific community.

Burton's Response to OTA's Clinical Trial Description

Burton responded to the OTA draft (116) stating that he had "not agreed to much of what you have chosen to include in your report,' and that the report ''reflects little more than an outline to obtain negative results. ' The letter goes on to state that "the pre-trial was a nonnegotiable prerequisite to the clinical trial of IAT in the U.S.,' and points out that, in an earlier letter to him, OTA had stated that "NCI had suggested just such a 'small non-randomized pilot phase.'" He terms it "strange" that the draft states his pre-trial would not be considered part of OTA's plan.

Burton had misinterpreted NCI'S proposed "pilot phase," which they clearly stated would be a small study preceding the randomized study in the United States, for the purpose of assuring the feasibility of the full trial and collecting information about potential toxic effects. These were not Burton's goals, and a pre-trial at his clinic would not have provided the information desired by NCI.

In his letter and in a telephone conversation with OTA, Burton signaled his wish to deal directly with NCI. Herdman responded (397) that he believed the OTA draft report was an accurate representation of the discussions and agreements that had been made and that 'the trial described in the draft would be the fairest, most expeditious initial evaluation of IAT." However, OTA accepted Burton's decision to proceed with the NCI as final.

In several telephone calls following shortly, one of Burton's representatives (the same one who had several years earlier represented Burton in discussions with NCI) and the President of the IAT Patients Association both attempted to reopen discussion with OTA. OTA agreed that this would, of course, be possible, if Burton himself wished to do

so, but no word was ever received from Burton himself; nor has he initiated discussions with NCI.

ADDENDUM

Memorandum of Understanding Between OTA and Lawrence Burton Concerning a Clinical Trial of IAT

On September 9, 1987, the Office of Technology Assessment of the U.S. Congress (OTA) and the IAT, Ltd. (Centre) of Freeport, Bahamas have agreed in principle to the following points regarding the design of a clinical trial protocol to evaluate the efficacy of Imnmno-augmentative therapy (IAT).

1. *Peritoneal mesothelioma will be the tumor candidate of choice for the protocol, provided both parties are satisfied that enough patients can be recruited for such a study within approximately 1 year of commencing recruitment efforts.*
2. *The study will be a randomized clinical trial in which patients will be assigned to treatment with IAT or some standard treatment.*
3. *The endpoints that will be considered for use in this protocol shall include survival time, quality of life, and tumor status.*
4. *Both the Centre and OTA agree that no interim data or study results will be published before the clinical trial is completed.*
5. *Patients will be eligible for the trial only if they have a confirmed pathological diagnosis of peritoneal mesothelioma, preferably confirmed by the Armed Forces Institute of Pathology or another medical institution to be mutually agreed upon. Efforts will be made to recruit patients with minimal or no prior chemotherapy or radiotherapy. Prior surgery will be acceptable. Patients with advanced disease (beyond the abdomen) will be excluded [referring specifically to peritoneal mesothelioma].*
6. *The trial will be conducted at a single site (to be mutually agreed upon at a later date) in the United States.*
7. *IAT blood analysis and preparation of IAT treatment materials will take place at the U.S. study site by personnel trained and supervised by Lawrence Burton, Ph.D., of the IAT or his designated representative. Data from IAT blood analysis will be transmitted to Dr. Burton, who will specify the daily IAT regimen for each patient. Information required for "standardization" of treatment material will be transmitted to Dr. Burton as he requires.*
8. *Methods of assessing the safety and sterility of all IAT materials to be given to patients will be included as part of the protocol. Such testing will be a pre-condition for beginning a clinical trial and will continue as appropriate throughout the trial. Such testing will be performed by an established clinical laboratory to be mutually agreed upon.*
9. *During the course of the trial, patient care, other than IAT treatments, will be provided by the patients' private physicians or licensed physicians at the agreed-upon study center.*
10. *As in all clinical trials, patients offered participation will be informed of all significant details relevant to both IAT and the other treatment before their consent is sought.*
11. *Interim studies (e.g. x-rays, ultrasound, CT scans, as specified in the final protocol) will be submitted to independent groups of qualified specialists in those particular disciplines. All such materials will be sent without revealing patient identifiers or, importantly, which treatment the patient is receiving.*
12. *OTA and the Centre will provide any and all non-proprietary materials (including articles, data, etc.) used to support recommendations or conclusions bearing on study design.*
13. *Lines of communication between OTA and the Centre will be kept open for the prompt exchange of pertinent information.*

Both the Centre and OTA will make a good faith effort to research these points and determine their feasibility in order to complete the design of a protocol as promptly as possible.

Office of Technology Assessment:

(signed by Roger C. Herdman, M.D.)

IAT Ltd:

(signed by Lawrence Burton, Ph.D., Director)