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REPORT TO THE MINISTRY OF HEALTH OF BAHAMAS
ON THE SITE VISIT TO THE
IMMUNOLOGY RESEARCHING CENTER, LIMITED
FREEPORT, GRAND BAHAMAS ISLAND, BAHAMAS

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SUMMARY

At the request of the Government of the Bahamas to the Director of the Pan American Health Organization (PAHO), a joint site visit to the Immunology Researching Center, Limited, located in Freeport, was performed by representatives of the Ministry of Health and PAHO. The purpose of this site visit was to perform an evaluation of the activities developed by this Center during the first ten months of its operation, especially the clinical consequences on cancer patients of the therapy being carried out at the Center.

Under the present arrangements between the Government of the Bahamas and the Center, periodical evaluations are to be performed. However, it is concluded that the present procedures of the Center do not permit any meaningful evaluation and that it is highly unlikely that any change in procedures will make the treatment evaluable. Further, it is emphatically stated that no consistent treatment effect has been achieved when assessed by objective criteria.

It is recommended, therefore, to close the Immunology Researching Center, Limited. However, should the Government choose not to close the Center at this time, a number of changes should be made, although, as stated before, it is highly unlikely that these changes will be able to improve the current situation.

OBJECTIVES

In July 1975, the Government of the Bahamas approved an application for the Immunology Research Foundation of Great Neck, New York to operate a Center in Freeport for a clinical investigation treatment program. It claimed that its scientific staff had made an experimental breakthrough in the treatment of cancer based on an immunological approach, although none of the clinical data presented had appeared in the medical literature.

The Foundation's request was based on results of research carried out at its facilities in Great Neck, New York, which may be summarized as follows:

1. Every healthy animal has in its blood serum certain complex bodies ("anti-cancer defense mechanism (IDMC)") which can protect against cancer by destroying malignant cells.
2. There exist also in the animal's blood chemical agents which can nullify the defense mechanism ("blocking agents (BA)") and thus permit the growth of cancer cells.
3. These blocking agents, which are closely associated with a growing tumor, operate by inhibiting two or three other substances, probably protein in nature ("deblocking protein (DBA)") which are associated with tumor destruction and therefore constitute the defense mechanism.
4. Two of these deblocking proteins (DBA^s) have, by a trial-and-error method, been isolated by the Foundation's scientists, from tumor-free individuals.
5. When these DBA^s are introduced into a tumorous animal, they reduce the concentration of the blocking agents, thus allowing the natural IDBC to destroy the tumor.
6. The bulk of the experimental work has been carried out on a strain of laboratory mice (C3H(t)), all female members of which spontaneously develop mammary adenocarcinoma.
7. Administration of the DBA^s to groups of mice with advanced breast tumors resulted, in every case, in actual or virtual disappearance of the tumors, within three days.
8. The same basic constituents of the murine IDMC are present in man and have been fractionated.
9. In cases of human cancer,
 - surgery increases the blood level of at least one of the DBA^s - i.e. is beneficial.
 - irradiation is associated with a reduction in these substances.

- standard chemotherapy also produces a decrease in the second of the DBA^s.

10. Limited studies on one hundred humans injected with DBA^s obtained from normal human sera showed no evidence of toxicity.
11. The DBA^s have been administered in the USA to 50 human cancer victims - terminal cases with poor prognosis - who had received, without positive results, all of the classical anti-cancer treatment. Of these,
 - 21 showed definite improvement; no detectable evidence of the disease;
 - 22 showed arrest of the disease process;
 - 7 died after showing some improvement.
12. The Foundation was anxious to accelerate the speed of such trials in man by treating one thousand to three thousand (1000-3000) cancer patients annually during a five-year period, at Freeport.

As part of the agreement with the Ministry of Health, the Center should allow the Ministry of Health or its agents to review its activities and at regular intervals of not more than nine months to evaluate the progress of the program; and if it is considered that it is not successful, "they may determine this indenture subject to such terms and conditions as they should deem just."

Consequently, the Ministry of Health requested of the Director of the Pan American Health Organization (PAHO) the cooperation of the Organization in jointly performing this evaluation. It took place at the Center site, with staff members and other participants representing the abovementioned Foundation and the Center and the joint team from the Ministry of Health and PAHO (Annex I, List of Participants).

DESCRIPTION OF WORK COMPLETED

1.1 Background

1.1.1 Physical Description of the Facilities:

The Immunology Researching Center (IRC) is located in a building directly attached to the Rand Hospital in Freeport, Grand Bahamas Island. The facilities include a large laboratory with a number of Sorvall centrifuges, a few Beckman Model L centrifuges, several spectrophotometers, including a Beckman recording spectrophotometer, and a variety of other smaller centrifuges and tabletop laboratory equipment. Adjoining the laboratory is an office which contains a computer. There is also a

physician's office with two patient examining rooms, and one small room that serves as the location for blood drawing and also for patient treatments. The remainder of the space includes a small patient waiting area, a secretarial office, a meeting room, and a number of animal rooms and a small laboratory for animal research.

1.1.2 Patient Admission Procedures:

The IRC is contacted by a patient either through the mail or by telephone. The patient is advised to submit medical records to the Center. Medical records are reviewed by Dr. Markwood or Dr. Weinberg. If the patient does not have characteristics leading to exclusion from the program (see the attached acceptance and exclusion criteria, Annex II), an appointment at the clinic is arranged. The patient brings relevant medical records to the clinic and the records are again reviewed. In addition, the patient has a chest X-ray, some laboratory tests and a general physical examination performed by either Dr. Markwood or Dr. Weinberg. The results of these examinations, when coupled with the re-review of the medical records, leads to a decision as to whether or not the patient should be a) rejected from the program; b) accepted into the program; or c) accepted into the program for a trial period.

A point-by-point review of the exclusionary criteria revealed the following:

- a) "Too much tumor" is apparently used in a subjective way by Dr. Markwood; and if he feels that a patient has a very large tumor burden, the patient is rejected. No objective criteria have been established to help reach this decision.
- b) Patients with ascites, pleural effusion, jaundice, or marked wasting are excluded from the program.
- c) People who have other medical complications which cannot be managed at the clinic are also excluded. Examples might be someone with severe angina with a suggestion of "impending infarction".
- d) It was not possible to elicit what "type of tumor" might conceivably be grounds for non-acceptance.
- e) The status of the "immune mechanism" as judged by Dr. Burton's test can lead to exclusion.
- f) The only example of a psychological exclusion was the possibility of a patient brought to the clinic against his will by a family who was anxious to have him treated.
- g) "Lack of ancillary care" apparently refers to the limited medical support circumstances. If the reviewing physician feels that the patient's problems will exceed available support, the patient will be turned down.

- h) "Insufficient medical records" is given as one of the criteria for exclusion. However, there were no clearcut examples of this criterion ever being used.

If a patient is denied entry into the program, the reason for this denial is supposedly explained to him. Inability to pay is not listed as one of the criteria, and it was indicated that this has not been a reason for exclusion. It was further indicated that approximately one-third of the patients pay the full amount, one-third pay a partial amount and one-third pay nothing at all. No documentation supporting these statements was presented. The fee for treatment at the clinic is \$5,000 and seems to be independent of the number of treatments received. It was stated that the \$5,000 was a donation, and not a fee, although an informational flyer prepared and distributed by the IRC states, "although not obligatory, it is expected that every patient donate at least this amount".

Some patients are accepted into the program but may then be terminated. This apparently occurs if a patient has a large tumor load, is considered borderline in terms of admission, is accepted into the program, but then has rapid progression of tumor growth. Similarly, if a patient with a small amount of tumor is taken into the program but has rapidly progressive growth of that tumor, the patient may be dropped from the program.

When a patient has been tentatively accepted into the program, a complete blood count, sedimentation rate, SGOT, LDH and alkaline phosphatase tests are performed. Other specific tests are also performed as required. Costs for these tests are direct to the patient. The patient is then assigned to a private physician on the Island and receives a separate evaluation by this doctor who can decide that the patient is too sick or is inappropriate for inclusion in the program. It was stated that this has happened ten to fifteen times, but no examples were presented. If the patient is considered acceptable by this physician, he becomes responsible for all medical care required while the patient is on Grand Bahamas Island. All costs of medical care provided by the private physician are paid for directly by the patient. Dr. Markwood was asked whether there were any patients who were refused entry into the program because more conventional therapy might be more suitable. He answered that this had happened on occasion but provided no specific examples.

1.1.3 Treatment Program:

The exact nature of the treatment is determined by tests performed on the patient's blood and then is further modified depending upon clinical response. In general, patients stay in the program for an average of ten to twelve weeks although there are some who have been at the clinic for four to five months. The patients live at various hotels while they are under treatment, and it is their responsibility to find appropriate accommodations. During the course of treatment, various laboratory and X-ray tests may be performed, frequently in Florida, thus requiring that the patients fly to the mainland periodically. Discharge from the clinic to return home seems to be dependent very much on financial resources or

other non-medical problems. Apparently, the clinic will continue to treat patients as long as they are able to pay for their stay in the Bahamas.

Each morning, the patient has blood drawn which is used to "evaluate the immune status". Blood is either drawn and permitted to clot or is drawn directly into some buffer. It was difficult to determine the actual routine laboratory procedure, but in the limited visit that was made to the laboratory itself, most of the test tubes seemed to contain blood clots. The blood clot is physically disrupted and the tube is spun in a centrifuge. The supernatant is removed and then is spun again at a higher speed. A sediment is obtained which is then resuspended in some buffer. This suspension is placed in a Beckman spectrophotometer and the wavelength is varied until the absorption is 50%. The wavelength at 50% absorption can be used to determine some number by using a chart that apparently was provided by the Beckman Instrument Co. This number is taken to represent the value of a blocking material referred to as B1.

The supernatant from the second centrifugation is incubated at 55°C for some period of time and then is centrifuged twice more, yielding another sediment which is again suspended in buffer and read in the spectrophotometer as described above. The wavelength giving 50% absorption is determined and the Beckman chart is used to obtain the value for another "blocking material" referred to as B2. The supernatant of the centrifugation is directly read at 279 nanometers in the spectrophotometer. Based on this reading, a "proper" amount of that supernatant is added to a standard "complement". The mixture is then incubated at 55°C, is recentrifuged and the sediment obtained is resuspended and read in the spectrophotometer as for B1 and B2. The number that is obtained from the spectrophotometer wavelength by using the Beckman chart is then fed into a computer which has been programmed in some unexplained way to calculate the amount of treatment material that the patient should receive.

Based on these determinations, the patient treatment is established. The treatment is with a mixture of serum fractions referred to as fraction I and fraction IV. These fractions are derived by differential centrifugation from normal blood. Sterile serum or plasma is allegedly detained from the Red Cross, and filtered three times through a 0.45 micron millipore filter. Fraction I and fraction IV are prepared by a series of differential centrifugations and precipitations and are prepared in bulk and frozen at -70°C. Fraction I supposedly contains alpha-2 macroglobulin as well as IgG, IgA and IgM. Fraction IV also supposedly contains some type of alpha-2 macroglobulin. Fraction I and fraction IV are only stored for two weeks and if not used in that period of time are discarded. Fraction I is tested in C3H mice for anti-tumor effect and also for ability to prolong bleeding time in a mouse whose toe is cut off. Fraction IV is also evaluated for its ability to prolong bleeding time.

Patient treatments consist of some mixture of fraction I, fraction IV and fraction II and the mixture is injected either subcutaneously or intramuscularly five days a week, although on occasion this may be six or seven days a week. Fraction II allegedly contains the third component of complement and is derived from the serum of a tumor-bearing individual. It was alleged

that in the treatments, the fraction II is actually derived from the patient's serum, but it was never quite clear precisely how this fraction II was prepared and re-administered.

When a patient is ready to leave the Bahamas, he is given a supply of fraction I and fraction IV and presumably a supply of fraction II. It is apparently up to the patient to locate a physician who will administer these treatments, or to locate syringes and needles for "self-treatment". Arrangements are then made for the patient to send a blood sample periodically (approximately every ten days to two weeks) to the IRC. Based on the results obtained by Dr. Burton's evaluation of the "immune levels" of this blood sample, the patient is instructed to modify his treatment.

1.2 Evaluation of Results:

It was impossible to achieve any evaluation of the clinical results obtained in this program. No tabular information was presented giving the number of patients who had been considered for admission to the program, the number accepted, the number with any particular tissue diagnosis, the numbers of patients living or dead, or durations of survival. Considerable time was spent in going over individual patient records. Full access was denied in the sense that patient names or given addresses or other identifying information was not shown. The reason given for not presenting this information was that the people at the Center wish to protect themselves against possible legal liability in terms of violation of doctor-patient confidentiality. Forty-nine charts were reviewed, which were selected by the Center staff to represent patients who had what the staff consider to be encouraging results. This included patients who allegedly had regression of disease or stability of disease. In the majority of these cases, the best thing that could be said is that there was insufficient information to reach any kind of judgment. All of these patients are ones who are still alive. The charts of any of the patients who had been in the program and who had died were not reviewed.

1.3 Evaluation and Critique:

1.3.1 Protocol:

The staff at the Center have consistently and flagrantly violated their own protocol. Patient eligibility requires that the patient have "proof of disease extension beyond reasonable hope of significant palliation by conventional therapy". Several of the case histories presented concerned individuals who had limited disease susceptible to conventional treatment. Patient eligibility also requires that patients have "measurable disease". Several of the case histories described patients whose disease was not measurable by any objective criterion. Patient eligibility states that "Patients who may reasonably expect to have beneficial effects from recently administered conventional modalities of treatment will be ineligible", yet repeated instances of this circumstance were included in the case histories presented. Patient eligibility also states that informed consent is obtained, but we were not shown informed consent forms and no information was presented that would permit us to determine if patients fully understand the experimental nature of their treatment,

or the potential risk of contracting hepatitis. Patient eligibility also requires that "histologic sections supplied by the referring physician will be read by a designated member of The Immunology Research Foundation to confirm eligibility", but all of the information provided indicated that this was never done. Criteria for response in terms of objective regression are listed in the protocol; but during most chart reviews, we were not given tumor measurements, either of the original lesion or of the lesion after IRC treatment.

The Center has changed the protocol in other ways without notifying the Ministry. For example, the list of reasons for excluding a patient from the protocol has been changed, and even the revised list given during the visit is not complete or accurate. The list of exclusions says nothing about children, but it was said that "children" are not accepted into the protocol. When pressed as to what the definition of a child was, there was some vague indication that perhaps 15 years was the cutoff point.

1.3.2 Patient Admission Procedures:

The financial requirements for admission to this program are not clear. According to the statement made by members of the Center, they adhere to a policy where any eligible patient is accepted into the program whether or not the patient is able to pay. At one point, however, the Center apparently had a policy of discriminating against those people who could not pay the full amount or any amount. These patients were put on separate waiting lists and had to wait considerably longer before being considered for the program. It was said that this was no longer the policy of the Center, and in addition that approximately one third of the patients pay the full amount, one third pay a partial amount and one third pay nothing at all. No evidence was provided to substantiate this claim. Conversations with patients and with the family of patients in the United States that were carried out prior to the visit to the IRC indicated that in fact considerable financial pressure is brought to bear on any patient who attempts to join the program.

It was also said that at the present time the waiting list for the Center is two to three weeks and that there were not separate waiting lists for those who cannot pay the full amount, but no information was provided that would permit us to evaluate this matter.

1.3.3 Patient Laboratory Evaluation and Treatment:

Insufficient data were presented to make it possible to determine whether any of the laboratory tests being performed are reproducible (in the sense of performing multiple determinations upon the same blood and knowing that the variance between results is less than 10 percent) or that the test has any stability from day to day (in the sense of showing a trend when results from the same patient are looked at daily) or whether the tests correlate with anything (as might be determined if the tests were performed blind and then correlated with the clinical status of the patient as determined by an independent individual who had no knowledge of the results of the blood test). It is therefore

impossible to determine whether this test is a test for anything and whether in any way the information that is being used to calculate the doses of the material administered to the patients has any validity whatever. 4)

The material being used to treat the 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.

1.3.4 Results of Treatment:

The review of the charts was essentially unrevealing. It is clear that the medical recordkeeping is marginal at best with frequent examples of alleged clinical observations of improvement without any notation amongst the loose pieces of paper that were contained within the manila folder that constituted the patient's chart. Repeatedly patient information was presented which allegedly showed regression of the tumor but where, on careful analysis, it was clear that one could only determine that there had been some regression of tumor when comparing X-rays or other objective determinations performed prior to or during a course of chemotherapy or radiotherapy and then compared to a determination performed at the present time. In almost no cases was there a baseline study performed after the consequences of conventional therapy had stabilized but before the immuno-augmentative therapy was initiated.

The protocol calls for study parameters to be performed after therapy. These include such items as weight, performance status, liver scans, chest X-rays, skeletal survey and measurements of indicator lesions. In most of the records presented, these were in fact not measured. There was no evidence that any patient had a real performance status evaluation either before therapy or after therapy and frequently, measurable lesions were referred to as "walnut-sized", "bea-sized", rather than being measured. All of these factors make evaluation of the results of treatment impossible.

It was difficult to pin down the nature of the follow-up procedures that have been or will be applied to patients who remain under treatment but who leave the Bahamas. There were comments indicating that physician cooperation amongst physicians in the United States was so poor that it was very difficult to obtain desirable follow-up information. This means that the only potential for accurate follow-up is when (or if) the patient returns to the clinic. The poor quality of medical evaluation at the clinic makes realization of even this limited potential unlikely.

The absence of any tabular information concerning numbers of patients and apparent survivals, etc., when coupled with the relatively primitive information in the charts makes it essentially impossible to evaluate the clinical consequences of the therapy being carried out at the Center. We can emphatically state that nothing presented led to conclude that there was any strong or even consistent treatment effect being achieved when assessed by objective criteria such as measurable regression, measurable stabilization, prolongation of remission or prolongation of survival.

CONCLUSIONS AND RECOMMENDATIONS

Before making recommendations, it is important to point out that had PAHO Advisors been consulted by the Ministry of Health prior to the establishment of the clinic, they would have advised against establishing it on the grounds that the scientific background as well as the clinical credentials of the people associated with the clinic were so poor that it would have seemed highly unlikely that any useful information would be obtained and that in fact the ability to evaluate the activities of the Center would have been doomed from the start. This could be construed as bias against the personnel of the clinic and/or against their activities. PAHO Advisors do not feel that they are biased and hope that a clear distinction will be made between negative professional opinions and bias.

The recommendations are as follows:

1. Close the Immunology Researching Center, Ltd. (IRC). This recommendation is made because it is understood that the purpose of the present arrangement between IRC and the Government of the Bahamas is to permit an evaluation of the treatment being performed at the Center. The site visit has been convincing that no meaningful evaluation of the treatment will result under present procedures, and it is highly unlikely that any change in procedure will make the treatment evaluable at the IRC.

There are many reasons why this trial is not evaluable. A consecutive series of patients is not being studied; rather all patients with the worst prognoses are excluded. This includes those not accepted in the first place, as well as those who are accepted and who have rapid growth of tumor. The only patients maintained on treatment are those who will be expected to do relatively well even if they receive no treatment. It will not be possible to compare their aggregate survival with any other group of patients--there is no appropriate comparison group. Moreover, the quality of medical evaluation prior to acceptance onto the protocol, the quality of medical evaluation while the patients are in the Bahamas, and the information obtained after the patients leave the Bahamas are all so poor and inadequate that even assessment of single patients for "unexpected" results will be unrevealing.

It is felt that closing the Center is in the best interest of the Government of the Bahamas, and also of the patients presently being treated at the Center.

2. Should the Government choose not to close down the Center at this time, a number of changes should be made, and the recommendations follow. It is important to emphasize, however, that it is highly unlikely that these changes will remedy the situation; and it is predicted that the studies will never be evaluable.

2.1 All advertising or informational bulletins circulated by the IRC should receive prior approval of the Ministry of Health.

2.2 Each week the Ministry of Health should receive a list of new patients accepted to the Center for treatment, including addresses and telephone numbers in their home country, as well as date of definitive diagnosis of cancer, type of cancer, date and type of last conventional anti-cancer treatment, date of initiation of treatment at IRC, and status with regard to payment (i.e., full payment, partial payment, no payment).

2.3 Weekly list of all patients considered by the Center (including addresses and telephone numbers) but not accepted for treatment and the reason why they were not accepted should be sent to the Ministry of Health. A random selection of these patients should be contacted by the Ministry of Health to determine whether the actual reason for non-acceptance was medical or financial.

2.4 A weekly list of all patients dying indicating date and whether or not an autopsy was performed should be sent to the Ministry of Health.

2.5 The agreement with IRC should be modified to require that each patient sign a form waiving confidentiality, so that the Center can release names and addresses to the Ministry of Health and/or their agents and patients can be contacted for follow-up information.

2.6 The Center should be warned to stick to the protocol and only accept patients with measurable disease. These measurements should be clearly indicated in the chart.

2.7 No further changes in the protocol should be made without prior approval of the Ministry of Health.

2.8 Informed consent forms should be prepared, submitted to the Ministry of Health for approval and should be a part of each clinical record. The forms as a minimum should indicate that the treatment of the Center is completely experimental and that there is a risk of acquiring hepatitis.

2.9 Recordkeeping at the IRC must be improved. Charts are incomplete and inaccurate and would not be acceptable at any medical facility in the United States.

2.10 The Ministry of Health should independently determine whether patients are being harassed to pay \$5,000 for their treatment, or whether this can really be considered a donation.

2.11 The medical credentials of physicians providing patient care at the Center should be at least as good as those of Bahamian physicians practicing medicine, and the Ministry of Health should review the physicians at the Center from this point of view.

ANNEX I.

LIST OF PARTICIPANTS

For the Immunology Research Foundation, Inc. and the Immunology
Researching Center, Limited

Lawrence Burton, Ph.D., Freeport, Bahamas
Carl C. Markwood, M.D., Freeport, Bahamas
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PATIENTS ACCEPTANCE AND EXCLUSION CRITERIA

A. Acceptance:

- 1) Full program, Immuno-augmentative Therapy alone
- 2) Full program, IAT & other therapies
- 3) Totally experimental

B. Rejection:

- I. Too much tumor
- II. Tumor-related complications
 - a) Ascites b) Pleural effusion c) Jaundice
 - d) Cachexia e) Other
- III. Nontumor-related medical/surgical complications
- IV. Type of tumor
- V. Immune mechanism too weak
- VI. Patients' psychological profile non-compatible with treatment
- VII. Lack of ancillary care
- VIII. Insufficient medical records

C. Deferred:

- 1) Further testing immune mechanism
- 2) Awaiting results laboratory studies
- 3) Awaiting additional medical records