Haematoxylon Dissolved in Dimethylsulfoxide Used in Recurrent Neoplasms

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Editorial Note

I am not greatly impressed by the results obtained and reported in this series of 37 cases. Too many of the patients, as is true of Case 32, had intensive x-ray therapy. Just about the time that I would expect the patient to begin to show some beneficial effect from the x-ray therapy, they started giving Haematoxylon and D.M.S.O. Subsequent decrease in size of the tumor and reossification of the bone occurred just as I have seen it in numbers of cases after x-ray therapy alone. Too many of these patients had a very short period of clinical evidence of improvement and then died, and in too many of them the effect of Haematoxylon and D.M.S.O. was certainly blurred by the administration of other medications simultaneously, such as F.U.

In spite of my criticisms, there are some parts of this study which do interest me very much. The fact that the Haematoxylon and D.M.S.O. solution had a particular affinity for neoplasms and did not stain other tissues in animals could be most significant. I hope that Dr. Tucker and Dr. Carrizo will continue with their work and that they will use other known anti-cancerous medications dissolved in D.M.S.O., and do this in patients who have not received many or all of the standard radiation or chemotherapeutic procedures simultaneously or preceding the use of the D.M.S.O. solution. Also, the follow-up on the cases reported here who are still alive is so short that it cannot make very much of an impression. If they would consider this a preliminary report and continue with their work, and then produce a paper covering a much longer period of time, something really remarkable might result from it.

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The concept of this treatment began some two years ago during the course of a search for a suitable vital stain for neoplasms in rats and mice. Several of the well known dyes were used in this vital staining experiment; however, it was noted that Haematoxylon dissolved in D.M.S.O. had a particular affinity for neoplasms but did not stain any other tissues of the rats' internal or muscular system. It was also noticed that practically all of the dye and the D.M.S.O. solution was concentrated into the neoplasm itself and there was a marked increase in central necrosis of the neoplasm.

Following this observation, further animal experimentation and toxicity studies ensued.

Materials Used

Haematoxylon has long been used as a pathologic stain for animal cells, particularly because of its affinity for nucleic acids. Haematoxylon, $C_{16}H_{14}O_6$, having the two loose hydrogen bonds, oxidizes readily to a red substance known as hematein, $C_{16}H_{12}O_6$. This property of rapid oxidation is often used as an indicator for alkaloid titrations. It has been used in the past internally as an astringent for the treatment of diarrhea and also in the past in the treatment of urinary infections because of the presence of the dye which is rapidly excreted in the urine. The dose recommended in the past has been from 0.6 to 2 grams.

Dimethylsulfoxide (D.M.S.O.) has been reported quite frequently in the current medical literature since 1963, when its properties were reported by Rosenkrantz et al,[4] Distefano and Borgstedt,[1] Rosenbaum and Jacob[3] and Jacob et al.[2] The chemical was used in this basic research initially because of high solvent properties, especially to the dyes; Haematoxylon being highly soluble in a strong alkaline solution and weakly soluble in the common solvents such as alcohol and ether. When D.M.S.O. came into being, it was found to be the ideal solvent because of its ability to dissolve relatively large quantities of Haematoxylon. The solution used in this work was 25 grams of Haematoxylon dissolved in 75 cc of D.M.S.O. This amount will be referred to hereafter in this article as Haematoxylon solution, which was found to be easily miscible with the usual parenteral intravenous solutions, namely 5% dextrose in saline and normal saline. Dogs used for acute toxicity studies had an average weight of 27 pounds. The Haematoxylon solution was injected without being diluted in any parenteral solution directly intravenously every 48 hours for a period of one month and then every 72 hours for another month before sacrificing the animals. Complete blood counts, hemoglobin, hematocrit, blood urea nitrogen and urine analyses were taken at 72-hour intervals. There was no change in the urinanalysis over a period of two months from this material with the exception of the color of the urine which, of course, was stained from excretion of the dye. There was no variation in urine sugar, albumin, specific gravity or macroscopic or microscopic analysis. There was no difference in the blood counts of the treated animals and the controlled. There was no leukopenia and no change in the hematocrit or hemoglobin. The only positive findings were in the blood urea nitrogen which declined sharply from a high of 41 mg in the controlled animals to as low as 15% in one instance in the treated animals. The decline of 50% in the B.U.N. was a constant finding in the animal toxicity studies.

Autopsies of the dogs showed no changes in the liver, kidneys, gastrointestinal tract, heart, bone marrow, lungs or brain. No dye was present in any of the tissues at autopsy. This same dosage of D.M.S.O. given into the jugular vein of dogs without Haema-

toxylon caused acute respiratory failure and shock and death in three out of four dogs. Therefore, the combination of Haematoxylon and D.M.S.O. was found to be much less toxic than the D.M.S.O. alone. Further studies in this respect with 250-gram albino rats disclosed that the rats would tolerate four times the amount of Haematoxylon and D.M.S.O. solution combined than D.M.S.O. alone.

Experimental Animals Treated With Haematoxylon Solution

The experimental animals treated with Haematoxylon solutions were divided into two classes—the induced tumors and the spontaneous tumors. The induced tumors included a methyl cholantranine transplant tumor (fibrosarcoma) in albino rats and adenocarcinoma of the breast (Walker's tumor) in albino rats. There was a marked increase in central necrosis of the fibrosarcoma transplant and duration of the tumor was prolonged an average of three weeks with the intravenous use of Haematoxylon solution. The tumor in no case completely regressed.

The adenocarcinoma was not affected by the intravenous injection of Haematoxylon solution alone. However, with small doses of androgen the tumor regressed rapidly in practically 100% of the cases. The same dose of androgen in controlled rats caused no regression.

Spontaneous tumors in dogs, horses and cattle were treated as follows:

One terminal case was a 35-pound dog with large-cell lymphosarcoma with huge masses in the neck and large masses over the entire body. The dog was treated with 2½ cc of Haematoxylon solution directly into the jugular vein every other day for a period of three weeks. All tumors completely regressed and the dog was in apparent excellent condition. He died from accidental food poisoning and an autopsy showed no active cells in the remaining nodules of the previous large lymphomatous nodules. Many ghost cells appeared in the microscopic sections. Autopsy of the organs showed no pathologic change due to the chemicals as before stated in the controlled toxicity studies.

Another small dog weighing some 12 pounds with terminal small-cell lymphosarcoma was given 1 cc of Haematoxylon solution intravenously three times weekly for a period of three weeks. The tumors regressed but did not completely disappear. The dog died two months after the withdrawal of treatment from a perforated heart caused by heart worms. There was no increase in size of the lymphomatous glands at autopsy. However, this tumor did not completely regress as did the large-cell lymphosarcomatous dog.

A large horse with a tumor of the right hind leg, diagnosed by a local university as osteogenic sarcoma, was treated by one injection intravenously of 15 cc of Haematoxylon solution in 500 cc of dextrose in water. Following injections were not done because of difficulty in restraining the animal. The tumor was then treated locally by application of Haematoxylon solution, 25 cc diluted in 500 cc of normal saline and glucose. Local application was continued for a period of approximately one year and the tumor disappeared. The animal is still alive with no evidence of recurrence locally or by metastasis.

An Arabian stallion with generalized malignant melanomas in and about the anus and under the tail was treated with 10 cc of Haematoxylon solution in 5% dextrose in saline twice weekly for a period of three months. The subcutaneous tumors slightly regressed and then remained static and are static at this period some two years later.

A small squamous-cell carcinoma of the eye in a white-faced cow was treated by

local injection of 15% Haematoxylon solution in normal saline and injected directly into the conjunctival sac daily for a period of three months. The squamous-cell tumor disappeared and has not recurred.

Mode of Administration

The dosage was determined by injecting the Haematoxylon in D.M.S.O. solution (25 grams of Haematoxylon and 75 cc of D.M.S.O.) by the intravenous injection in 250-gram rats and 25-pound dogs. The nontoxic dose in 25-pound dogs was lowered seven times and the figure was then arrived at for the administration parenterally to humans. This dose was estimated to be 1 cc of the Haematoxylon and D.M.S.O. solution for a 75-pound body weight of humans. This material has been administered intravenously, intra-arterially and topically. In the administration of the solution intravenously or intra-arterially, the parenteral solution was preferably 5% dextrose in saline. The parenteral solution should be started first and when the desired rate is established then the Haematoxylon and D.M.S.O. solution is instilled directly into the bottle—not into the tubing. The resultant solution should be a pale yellow to green. Should the solution turn red, it means that the Haematoxylon has oxidized and should be discarded and a fresh solution used. The intravenous rate of injection should not exceed 40 drops per minute. Care should be exercised to prevent any of the solution from escaping into the subcutaneous tissue. This invariably causes a periphlebitis which damages the vein for future use but has never caused a slough. Too rapid administration results in dyspnea. In the case of large tumor masses, a febrile reaction often occurs. This is thought to be due to rapid absorption of necrosing tumor. The treatment should be discontinued and restarted at a later date with a greatly reduced dose. Treatment for the febrile reaction has been aspirin orally and Demerol* intramuscularly. The injection should be discontinued immediately and the usual dose of Demerol for that particular individual should be given immediately intramuscularly. In intra-arterial injections, the same caution should be used —that is, starting of the parenteral solution first and establishment of a regular amount before instilling the Haematoxylon-D.M.S.O. solution into the solution bottle.

Topical application has been used in many open lesions of malignancies with encouraging results. A 15% solution of Haematoxylon and D.M.S.O. is made with 5% dextrose and saline and applied over the sloughing malignancy. The solution is applied with cotton applicators and the lesion, if possible, should not be covered or dressed. Often a dressing with the solution causes an irritation of the growth and some increase in its size. No toxicity has been noted by this method of application.

Vaginal packing with a 15% solution has been found to be most effective in controlling hemorrhage and odor from irradiation slough. A small saturated pack is placed against the cervix and left for three hours and then removed.

Selection of Cases

Included in this series were patients with recurrent neoplasms with or without distant metastasis. Preterminal cases were not excluded but terminal were excluded. Patients with hematologic abnormalities were not excluded but those with markedly elevated blood urea nitrogen were excluded (Tables 1 and 2).

Clinical Examples of Tumor Retardation

Case 1.—The first human patient that

*Demerol,® Winthrop Laboratories, New York, N.Y.

this material was administered to was a 66-year-old female with an inoperable leiomyosarcoma of the abdomen which extended from the floor of the pelvis to the diaphragm on the left side just past the umbilicus in the midline. Haematoxylon and D.M.S.O. solution, 1½ cc, was instilled in 500 cc of 5% dextrose and saline and given at the rate of 40 drops per minute intravenously. No reaction occurred. This treatment was repeated at 48-hour intervals for a period of three weeks. At the end of this time, the tumor had regressed markedly to well below the umbilicus. After the third week, the patient had febrile reactions and the treatment was discontinued. The toxic symptoms subsided. At the end of this time, all abdominal pain

Table 1.—SERIES OF PATIENTS RECEIVING OTHER THERAPY

Patient Number	Age	Sex	Primary Tumor and Cell Type	Surgery	Other Chemotherapy and Radiation	Response to Other Therapy Alone
1	66	F.	Leiomyosarcoma (inoperable) of abdomen.	3 unsuccessful attempts at removal. One successful.	None	Removal of necrotizing tumor.
2	27	F.	Chondro-osteosarcoma. Terminal.	2-10-65 Biopsy	None	None
3	73	M.	Adenoca. of prostate and bladder. Generalized metastasis. Preterminal.	None	None	None
4	72	F.	Squamous-cell ca. of neck with metastasis.	Multiple resections of neck.	Max. radiation only.	Retardation of local tumor growth.
5	58	F.	Adenoca. of breast with extensive metastasis—Grade 4.	Radical mastectomy.	No chemotherapy. Max. x-radiation at operative site.	None
6	84	F.	Large fungating adenoca. of breast with metastasis to lung.	Simple mastectomy.	None	None
7	52	F.	Squamous-cell ca. of pelvis with large metastases. Preterminal.	Pan-hysterectomy.	Max. radiation, 5 F.U. 1800 mg total dosage.	Poor
8	51	M.	Squamous-cell ca. of lung with metastasis to neck.	None	None Max. x-radiation to lungs.	Poor
14	86	F.	Adeno-ca. of breast with fungating postop. area.	Radical mastectomy.	Max. x-radiation to operative site.	Fungating growth at operative site.
18	60	M.	Malignant giant-cell tumor of femur.	None Biopsy only.	Total F.U. 8,810 mg.	Poor
20	52	M.	Squamous-cell ca. ulcerating of face.	None	Max. local x-radiation. Total F.U. 1,120 mg.	Moderate
24	50	M.	Adeno-ca. of prostate. Metastasis to vertebrae.	Suprapubic cystotomy.	None	None
27	45	M.	Squamous-cell ca. of mouth. Preterminal.	Radical neck resection and hemimandibulectomy.	Total F.U. 1,600 mg.	Moderate
32	24	F.	Malignant giant-cell tumor of upper ⅓ left femur, advanced.	None	Max. x-radiation. Total F.U. 4,800 mg.	Poor

Table 1.—SERIES OF PATIENTS RECEIVING OTHER THERAPY CON'T

Patient Number	Age	Sex	Primary Tumor and Cell Type	Surgery	Other Chemotherapy and Radiation	Response to Other Therapy Alone
33	45	F.	Mixed tumor of uterus (undifferentiated).	None	Total F.U. 400 mg.	Poor
40	44	F.	Adeno-ca. of breast Preterminal.	Radical mastectomy. Exploratory laparotomy.	Max. x-radiation. Total F.U. 1,600 mg.	Poor
41	63	F.	Large-cell lymphosarcoma. Generalized metastasis.	Splenectomy	Total Cytoxan 1,050 mg.	Fair
56	50	F.	Squamous-cell ca. of cervix. Preterminal.	No surgery.	None	None
57	40	F.	Squamous-cell ca. of cervix.	No surgery.	No radiation. No drug therapy.	Poor
58	48	F.	Adeno-ca. of cervix; advanced.	None	None	Poor
59	50	F.	Squamous-cell ca. of cervix. Preterminal.	None	None	None
61	68	M.	Squamous-cell ca. of soft palate.	None	M.T.X., I.A. Total dose 200 mg.	Fair
66	60	M.	Adeno-ca. of stomach. Inoperable.	None	Total F.U. 800 mg.	None
67	56	M.	Adeno-ca. of bladder and prostate.	Suprapubic cystostomy.	None M.X.T. Total dose 200 mg. F.U. total 2,800 mg.	Moderate
75	22	F.	Advanced adeno-ca. of ovary, with metastasis to abdomen.	Exploratory and biopsy only.	No radiation. Total thio-tepa I.A. 200 mg.	Fair
79	64	F.	Squamous-cell ca. of soft palate.	None	None	Poor
81	90	F.	Squamous-cell ca. of soft palate.	None	M.T.X., I.A. Total dose 650 mg.	Fair
82	84	F.	Squamous-cell ca. of mouth.	None	M.T.X., I.A. Total dose 650 mg.	Fair
83	28	F.	Chorio-epithelioma. Terminal.	None	None	Poor
10	56	F.	Bronchogenic ca. with metastasis to left lung.	Removal of right lung.	No x-radiation or other cancer drug.	Poor
12	58	M.	Ca. of stomach. Preterminal.	None	None	None
13	70	F.	Squamous-cell ca. of soft palate.	None	None	None
19	40	M.	Adenoca. of penis with metastasis.	Amputation of penis.	None	None
28	42	M.	Squamous-cell ca. of penis.	Amputation of penis.	None	None
62	89	M.	Squamous-cell ca. of larynx.	Laryngectomy.	None	Poor
63	50	F.	Advanced adenoca. of cervix.	None	M.T.X., I.A. Total dose 650 mg.	Fair
66	66	M.	Adenoca. of stomach.	None	Total F.U. 1,200 mg.	Poor

Ca. = Carcinoma
D.M.S.O. = Dimethylsulfoxide
F.U. = Fluorouracil
H. = Haematoxylon
MTX = Methotrexate

Table 2.—EFFECT OF HAEMATOXYLON AND D.M.S.O.

Case No.	Date of Administration Haematoxylon-D.M.S.O. Dosage	Total Dosage and Response	Present Status
1	10-23-67 2 cc H.-D.M.S.O., I.V.	50 injections. Tumor regressed and was removed June, 1966.	November, 1967—patient still surviving.
2	4-11-65 1½ cc H.-D.M.S.O., I.V.	48 injections. Tumor regressed for 3 months.	Died 12-24-65.
3	11-5-65 2 cc H.-D.M.S.O., I.V.	56 injections. Tumor regressed for 4 months.	Died 5-12-66.
4	11-12-65 2 cc H.-D.M.S.O., I.V.	60 injections. Tumor regressed for 5 months.	Died August, 1966.
5	11-26-65 2 cc H.-D.M.S.O., I.V.	28 injections. Tumor regressed for 3 months.	Died April, 1966.
6	1-5-66 2 cc H.-D.M.S.O., I.V. Local application of 15% H.-D.M.S.O.	47 injections. Local applications 7 months. Complete regression of lung metastasis.	Died 8-5-66. Heart disease.
7	1-5-66 2 cc H.-D.M.S.O., I.V.	27 injections. Complete regression of metastatic masses.	2-7-66 in complete remission. Died 5-3-66 of drug addiction.
8	2-7-66 2 cc H.-D.M.S.O., I.V.	54 injections. Remission for 6 months.	Died October, 1966.
14	10-7-66 Local application to fungating area only. 15% H.-D.M.S.O.	Daily for 8 months. Complete relief of pain. Lesion regressed. Odor subsided.	Died June, 1967. Heart disease.
18	10-5-66 2 cc H.-D.M.S.O., I.V.	102 injections. Complete remission. No tumor formation by biopsy or x-ray.	11-9-67 date of complete remission.
20	4-5-67 2 cc H.-D.M.S.O., I.V. Local application of 15% H.-D.M.S.O.	72 injections Local applications daily for 7 months. Complete relief of pain and odor.	11-9-67 tumor continues to regress.
24	2 cc H.-D.M.S.O., I.V.	54 injections. Prostatic tumor regressed.	7-17-67 discharged 11-15-67 still in remission.
27	4-2-67 2 cc H.-D.M.S.O., I.V.	36 injections. Remission	Dismissed August, 1967. 11-15-67 still in remission.
32	5-2-67 2 cc H.-D.M.S.O., I.V.	72 injections. Tumor regressing rapidly, with bone regeneration.	11-16-67 patient continued to improve.
33	3-4-67 2 cc H.-D.M.S.O., I.V. Local application of 15% H.-D.M.S.O.	16 injections. Pain, hemorrhage and odor ceased.	Died 4-2-67.
40	9-14-67 1½ cc H.-D.M.S.O., I.V.	27 injections. Complete regression of abdominal masses.	11-22-67 patient continues to improve.
41	8-5-67 2 cc H.-D.M.S.O., I.V.	21 injections. Complete regression.	11-23-67 complete regression.
56	8-5-67 2 cc H.-D.M.S.O., I.V. Local application of 15% H.-D.M.S.O.	12 injections. Remission.	11-10-67 progress continues.
57	10-24-67 2½ cc H.-D.M.S.O., I.V. Local application daily by vaginal pack 15% H.-D.M.S.O.	5 injections. Regression of pain, odor and hemorrhage.	11-9-67 patient continues to improve.
58	10-2-67 2 cc H.-D.M.S.O., I.V. Local application by vaginal pack 15% H.-D.M.S.O.	12 injections. Patient has relief of odor, pain and bleeding.	10-11-67 patient continues to improve.

Table 2.—EFFECT OF HAEMATOXYLON AND D.M.S.O. CON'T

Case No.	Date of Administration Haematoxylon-D.M.S.O. Dosage	Total Dosage and Response	Present Status
59	9-7-67 2 cc H.-D.M.S.O., I.V.	13 injections. Patient free of pain and softening of parametrium.	10-11-67 patient continues to improve.
61	5-25-67 2 cc H.-D.M.S.O., I.V.	36 injections. Had remission and dismissed from hospital. Had recurrence 1 mo. later.	Released after 24 injections, with another remission & same remission as of 11-10-67.
66	10-9-67 2 cc H.-D.M.S.O., I.V.	24 injections. Patient free of pain and able to eat without pain. No hemorrhage.	11-9-67 continues in state of symptomatic remission.
67	9-19-67 2 cc H.-D.M.S.O., I.V.	22 injections. Patient dismissed from hospital in remission.	10-11-67 progress of patient continues.
75	8-15-67 2 cc H.-D.M.S.O., I.V.	23 injections. Palpable tumor reduced 50% of original size and patient free of pain.	10-11-67 progress of patient continues.
79	10-26-67	11 injections. Tumor static.	11-15-67 patient free of pain.
81	10-21-67 2 cc H.-D.M.S.O., I.V.	11 injections. Tumor static.	11-15-67 patient free of pain.
82	9-18-67 2 cc H.-D.M.S.O., I.V.	24 injections. Marked regression of size of tumor.	11-11-67 regression continues.
83	10-5-67 2 cc H.-D.M.S.O., I.V.	Immediate response after 12 injections. Gononadotrophin hormone level reduced from 350,000 I.U. to 35,000 I.U.	Died 11-5-67.
10	5-23-66 2 cc H.-D.M.S.O., I.V.	59 injections.	Patient survived 16 months. Died 9-6-67.
12	11-7-66 2 cc H.-D.M.S.O., I.V.	40 injections.	Died 4-3-67. Massive hemorrhage.
13	9-7-66 2 cc H.-D.M.S.O., I.V.	36 injections. Patient had remission.	No treatment for 4 months—deserted. Died 4-4-67.
19	9-7-66 2 cc H.-D.M.S.O., I.V. plus local application.	52 injections with daily local applications. Tumor remained static. Dismissed 6-17-67.	11-15-67 exact condition unknown but patient surviving.
28	4-10-67 2 cc H.-D.M.S.O., I.V.	54 injections. Daily local injections. Pain reduced.	11-15-67 tumor is static.
62	10-30-67 2 cc H.-D.M.S.O., I.V.	12 injections. Relieved of pain.	11-10-67 patient in state of remission.
63	10-5-67 2 cc H.-D.M.S.O., I.V.	14 injections. Relieved of pain.	11-10-67 tumor static.
66	10-9-67 2 cc H.-D.M.S.O., I.V.	12 injections. Relieved of pain.	11-10-67 patient in symptomatic remission.

D.M.S.O. = Dimethylsulfoxide
H. = Haematoxylon

had completely subsided. Three months later she was readmitted to the hospital and the second series of treatments was instituted for another three weeks. She was then followed as an out-patient and given weekly injections for a period of three months. Following this period of time, the tumor mass had subsided to approximately four inches in diameter and was within the pelvis. A third exploratory laparotomy was

done and the necrotizing tumor was removed and a large quantity of nitrogen mustard was left in the abdomen. This patient has survived now some 18 months as of November 15, 1967. Because she has moved to a distant part of the country, further evaluation of the case cannot be made. It was learned through relatives that she is still surviving, however, in a very poor state of nutrition. She cannot be reached for further treatment or observation.

Case 2.—Female, age 24, admitted to a general hospital, Orthopedic Section, September 1, 1966, with an intertrochanteric fracture of the left femur (Fig. 1). Treatment consisted of external immobilization. Another fracture occurred and she was readmitted in December. Biopsy at this time showed a malignant giant-cell tumor of the femur. She was readmitted in January, 1967 with advanced osteolytic changes (Fig. 2). A maximum 6,000 roentgens total dosage in air of x-radiation was given with a 250 K.V. machine. The tumor progressed with marked increase in size and bone destruction. Constant increase in pain and a daily febrile reaction continued. She was transferred to the Cancer Center May 1st for relief of severe pain (Fig. 3).

Haematoxylon and D.M.S.O. solution in

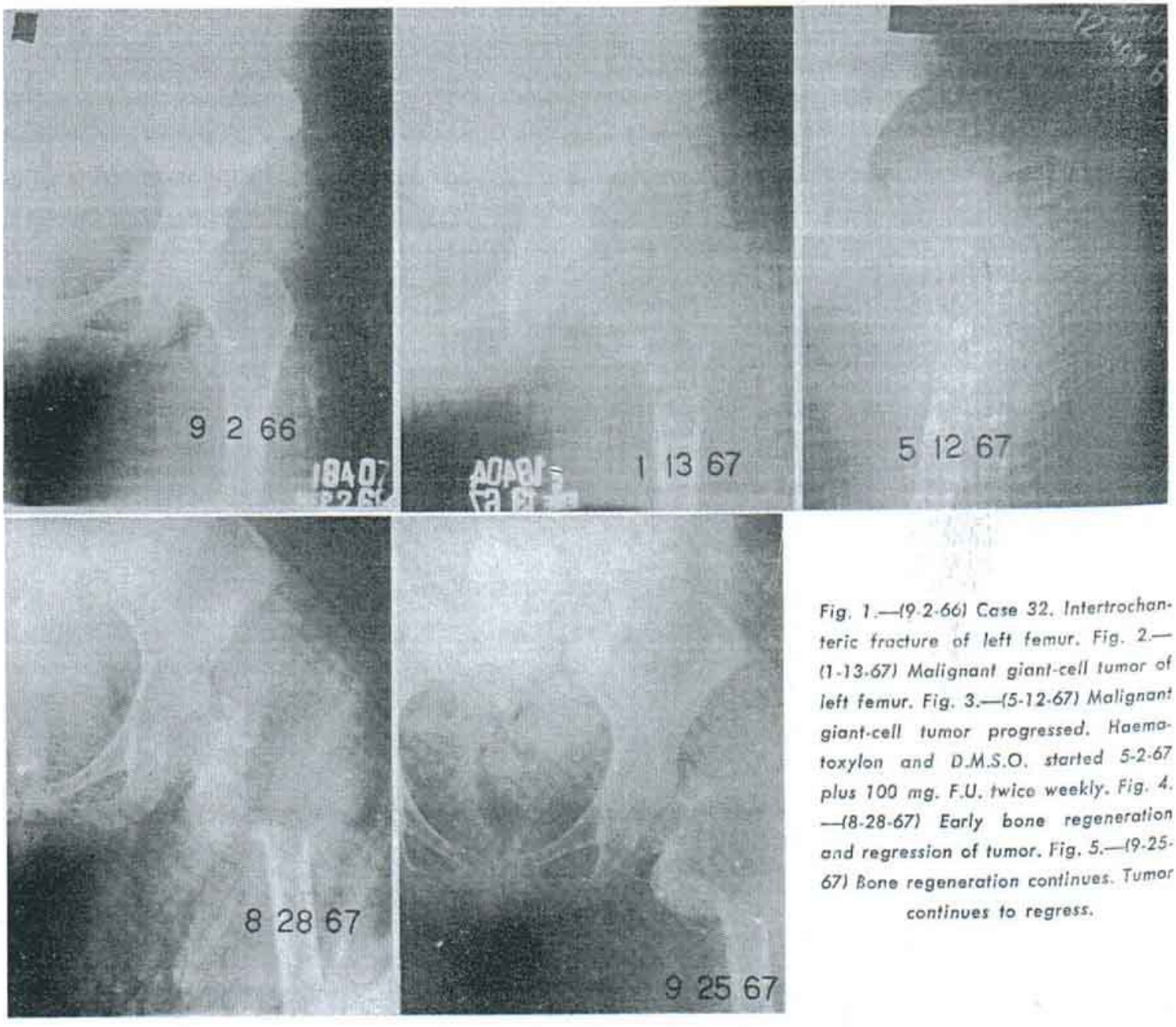

Fig. 1.—(9-2-66) Case 32. Intertrochanteric fracture of left femur. Fig. 2.—(1-13-67) Malignant giant-cell tumor of left femur. Fig. 3.—(5-12-67) Malignant giant-cell tumor progressed. Haematoxylon and D.M.S.O. started 5-2-67 plus 100 mg. F.U. twice weekly. Fig. 4.—(8-28-67) Early bone regeneration and regression of tumor. Fig. 5.—(9-25-67) Bone regeneration continues. Tumor continues to regress.

5% dextrose and saline was given three times weekly, starting on April 5th. Fluorouracil 100 mg was given intramuscularly twice weekly. Prednisone 100 mg twice weekly and Osteotrophin orally were started in May. In August there appeared evidence of bone regeneration in the area of the greater trochanter (Fig. 4). There was a febrile reaction from the first three injections of Haematoxylon and D.M.S.O. The patient then became completely afebrile on June 5th. She has been free of fever and pain since this time. Bone regeneration continued to improve with marked regeneration of the entire osteolytic area in September (Fig. 5). Monthly eye examinations showed no evidence of lenticular changes.

Laboratory blood results before radiation: hematocrit 34%, hemoglobin, 11.3 gm, white blood cell count 8,500, normal differential. Post radiation: Hct 28.5%, Hgb 10 gm, W.B.C. 5,500, polys 60%, S.M. 34%, eos 6%. April 11: Hgb 8.6 gm, Hct 23%, W.B.C. 6,500 (transfusion given). May 14: Hgb 10 gm, Hct 31.5%, W.B.C. 4,100, polys 73%, monos 25%, eos 7%. Blood has remained stable—no further transfusion necessary to date—November 10, 1967.

Urinalysis: two episodes of cystitis. Culture positive for Clostridium, controlled with antibiotics.

On November 10, 1967 the patient still was receiving combined therapy of Haematoxylon and D.M.S.O. solution—2 cc I.V. three times weekly. She is also receiving 100 mg fluorouracil I.M. twice weekly and prednisone 100 mg twice weekly and beef bone extract orally. This patient is asymptomatic and is on restricted motion of the left hip without pain.

Case 3.—Male, age 60, malignant giant-cell tumor involving the condyles of the left femur. Biopsy taken October, 1966. The tumor progressed to approximately 22 cm in diameter with marked flexion deformity. Pain and daily febrile temperature curve persisted. On April 5, 1967 Haematoxylon and D.M.S.O. solution, 2 cc in 500 cc dextrose in saline, was administered intravenously. It was administered thereafter twice weekly. He was relieved of pain after four weeks of treatment. After two months the dosage was reduced to 1 cc in 500 cc 5% dextrose in saline. No reaction occurred at any time during treatment. The treatment was discontinued August 5th. Concurrent medications given with Haematoxylon were 100 mg fluorouracil solution intramuscularly twice weekly and 20 mg prednisone intramuscularly once weekly. The patient was observed and given physiotherapy for one month. Motion returned to 170° extension and 90° flexion. An x-ray of the condyles of the left femur August 5th showed normal bone formation. The patient has since been under observation as an out-patient. As of November 10, 1967 there has been no recurrence of tumor formation, pain or fever. Eye examinations made at monthly intervals during the entire course of treatment were normal.

Case 4.—Female, age 44, adenocarcinoma of the left breast. In April of 1964 this patient had a radical mastectomy for a Grade 3 adenocarcinoma of the left breast. Metastatic nodules were found in the axilla. There was no radiation to the operative site following the surgery.

On August 9, 1967 she developed drainage from the umbilicus which was removed and was found to have the same malignancy as the original tumor.

On August 19th a laparotomy was performed for removal of the ovaries. At this time it was found that the entire abdominal cavity and intestines were studded with seedlings of adenocarcinoma. After removal of the ovaries, nitrogen mustard was left in the abdominal cavity with drainage. The patient had a stormy convalescence from this surgery, was unable to eat for a long

period of time and decreased in weight to 86 pounds. She developed a paralytic ileus and became markedly distended and also had two large masses in the pelvis.

On September 13, 1967 the following treatment was started: 1½ cc of Haematoxylon in D.M.S.O. solution dissolved in 500 cc of dextrose in saline, given twice weekly. The patient had a mild febrile reaction following the first three injections. The reactions then completely subsided. These injections were then alternated with administration of 100 mg of F.U. intramuscularly twice weekly on alternating days. Testosterone in the amount of 100 mg per week was added to the treatment together with multiple transfusions. This patient responded rapidly to this treatment. She began gaining weight due to the return of her appetite and generalized feeling of well-being. Within two weeks she became completely ambulatory and was afebrile and free of pain. By the 15th of November her weight had returned to a normal of 116 pounds. She was free of distention, fever and pain and was leading a normal life. The pelvic and rectal examination disclosed two small nodules approximately 3 cm in diameter within the pelvis.

Complications

Complications from the administration of Haematoxylon and D.M.S.O. in the above-stated concentrations have been very slight. Sixteen of the 37 cases had regular eye examinations and in no case was there any evidence of lenticular opacity. The longest case that was followed for possible eye complications was Case No. 32, who has thus far received some 72 intravenous injections of 2 cc of Haemotoxylon and D.M.S.O. solution. Weekly examinations are being continued of her eyes and thus far there has been no change detected.

The rapid administration of this solution of Haematoxylon and D.M.S.O. intravenously did cause dyspnea in a minimum number of cases. This condition was controlled immediately by withdrawing the injection and administering Demerol. No permanent damage was experienced from this mode of administration. Febrile reactions occurred in the majority of cases with large tumor masses in the first weeks of treatment. This seemed to subside as the tumor began to regress.

A skin rash was noted in three cases. The dermatologist felt that this was not a drug reaction but toxic reaction from absorption of necrotic tumor material.

The most severe complications were from the absorption of large amounts of necrotic tumor material from large mass tumors. The material was therefore used very cautiously in terminal cases with poor results because of this complication. In terminal cases with high uric acid levels, large tumor masses seemed to develop a complete anuria quite rapidly. It is hoped that in the very near future use of artificial kidney machines should be of value in this regard.

The lack of leukopenia and secondary anemia from these injections is of value in treating neoplastic cases that are also being treated with other chemotherapeutic agents. The fact that there is no change in the blood elements with the Haematoxylon and D.M.S.O. solution makes it a valuable adjunct by being able to lower the toxic dose of other chemotherapeutic agents.

Results

In this series of 37 preterminal cases of malignancy that were treated with dimethylsulfoxide and Haematoxylon therapy, there was an improvement in 70.5% of the cases when used with combined current cancer therapeutic agents. These agents included surgery, radiation, 5-fluorouracil,

methotrexate and thio-tepa. There was improvement in only 5.4% of those cases treated with the above measures without the use of dimethylsulfoxide and Haematoxylon. Of the cases treated with Haematoxylon and D.M.S.O. alone, there was improvement in 38.1%. This was largely on the symptomatic side with the exception of one case of leiomyosarcoma (Case No. 1).

The most striking results were observed in the two cases of large-cell lymphosarcoma and two cases of malignant giant-cell tumor of the bone. There was complete regression in both of the cases of large-cell lymphosarcoma with no recurrence to date. There was also complete regression in one case of malignant giant-cell tumor of the femur with no recurrence to date and one case of a highly malignant giant-cell tumor of approximately one-third of the femur which is still in a state of regression with bone regeneration. Cancer of the cervix in the preterminal stage had its greatest benefit only by local application and on a symptomatic basis. There was very little local regression of the tumor itself in advanced squamous-cell carcinoma of the cervix. However, there was a marked relief of pain and a diminution of bleeding and odor, especially following local radiation treatments.

Comments

Recent reports on parenteral chemotherapy for neoplasms has been discouraging (Tindel).[5] It therefore has been the hope for some time that a chemotherapeutic agent would be available of lower toxicity that could be used in conjunction with other chemotherapeutic agents to lower the toxicity of these agents in synergism.

The results with the Haematoxylon and D.M.S.O. solution in the treatment of spontaneous tumors in animals showed similar results in clinical cases. The large-cell lymphosarcoma which so dramatically receded in the dog showed a similar response in two clinical cases of lymphosarcoma. The response to local application in animals was dramatic and the local application of the solution to carcinoma of the cervix also showed encouraging local improvement.

The experience in this series of 37 preterminal cases makes us feel that this material is in the field of this usefulness. The facilities for cancer research in conjunction with this material are being expanded quite rapidly in Panama. There is added hope on the horizon for the relief of pain of preterminal and terminal cancer patients, together with a prolongation of life from a substance which has a very low toxicity and is relatively free of complications.

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