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June 14, 1949

Shields Warren, M. D.
Director, Division of Biology and Medicine
U. S. Atomic Energy Commission
1901 Constitution Ave., N. W.
Washington 25, D. C.

Dear Dr. Warren:

Forwarded herewith, for your information, is a copy of the following report:

BIOLOGICAL STUDIES WITH ARSENIC[76]
Matthew Block, L. O. Jacobson, William Neal

The above report is for publication in the Journal of Laboratory and Clinical Medicine.

Very truly yours,

Argonne National Laboratory

By Hoylande D. Young
Hoylande D. Young, Director
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BIOLOGICAL STUDIES WITH ARSENIC[76]

III. The Effect of Arsenic[76] upon the Clinical Course of Patients with Tumors of the Hemtopoietic Tissues

by

Matthew Block, Ph.D., M.D.*, Leon O. Jacobson, M.D., and William Neal, M.D.

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From the Argonne National Laboratory and Departments of Medicine and Surgery of the University of Chicago

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* Fellow of the United States Public Health Service

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Matthew Block, Ph.D., M.D., Leon O. Jacobson, M.D., and William Neal, M.D.

INTRODUCTION

Since both arsenic and irradiation have been used independently in the treatment of tumors of the hematopoietic tissues it was thought that it might be advantageous to utilize radioarsenic (As^{76}), a substance that is metabolized like stable arsenic, exerts a similar chemotherapeutic effect, and is, at the same time, a source of radiation. In this way it might be possible to benefit the patient by simultaneous chemotherapy and radiation therapy.

As^{76}, which has a half-life of 26.8 hours and which emits energetic beta and gamma rays, was prepared by pile irradiation of arsenic trioxide, and later in higher specific activity by pile irradiation of cacodylic acid. It was injected intravenously as sodium arsenite. The stable arsenic content usually varied from 3 to 10 mg of arsenic per single injection of 1 to 80 mc of As^{76}. Cacodylic acid, as obtained by pile irradiation at the Argonne National Laboratory, is prepared for injection by remote control. The operator must work behind lead shields since the acid emits penetrating gamma rays. The details of the preparation of As^{76} and its metabolism have been given in two earlier reports.[1,2]

METABOLISM OF ARSENIC

Arsenic is distributed rapidly to all tissues after intravenous injection. Highest levels are reached within 12 to 24 hours in the spleen, liver, and kidney. Fifty per cent is excreted within 72 hours, primarily by the kidney. It is estimated

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that 1 mc of As^{76} will deliver about 1 r of total-body irradiation.

METHODS

Twenty-four patients with tumors of the hematopoietic tissues, 2 with polycythemia rubra vera, and 1 with a metastatic carcinoma, form the basis of this study. The diagnosis was substantiated microscopically in every case. Many of the patients had repeated biopsies of bone marrow, liver, lymph node, and spleen, which will be discussed in a future report.

The first few patients in this study were treated with extremely small amounts of As^{76} as far as specific radiation effect was concerned, although they received, at the same time, enough stable arsenic to exert a mild chemotherapeutic effect. The first doses that were given were about 0.5 to 2.0 mc, but within a short period of time these amounts were increased, partly because of experience with the inadequacy of the doses, and partly because of the availability of arsenic with a higher specific radioactivity. As much as 90 mc with about 5 mg of stable arsenic were administered in a single injection to the most recently treated patients. In addition, each patient received such supplemental treatment as transfusions, antibiotics, digitanid and mercurials, and toluidine blue or protamine sulphate as indicated.

RESULTS

(Table 1)

Hodgkin's disease: Each of 4 patients with Hodgkin's disease received from 1.0 to 13.0 mc of As^{76} and up to 52 mg of stable arsenic in divided doses. The longest remission, 2 months, was obtained in a patient receiving 52 mg of stable arsenic and 13.6 mc of As^{76}. However, it was felt that the amount of stable arsenic was such as to be sufficient in itself to produce a remission, and that the As^{76} had not been given an adequate trial in this group.

Acute leukemia: Both patients experienced a sharp drop in the white count and platelets but no significant change in the differential (Figure 1). Case 1 developed

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a severe hemorrhagic process and Case 2 had a terminal rise in the white count to 180,000. Both patients had an intractable anemia which failed to respond to therapy of any nature including massive transfusions.

It is clear that these 2 patients failed to show any better response to As^{76} than has been noted in the past to urethane[3], P^{32}[4,5], nitrogen mustard[6-9], or X ray.[10] It is probable that aminopterin[11,12] will be more effective than As^{76} in the treatment of acute leukemia.

Subactue myelogenous leukemia: Case 4 did not receive enough As^{76} to exert a therapeutic effect. Case 5 had an extremely short remission but the patient was in very poor condition when treatment was initiated. The results obtained in Case 3, who had 3 remissions varying from about 4 months to 2 months in spite of the handicap of a severe intractable suppurating osteomyelitis, are superior to those reported following any of the more common therapeutic agents[4,7-10,13] and radiosodium.[14] If this result can be duplicated in other cases of subacute myelogenous leukemia, it would appear that As^{76} is about as effective as aminopterin[12] in the treatment of this condition.

Chronic myelogenous leukemia: Four (Cases 6, 8, 9, and 11) of the 6 patients were previously untreated, and 1 (Case 7), who had 1 course of urethane, should also be classified as an early case. Four patients responded with remissions from 4 to 16 months in duration (Figure 2) and 2 (Cases 7 and 10) responded in a similar manner to a second course of As^{76}. The other untreated patient (Case 11) had only slight symptomatic improvements. The sixth patient (Case 6), refractory to X-ray therapy, died of a cerebro-vascular accident. However, the patient's anemia failed to respond to transfusions following As^{76} and he may be classified as a therapeutic failure which is usually the result in patients of the nature.[4]

Chronic myelogenous leukemia is a disease that shows great variation in its course. Patients have been known to live as long as 3 to 5 years without any subjective symptoms.[15,16] However, only a minority (16 per cent) of patients have

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spontaneous remissions once the disease produces anemia or subjective symptoms.[15] Therefore, any good result obtained in patients who were treated merely on the basis of a positive diagnosis may be ascribed to the benign nature of the disease rather than to the direct effect of therapy.

With this reservation in mind it would appear that even the greater differences in response reported in previously untreated patients following X ray[16-18], P^{32}[4,5,18], urethane[3,19], Fowler's solution[20], and Na^{24}[14] may well be due to variation in the biologic nature of each patient's disease. It would, therefore, appear that remissions of 4 to 16 months in the untreated cases that were studied represent no better than an average response (Figure 2). Like other generalized methods of therapy, As^{76} is not as efficacious in reducing the size of a huge spleen as local X-ray therapy[4], but like P^{32}[4,5,18] and Na^{24}[14], it rarely produces any toxic symptoms.

<u>Subacute lymphatic leukemia</u>: Two (Cases 13 and 14) of 4 patients were previously untreated and had symptoms of comparatively short duration. Case 15 had received X-ray therapy with very little benefit and Case 12 had received urethane without improvement. Three (Cases 14, 15, and 16) responded to therapy with an improvement in appetite, decrease or absence of fever, decrease in lymphadenopathy, and lowering of the white count for about 2 months. However, 2 (Cases 13 and 15) of the 3 experienced the onset of a severe infection, tuberculosis in one, furunculosis in the other.

The fourth patient (Case 12) had a hematological response with a drop in white count and a decrease in fever, but because of an associated hemolytic anemia continued as an invalid until his death 1 year later following splenectomy in another institution.

These results are, in general, comparable to those reported in the literature following treatment with aminopterin.[12] Possibly subacute lymphatic leukemia may show a better response to As^{76} than that reported after P^{32}[4,5], urethane[3,19], or nitrogen mustard.[13] The occurrence of 2 severe infections (Cases 13 and 15) at the

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time of greatest depression of the white count should warn against the use of As^{76} in the presence of any generalized infection, especially tuberculosis. We have been impressed by the occurrence of a flare-up in cases of previously quiescent tuberculosis following generalized cytocidal therapy such as As^{76} and nitrogen mustard in the treatment of leukemias and lymphomas.[21]

Chronic lymphatic leukemia: Four patients were treated with fairly adequate amounts of As^{76}. Only 1 (Case 16) was previously untreated. The patient was in a severe mental depression and failed to respond to therapy. Two patients (Cases 17 and 18), each of whom had been subjected to extensive X-ray therapy in the past, succumbed to complicating diseases. A spectacular result was obtained in the last patient (Case 18) since an intractable anemia was relieved and massive lymphadenopathy and splenomegaly were decreased (Figure 3).

Our results, in general, are not as consistent or favorable as those reported after X ray[16,22] or P^{32}[4], nitrogen mustard[7], urethane[3,19], or Na^{24}.[14] Particularly discouraging was the complete failure in Case 16, who was previously untreated. However, Reinhard has encountered a similar result after P^{32} as we have after nitrogen mustard.[21] The response of Case 19, who had remained severely anemic in spite of massive transfusions and several types of therapy, was most encouraging since this is the type of case that is notoriously difficult to manage.

Polycythemia rubra vera: The response of Case 20 was fairly satisfactory and also was qualitatively similar to that described after P^{32}.[4,5,23] However, much longer remissions are not at all unusual after P^{32} so that As^{76} has little to offer that is superior to the results already achieved by P^{32}. Another case was treated by administration of a total of 2.5 mc of As^{76} and by phlebotomies. Since this amount of As^{76} is too small to be effective, the brief remission was probably due to the phlebotomies.

Multiple myeloma: This disease is almost always characterized by a rapidly progressive downhill course and by unrelenting pain in untreated cases although

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occasional chronic cases such as Case 21 have been recognized.[24] Remissions similar in extent to that experienced by Case 22 have been reported after urethane[25] and stilbamidine.[26, 27]

Mycosis fungoides: In many respects the therapeutic results in this disease are similar to those achieved in Hodgkin's disease. In Case 23, treated 4 months before death, it was quite clear that the skin and pulmonary lesions were still in part amenable to local X-ray therapy after they had failed to respond to As^{76} or nitrogen mustard.

Metastatic carcinoma: The results in Case 24, who had a carcinoma of the stomach, are difficult to interpret. Carcinoma of the stomach may occasionally give rise to masses that respond to X-ray therapy by a decrease in size as did this patient's liver metastases. There was little else in the patient's course to suggest that As^{76} would prove curative or even beneficial in carcinoma of the stomach.

DISCUSSION

It appears, therefore that As^{76} resembles numerous other therapeutic agents such as X ray, urethane, nitrogen mustard, radiophosphorus, radiosodium, and Fowler's solution, in that it has the capacity to produce a remission in certain of the more chronic and benign tumors of the hematopoietic tissues and that it is not a cure for these diseases. The more acute forms of the diseases, with the possible exception of subacute leukemia, do not seem to be particularly amenable to As^{76} therapy.

In evaluating the clinical usefulness of As^{76} one is forced to consider whether it is more effective than previously used materials in producing a remission, whether it will produce a remission where other agents have failed, and whether the advantages, if any, are sufficiently great to warrant using a substance that is so difficult and expensive to prepare and so dangerous to handle. Unfortunately, because of numerous factors, such as intercurrent disease, variations in the clinical course of patients with the same disease, duration of disease, previous therapy, supplemental therapy, and rest and psychic factors, it is very difficult to compare any series of patients.

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Anyone who has worked with a number of these patients cannot but be impressed by the not rare patient who responds to therapy in a manner that is entirely unexpected and inconsistent with the usual response characteristic of those who have that disease.

The criteria for evaluating a clinical remission are not similar. For example, depression of the white count has frequently been used as a means of estimating the response to therapy. However, particularly in acute leukemia and the terminal stages of chronic leukemia, the height of the white count may bear no relation to such response. In this study we have followed the blood counts carefully and have noted a depression of the white count varying from 20 per cent to 80 per cent of the pre-treatment figure in almost every case treated without there being invariably a similar response in the clinical condition of the patient. Consequently the white counts have not been reported in detail. There has been no marked tendency of the peripheral blood differential count to return to normal following treatment except in a few cases of chronic myelogenous leukemia. An alleviation of the anemia is generally acceptable as an indication of a good therapeutic response. Since practically every one of the patients in this study received numerous transfusions, this criterion was rendered unreliable.

In general we have felt that the ability of the patient to live a more comfortable and more useful life was the best indication of a response to therapy.

On this basis our results seem to have been unusually good in a single case of chronic lymphatic leukemia characterized by severe anemia, possibly favorable in sub-acute lymphatic leukemia, and worthy of further evaluation in multiple myeloma. In the other diseases treated, the recognized agents such as X ray, P^{32}, urethane, and nitrogen mustard will give similar results with far less expense and with more readily available and less hazardous materials.

It is of importance to note that we have not attained a maximum safe clinical dose level of As^{76} nor have we fully explored the combination of stable and radio-

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arsenic nor the effect of repeated small doses of As^{76}. It is possible that when such information is available a better clinical response may be achieved. However, the problems of handling the amounts of As^{76} we have used are so great that it hardly seems practical or worthwhile to attempt to use larger quantities on the basis of the response of the patients in this study.

CONCLUSIONS

1. Twenty-four patients with tumors of the hematopoietic tissues, 2 with polycythemia rubra vera, and 1 with metastatic carcinomas have been treated with intravenous injections of radioarsenic (As^{76}).

2. This radioisotope, under the conditions used in this study, appears to offer no advantages over the types of therapy already in use for these conditions.

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