Among the six laboratory workers who contracted infection with Coxsackie viruses three different types of this group were represented. In each case the virus was isolated from one or more sources and the development of antibodies against the homologous and a related strain was clearly demonstrable. In each case the virus appeared to have caused the associated illness, and the evidence indicated that infection was probably contracted in the laboratory. The clinical manifestations of illness varied considerably in these patients, and in the one on whom a lumbar puncture was done, pleocytosis of the cerebrospinal fluid was demonstrated.

BIBLIOGRAPHY

1. Dalldorf, G., and Sickles, G. M.: An unidentified, filtrable agent isolated from the feces of children with paralysis, Science **108**: 61–62, 1948.
2. Dalldorf, G. Sickles, G. M., Plager, H., and Gifford, R.: A virus recovered from the feces of "poliomyelitis" patients pathogenic for suckling mice, J. Exper. Med. **89**: 567–582, 1949.
3. Melnick, J. L., Shaw, E. W., and Curnen, E. C.: A virus isolated from patients diagnosed as non-paralytic poliomyelitis or aseptic meningitis, Proc. Soc. Exper. Biol. and Med. **71**: 344–349, 1949.
4. Curnen, E. C., Shaw, E. W., and Melnick, J. L.: A disease resembling non-paralytic poliomyelitis associated with a virus pathogenic for infant mice, J. A. M. A. **141**: 894–901, 1949.
5. Dalldorf, G.: The Coxsackie viruses, Bull. N. Y. Acad. Med. **26**: 329–335, 1950.
6. Curnen, E. C.: Human disease associated with the Coxsackie viruses, Bull. N. Y. Acad Med. **26**: 335–342, 1950.
7. Melnick, J. L.: Studies on the Coxsackie viruses: properties, immunological aspects, and distribution in nature, Bull. N. Y. Acad. Med. **26**: 342–356, 1950.

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MULTIPLE MYELOMA: A STUDY OF 24 PATIENTS TREATED WITH RADIOACTIVE ISOTOPES (P^{32} AND SR^{89}) *

By JOHN H. LAWRENCE, M.D., and LOUIS R. WASSERMAN, M.D., F.A.C.P., *Berkeley, California*

THE treatment of multiple myeloma has always been discouraging. As in other inoperable malignant conditions, x-ray therapy has been used wherever indicated, and the use of stilbamidine by Snapper has been successful in relieving pain due to myeloma, but no prolongation of life has been apparent.[1] Urethane has recently been used in the treatment of multiple myeloma by Loge and Rundles.[2] Subsidence of pain and a decrease of abnormal cells occurred in some cases. In a series of 83 patients studied by Bayrd and Heck, the average length of life in multiple myeloma was 19 months, and the duration seemed to be independent of treatment.[3] In evaluating the beneficial effects of treatment of multiple myeloma, it must be kept in mind that this disease varies markedly in its rate of progression, and that temporary improvement after various forms of therapy may occur. The relatively benign cases of myelomatous proliferation characterized by solitary localization are responsive to local x-ray therapy. These tumors, besides being highly radiosensitive, may remain localized at their primary site for relatively long periods of time. Other types of myeloma spread rapidly and are not so amenable to therapy. Thus, the benefit obtained from various therapeutic agents must be considered from these points of view. The most favorable results have naturally been obtained in the cases of solitary myeloma which, as a rule, respond well to x-ray therapy, and the duration of life has probably been prolonged in these cases. In a recent review of this problem, Gootnick estimated that the duration of life in cases of solitary myeloma treated by roentgen irradiation was seven years after the onset of symptoms.[4]

Fitz-Hugh and Hodes report their experience in one case of multiple myeloma treated with radiophosphorus in which no benefit was obtained.[5] Treatment of one case of plasma cell leukemia and three cases of plasma cell myeloma with P^{32} was reported by Warren.[6] In the case of the plasma cell leukemia, treatment with P^{32} had no effect, and of the three cases of plasma

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From the Division of Medical Physics and the Donner Laboratory of Medical Physics, University of California, Berkeley.
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cell myeloma, two were helped. Bayrd and Hall have recently reported an unusual remission in the case of acute plasma cell leukemia following P^{32} therapy.[7]

Reinhard, Moore, Bierbaum and Moore analyzed their results in eight patients with multiple myeloma treated with radioactive phosphorus, the dosage ranging from 5 mc. to 16.7 mc. with an average dose of 9.6 mc. Aplastic phenomena were marked in 5 cases where the white blood count fell below 4000 and in two cases below 2000. They believed that there was little doubt that in two patients the rapid lethal outcome was due to bone marrow inhibition caused by the radioactive phosphorus. Improvement was noted in only two cases, both of whom received transfusions in addition to isotope therapy.[8]

Multiple myeloma is a rare disease, its incidence having been reported as only 0.03 per cent of all malignant growths,[9] and it is generally considered to be a disease of later life. Wintrobe[10] states that 80 per cent of the cases occur after the age of 40. Geschickter and Copeland, in a review of 425 cases of multiple myeloma, found that 73 per cent of the patients had an onset of the disease between the ages of 40 and 70, and that it occurred more frequently in males than in females.[9]

The clinical picture of the disease is characterized by pain, often in the ribs, back or sacrum, and the involved areas are sometimes extremely tender to pressure. Pathological fractures of the affected bones and neurological symptoms are very common. The skull is frequently involved. Isolated or multiple tumors may occur and anemia is the usual finding.

The administration of radioactive phosphorus results in its wide distribution throughout the whole body with its greatest initial concentration in rapidly metabolizing tissue such as liver, bone marrow, and tumor tissue, and its subsequent deposition in the bony skeleton.[11] Radioactive strontium has been shown to behave similarly to calcium in the body.[12] The biological action of these isotopes on tissue is similar to that of other penetrating radiations, but because of their localization in rapidly growing tissue and in bone, their therapeutic trial in metastatic bone tumors and in multiple myeloma seemed to be indicated. At the outset, it was realized that since only a limited amount of irradiation could be administered to the tumor masses without causing undue damage to the adjacent and normal hematopoietic bone marrow,[13] much improvement over conventional methods of irradiation could not be expected. The treatment of multiple myeloma with artificially radioactive isotopes was first attempted by us in 1939, and preliminary results from this laboratory were reported in 1941 and 1942 on 11 patients with multiple myeloma treated either with radioactive phosphorus or radioactive strontium or both.[14, 15] The response of these patients to the radioactive elements was not uniform and seemed to be closely correlated to the condition of the patient at the time treatment was started. In some patients, there was marked relief of pain and at times a restoration to almost

TABLE I

Summary of History of 24 Cases of Multiple Myeloma

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease Years: Before Isotope Therapy	Duration of the Disease Years: Useful	Duration of the Disease Years: Total	Response to Isotope Therapy	Complications
		F	Backache, rigid pain; x-rays show diffuse bone involvement	Biopsy of rib; Bence-Jones pos.	X-ray; 9911 ri; Coley's toxin	1.0	None	1.2	None	Due to x-ray anemia; required transfusions; received 20 mc. r additional
		M	After fall x-ray showed rib fracture and lesion in femur	Biopsy of rib	X-ray; 1800 r	1.2	1.0	2.8	Good	Anemia, leukopenia; required transfusions
		M	Backache, root pain; x-rays show diffuse involvement	X-ray; sternal pos. 13% myeloma cells; Bence-Jones neg.	None	0.2	None	0.5	None	Anemia; required transfusions
		M	Pain in back, root pain after fall; x-rays showed fracture T8, 9, 10; lesions in skull and ribs	X-ray; sternal pos. Bence-Jones pos.	X-ray	0.5	6.5	7.2	Good	None
		F	Pain in back; x-rays showed osteoporosis of spine, ribs	X-ray; sternal pos. Bence-Jones pos.	X-ray; transfusions for severe anemia	1.1	1.6	1.8	Fair	Thrombopenia
		M	Pain in arm, shoulder, neck; laminectomy with meningitis; x-rays showed bone involvement	X-ray; sternal pos. Bence-Jones neg.	X-ray	1.0	0.3	1.2	None	None

TABLE 1—*Continued*

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years)			Response to Isotope Therapy	Complications
						Before Isotope Therapy	Useful	Total		
		F	Pain with rib fracture; x-rays showed diffuse bone involvement	X-ray; Bence-Jones pos.	X-ray; transfusions	1.8	1.0	2.4	None	Anemia; leukopenia more severe; required transfusions
		M	Slipped and fractured rib and vertebrae; tumor of chest wall	Biopsy of tumor showed plasmocytoma	X-ray; 10,000 r	2.5	2.7	3.0	Slight	None
		M	Albumin in urine proved to be Bence-Jones; x-ray showed diffuse involvement. Sternal pain	X-ray; Bence-Jones pos.	None	0.5	1.0	1.3	Slight	Anemia
		F	Upon sitting up in bed fractured left trochanter. Amputation two years later	Biopsy of leg	X-ray; transfusions	7.0	7.25	8.7	None	Anemia; leukopenia; required 35 transfusions
		F	Pain in arm, chest, shoulder; fractured rib; x-ray showed diffuse involvement	X-ray	None	0.3	0.2	0.5	None	None
		M	Albumin in urine; weakness; weight loss	Sternal pos. 24% myeloma cells; Bence-Jones pos.	None	0.8	2.9+	2.9+	Slight	Slight anemia
		M	Backache; albumin in urine; x-rays show diffuse involvement	Sternal pos. Bence-Jones pos.	X-ray	0.9	1.4	1.9	Fair	Anemia; leukopenia; thrombopenia

TABLE 1—*Continued*

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years)			Response to Isotope Therapy	Complications
						Before Isotope Therapy	Useful	Total		
		F	Pain in arms, neck, shoulders; tumor over sternum; "soft spots" in skull	Sternal pos.	None	—	0.3	1.0		
		M	Numbness and tingling of hands; sacroiliac pain; pain in left lower thorax	X-ray	None	1.6	0.9	1.8	Slight	None
		F	Bone pain; x-rays show diffuse involvement	Sternal pos. x-ray	X-ray; 8 transfusions	0.8	3.0	4.0	Good	None
		F	Pain in spine; root pain; bedridden	Biopsy of ilium	X-ray	3.1	5.7	7.0	Fair	Aplastic anemia; purpura; required transfusions
		M	Pain in back; x-ray showed tumor of vertebrae	X-ray; sternal pos.	X-ray; transfusions	3.0	1.0	3.6	Slight	Aplastic anemia; purpura; hemorrhage; required transfusions
		M	Extreme fatigue; poor vision, headache and vertigo; pain in lower dorsal spine and chest	X-ray	None	1.5	3.6	5.0	Slight	Polycythemia; neuronitis
		M	Backache, 4 months' duration; fatigue 9 to 10 months	X-ray lesions in skull, vertebrae, ribs. Bence-Jones pos.; sternal marrow	Deep x-ray to L 1.		0.4	0.5		Anemia

TABLE 1—*Continued*

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years) Before Isotope Therapy	Duration of the Disease (Years) Useful	Duration of the Disease (Years) Total	Response to Isotope Therapy	Complications
1	57	M	Pain in shoulder; then mass	Biopsy of acromial process, L. scapula; x-ray lesions 11th, 12th dorsal vertebrae, L. radius and ulna; pos. Bence-Jones; sternal marrow	None	0.6	0.7	0.7	None	Anemia; hemorrhage from biopsy wound; death 8 mos. after first symptoms
2	57	M	Pain in L. sacroiliac region, intermittent 3 years; swelling over eye	X-ray destructive lesions in L. ilium, R. clavicle, skull, R. 12th rib; biopsy of R. 9th and 12th ribs	X-ray	3.0	3.0	—	None	Anemia
3	57	F	Paresthesias of hands, feet; weakness of legs, incoordination, 8 months later	X-ray myeloma of ribs, acetabulum, sternal and iliac marrow.	X-ray to spine	0.8	0.9	1.1	Slight	Cord compression
4	57	F	Pain in arms and legs	Bence-Jones pos.; increased plasma cells in sternal marrow	None	—	2.4	—	—	Polycythemia; diabetes mellitus

* Indicates date first seen by us.

normal activity. The present series of 24 patients (14 men and 10 women) includes in summary all previously reported cases from this laboratory.[16, 18]

The ages of onset of multiple myeloma in this series of patients ranged from 29 to 69 years with the average at 51.9 years. Fifteen of the patients were over 50 years old at the onset of the disease. Only 2 of the patients are still living. (Cases 22 and 24). The clinical and hematological data on all patients are summarized in tables 1, 2 and 3.

Fifteen of the patients had received x-ray therapy before they came under our observation. Anemia, in some instances probably due to previous x-ray therapy, was noted in 11 cases prior to the beginning of treatment with radioactive isotopes, and anemia of variable severity developed in 10 of the other patients while they were under our observation. Leukopenia was noted in four cases when first seen by us, and in three additional cases there was a marked fall in the white blood cell count during treatment with P[32].

TABLE II

Hematologic Data in 24 Cases of Multiple Myeloma

First horizontal column in each case signifies blood count when first seen; second column after therapy had been completed. (This period of time does not necessarily correspond to the duration of treatment as noted in table 3. The time elapsed between blood counts here is actually the time from the first blood count to the final significant blood count after therapy had been completed and had had time to become effective.) Case 22 is a living patient and therapy has not yet been completed. Case 24 is a living patient, but no isotope therapy has been given her at this writing.

Case No.	Elapsed time (months)	Hemoglobin grams %	RBC X 10^6/mm.^{3}	WBC X 10^3/mm.^{3}	Platelets X 10^3/mm.^{3}	Polys. Series %	Lymphocyte %	Monocyte %	Plasma %
1	0	10.2	3.16	7.05	240	86	5	9	
	1.5	7.5	2.36		190				
2	0	12.4	4.41	6.35	80	56	31	13	
	12	12.5	2.98	2.65		57	42	1	
3	0	13.1	4.39	6.7		43	54	3	
	6	anemia							
4	0	14.2	1.32	9.2		45	53	2	1
	80	10.2	3.85	11.75		63	31	6	2
5	0	8.5	2.75	4.0	160	68	26	5	
	1.5	7.8	2.89	4.2	45	68	23	7	
6	0	7.6	2.52	6.4	220	66	30	4	
	2	10.0	3.77	8.9		78	18	4	
7	0	9.9	3.1	10.4		72	22	6	
	7	5.1	1.74	1.6	18	64	33	3	
8	0	12.2	3.65	5.8	310	73	15	12	
	1.5	10.4	3.11	7.0	95	66	30	4	
9	0	10.9	5.6	15.0	365	71	29	3	
	9.5	9.3	2.95	7.45	120	86	11		
10	0	9.0	3.6	7.45	115	64	26	10	
	5	5.9	2.14	4.4	275	66	30	4	

TABLE II—*Continued*

Case No.	Elapsed time (months)	Hemoglobin grams %	RBC X 10^6/mm.^{3}	WBC X 10^3/mm.^{3}	Platelets X10^3/mm.^{3}	Poly Series %	Lympho cyte %	Mono-cyte %	Plasma %
11	0	9.0	2.46	8.2		66	26	8	
	1	8.0	2.65	8.8		75	23	2	
12	0	11.9	4.53	7.8	315	34	63	3	
	4	7.0	3.1	5.3	235	48	43	9	
13	0	13.7	4.3	4.57	400	37	63		
	11	4.7	2.03	0.85	6	34	55	10	1
14	0	7.2	2.34	11.1	47	60	36	4	
15	0	10.2	3.57	29.95	200	64	27	9	
	9	11.9	3.02	12.6	190	39	53	8	
16	0	6.9	2.42	5.05		63	30	7	
	37	11.0	3.87	4.8	290	67	23	10	
17	0	10.9	4.62	7.75		73	23	4	
	46	4.3	1.48	5.9					
18	0	6.2	2.5	2.0		76	16	8	
	6	9.0	3.9	1.9					
19	0	15.8	6.18	14.5	440	65	31	4	
	7	15.6	4.96	16.4		72	24	4	
20	0	11.0	3.22	4.35	83	72	17	10	1
21	0	10.3	3.88	7.2	220	60	31	4	5
	1	10.4	2.99	6.85		67	25	8	
22	0	13.0	4.44	7.25	240	68	24	4	
23	0	17.5	4.95	15.0	380	78	15	7	
24	0	14.0	5.10	11.3	370	63	36	2	

Treatment with radioactive isotopes was undertaken in all but three cases (Cases 14, 20 and 24). Case 14, a white female, [redacted], had marked bone changes, severe anemia, evidence of kidney damage and was treated symptomatically. Case 20, a white male, [redacted] died shortly after he was first seen by us and before isotope therapy could be started. The third patient (Case 24), a [redacted] year old female of Spanish origin, has, in addition to multiple myeloma, polycythemia and diabetes mellitus, and no treatment has as yet been given her.[16] Cases 19 and 23 [16] also had this associated picture of polycythemia and myeloma. Of the 21 patients who were treated with radioactive isotopes, nine received combined P^{32} and Sr^{89} treatment, 11 were treated with P^{32} alone, and one (Case 22) received only colloidal radioactive yttrium (Y^{90}).

RESULTS OF THERAPY

Seven of the 21 cases were not definitely benefited by treatment with P^{32} or Sr^{89} or both (Cases 1, 3, 6, 7, 10, 11 and 21). In five of these cases

TABLE III

Analysis of Dose Schedule of P^{32}, Sr^{89} and Y^{90}. All doses are intravenous unless specified

Case No.	Amount P^{32} per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Amount Sr^{89} per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Total Duration Treatment (days)
1	7.6 –8.0*	14	2	15.5	14						14
2	0.4–1.4 1.0–5.0*	3–57	18 6	26.1 (14.8, 11.3*)	251						251
3	1.5 –1.6 5.0*	2–6	2 1	8.1 (3.1 5.0*)	9	0.14–1.9	2–3	4	3.9	7	13
4	1–3 5–8*	7–480	21 9	103.0 (84.5 18.5*)	2390						2390
5	6.0*	42	4	21.0	120						120
6	1.1 –2.1	7–18	4	6.9	42						42
7	5.0*	39–50	3	15.0	90	1.0 –2.0	7	6	8.95	42	180
8	0.7 –1.2	3–7	5	4.8	21	0.2 –0.3	2–14	4	0.8	21	44
9	0.3 –1.6	6–94	9	8.6	240	0.3	none	1	0.3	1	240
10	4.0 –4.8*	14–15	4	16.8	42						42
11	1.1	none	1	1.1	1	0.7	none	1	0.7	1	7
12	0.54–1.2	9–49	5	4.3	86	0.3 –0.8	2–5	4	1.9	14	86
13	2.6 –6.0 8.0*	17–42	2 3	23.6 (8.6 15.0)*	291	0.6 –1.6	4–83	3	4.7	56	291

TABLE III—Continued

Case No.	Amount P^{32} per Dose (mc.)	Interval between Doses (days)	Number of Doses	Total Dose (mc.)	Duration of Treatment (days)	Amount Sr^{89} per Dose (mc.)	Interval between Doses (days)	Number of Doses	Total Dose (mc.)	Duration of Treatment (days)	Total Duration of Treatment (days)
14	none					none					
15	0.5 –1.5 0.3*	16–52	9 1	6.8 (6.5 0.3*)	270	0.55	7	2	1.1	7	270
16	1.0–6.0*	7–210	16	62.8	1130						1130
17	5.0*	360	2	10.0	360	0.6 –1.0	3–4	6	5.3	14	1350
18	2.0 –3.0 6.0*	15–57	2 2	17.0 (5.0 12.0*)	174						174
19	0.33–7.3 2.42*	3–85	9	20.98	201	none					201
20	none										
21	1.0	2–11	4	4.0	17						17
22						Y* 3.0 –4.0	9–12	3	10.0	22	22
23	1.0	7–38	6	6.0	66						66
24	none					none					

* oral

(Cases 1, 3, 6, 11 and 21) the patients were first seen in a very advanced stage of the disease, so that probably no treatment of any kind would have been beneficial. Case 7 had a severe anemia when first seen by us, and treatment with fairly large doses of isotope was unsuccessful. In Case 10, seven years after the first symptoms appeared, widespread metastases were noted, although the initial lesion, localized in the left femur, had been solitary for many years. This patient, when first seen by us, had a moderate anemia, and no benefit resulted from isotope therapy. Case 22, treated with colloidal radioactive yttrium, was not benefited by this isotope.

In eight other cases the benefit from treament with radioactive isotopes was rather questionable (Cases 8, 9, 12, 15, 17, 18, 19 and 23). Case 8, a physician , started treatment with P^{32} two and a half years after the date of onset, felt "much better" during the treatment with P^{32} and Sr^{89}, but the progress of the disease was not influenced and the patient died three months after beginning therapy. Case 12 had no bone changes at the onset of treatment, and the therapeutic response was minimal. Case 15 started treatment relatively late and felt better for a short time, but his disease progressed and the patient became bedridden. Treatment in another patient (Case 17) was followed by temporary improvement, but because of the development of a severe anemia which required transfusions, therapy had to be discontinued. Cases 9 and 18 had slight symptomatic improvement, but the progress of the disease was not markedly influenced. Case 19 is interesting in that the patient was thought to have polycythemia vera when therapy with P^{32} was instituted. Later, shortly after the beginning of therapy with P^{32}, the patient developed definite lesions of the vertebrae and eventually died with the picture of multiple myeloma which may have been present from the very beginning in view of the rare but definite occurrence of polycythemia and multiple myeloma in the same patient.[18] During the period of about three years prior to his death, the patient received considerable benefit from the P^{32} therapy, and the progress of the multiple myeloma may have been temporarily inhibited. In Case 23, there was some temporary improvement in the subjective symptoms but no clear-cut effect on the progress of the disease.

In five patients (Cases 2, 4, 5, 13 and 16) the results of treatment with radioactive isotopes were relatively satisfactory. Case 2, described by us in 1942,[18] had an excellent response for about one year. At the start of treatment, his legs were atrophied, he required crutches for any movement, and he was unable to walk or work. After two months of treatment, his improvement was so marked that he was able to walk without crutches and had resumed his work. However, this remission was of only approximately a year's duration, and at the end of that time the patient was confined to bed with a terminal mild anemia and leukopenia which interfered with the planned treatment and prevented further radioactive isotope therapy.

Case 4 (H. A. B.) was especially remarkable since the duration of the disease, extending over a period of more than seven years, was unusually

long and because the patient did exceedingly well under treatment with radioactive phosphorus. H. A. B., a 52 year old physician, slipped in February, 1940, and developed severe back and root pain. In May, 1940, x-ray revealed compression fractures of T 8, T 9, and T 10 with osteoporosis and radiolucent areas in the ribs, pelvis and skull. When he was first seen by us in September, 1940, physical findings were essentially negative. The blood count was normal with the hemoglobin 103 per cent, red blood cells 4,320,000, white blood cells 9200 with 53 per cent lymphocytes. The urine was negative for Bence-Jones protein. Sternal biopsy revealed the presence of many myeloma cells, and oral P^{32} therapy was started. The total dosage of 103 mc. over a period of six and one-half years was as follows:

1940	33.0 mc.
1941	26.5 mc.
1942	13.0 mc.
1943	no treatment
1944	7.5 mc.
1945	4.5 mc.
1946	14.5 mc.
1947	4.0 mc.

In 1940, the patient was in bed for several months because of severe girdle pain, but by the next year he had improved sufficiently to drive his car and go hunting and fishing. He remained well until 1945 when definite progression of the disease was noted, followed a year later by a mild degree of anemia, extensive involvement of the skull, and involvement of the mandible from which the patient suffered considerably. Treatment with stilbamidine, instituted by [redacted] produced no marked effect, and the patient deteriorated steadily until his death four months later.

Case 5, a white female [redacted] had a severe anemia and after each dose of P^{32} a marked diminution of the platelet count occurred (from 160,000 to 45,000). However, after treatment the patient was able to get about easily and pain was relieved. In spite of pancytopenia, the rate of progress of the disease was definitely diminished and pain was relieved more effectively than by x-ray or opiates.

In Case 13, the benefit obtained by P^{32} and Sr^{89} was only temporary. The patient complained of severe pain in the back which had become increasingly severe up to the time of treatment. During the treatment with P^{32} and Sr^{89}, these pains disappeared completely. However, at the same time severe anemia, leukopenia and thrombopenia developed and the patient ultimately died despite many transfusions. Bone marrow biopsy, performed shortly before death, revealed hypoplasia of the marrow elements.

Case 16 was bedridden for almost a year. Treatment with radioactive phosphorus was followed by marked improvement, so that the patient was able to be up and about. It seemed almost unbelievable that this patient, who had been in extreme pain almost constantly and had been unable to move unaided in bed a year previously, had become pain free and was able to resume her previous occupation as a teacher. This remission lasted for one

and one-half years after which the patient again became bedridden because of collapsed vertebrae and fractured ribs, and she died in coma. The result, although temporary, was quite striking.

Of the patients who were treated and are now dead, the length of life after onset of the disease ranged from six months to nearly nine years, with an average length of life of approximately three years after onset. This is slightly longer than in previously reported series[8, 9] but not markedly so.

Dosage

At the beginning of treatment with radioactive phosphorus, large single doses at short intervals of two to three days were tried in order to build up a high radiation level (table 3). Later smaller weekly or bi-weekly treatments were given. More positive knowledge about the dosage and frequency of treatment is, of course, highly desirable, but we cannot at the present time recommend any precise line of treatment. The general condition of the patient and hemogram must be considered at the time the patient is first seen and treatment started. The dosage must be individualized and the patient carefully followed with special attention directed to the state of his hematopoietic system. One millicurie of P^{32} intravenously once or twice a week for four to six weeks, or about 5 to 10 mc. per course, is suggested. After three to four months, if the blood picture is satisfactory, more radiophosphorus may be given if it is indicated.

The dosage and frequency of therapy of the nine patients who were treated with radioactive strontium are shown in table 3. Inasmuch as Sr^{89} treatment was used in a limited number of cases, and since P^{32} was usually administered also, it is difficult to evaluate the treatment of multiple myeloma with Sr^{89} from these observations. There was no evidence that the combination of Sr^{89} and P^{32} proved more effective than P^{32} alone.

Comment

The results of our treatment of multiple myeloma with these radioactive elements were not markedly better than those obtained with x-ray and with stilbamidine.[1, 3] Radiosensitive cases may be influenced equally well by x-ray or by artificially radioactive elements, although it is not certain that we are influencing the course of the disease by any type of radiation. In view of the fact, however, that the radioactive isotopes are more easily applied than x-ray therapy and have no side effects, this treatment is worth trying in multiple myeloma. The symptomatic improvement and the relief of pain obtained by the use of artificially radioactive isotopes were in some cases so striking that the favorable effect of this type of therapy seemed definite. At times, it seemed to us that a combination of isotope therapy plus x-ray was more effective in causing improvement. Likewise, it seems unlikely that radiostrontium will be a valuable therapeutic agent because of

its selective deposition and long half life (55 days), and since, as in the case of P^{32}, the bone marrow is constantly being irradiated during this period. Thus, an amount of radiostrontium sufficient to destroy tumor cells would produce damaging effects on the normal marrow components before destruction of the neoplastic lesions could be achieved. More intensive work with strontium 89 in the treatment of myeloma and other bone lesions is necessary for its evaluation as a therapeutic agent. Similarly, combination therapy with P^{32} or Sr^{89}, the diamidine compounds, and urethane would seem to be a worthwhile approach to the treatment of this disease which has thus far proved to be such a discouraging problem. Finally, radioactive stilbamidine, now being studied in this laboratory, may be of therapeutic value because of its combined chemotherapeutic and possible selective irradiation effects.* There is little doubt in our minds that radiation is of some benefit in myeloma, and if it can be delivered to the plasma cells by some selectively localizing radioactive compound, considerable improvement in the results with an increase in comfortable life and life expectancy can be anticipated. But, until such a satisfactory therapeutic agent is discovered, the prolongation of useful life must remain an important consideration in the treatment of multiple myeloma.

Conclusions

1. Radioactive phosphorus and radioactive strontium have been used as therapeutic agents in multiple myeloma. Improvement was noted in some cases. The average length of life after the onset of the disease in this group of patients was approximately three years.

2. These isotopes are valuable in producing whole body background irradiation which may in itself afford some relief. The combination of isotope therapy and x-ray or stilbamidine or urethane is suggested.

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BIBLIOGRAPHY

1. Snapper, I.: Stilbamidine and pentamidine in multiple myeloma, J. A. M. A. 133: 157-161, 1947.
2. Loge, J. P., and Rundles, R. W.: Urethane (ethyl carbamate) therapy in multiple myeloma, Blood, J. Hematol. 4: 201–216, 1949.
3. Bayrd, E. D., and Heck, F. J.: Multiple myeloma. A review of 83 proved cases, J. A. M. A. 133: 147–157, 1947.
4. Gootnick, L. T.: Solitary myeloma: Review of 61 cases, Radiology 45: 385-391, 1945.
5. Fitz-Hugh, T., and Hodes, P. J.: Clinical experience with radio-phosphorus in the treatment of certain blood dyscrasias, Am. J. M. Sc. 204: 662-665, 1942.
6. Warren, Shields: The therapeutic use of radioactive phosphorus, Am. J. M. Sc. 209: 710–711, 1945.

* Recent studies on one patient with multiple myeloma given radioactive stilbamidine in this laboratory, have not shown a sufficiently high degree of localization to indicate its use in therapy. (Personal communication from Dr. John Weaver.)

7. Bayrd, E. D., and Hall, B. E.: Unusual remission after radiophosphorus therapy in a case of "acute plasma cell leukemia," Blood, J. Hematol. 3: 19, 1948.
8. Reinhard, E. H., Moore, C. V., Bierbaum, O. S., and Moore, S.: Radioactive phosphorus as a therapeutic agent, J. Lab. and Clin. Med. 31: 107–218, 1946.
9. Geschickter, C. F., and Copeland, M. M.: Multiple myeloma, Arch. Surg. 16: 807–863, 1928.
10. Wintrobe, M. M.: Clinical hematology, 1946, Lea and Febiger, Philadelphia, p. 774.
11. Lawrence, J. H., Tuttle, L. W., Scott, K. G., and Connor, C. L.: Studies on neoplasms with the aid of radioactive phosphorus. Total phosphorus metabolism of normal and leukemic mice, J. Clin. Invest. 19: 267–271, 1940.
12. Pecher, C.: Biological investigations with radioactive calcium and strontium, Proc. Soc. Exper. Biol. and Med. 46: 86–91, 1941.
13. Graff, W. S., Scott, K. G., and Lawrence, J. H.: The histologic effects of radiophosphorus on normal and lymphomatous mice, Am. J. Roentgenol. and Rad. Ther. 55: 44–54, 1946.
14. Erf, L. A., Tuttle, L. W., and Lawrence, J. H.: Clinical studies with the aid of radiophosphorus. Retention in blood, the excretion, and the therapeutic effect of radiophosphorus on patients with leukemia, Ann. Int. Med. 15: 487–543, 1941.
15. Low-Beer, B. V. A., Lawrence, J. H., and Stone, R. S.: The therapeutic use of artificially produced radioactive substances, Radiology 39: 573–591, 1942.
16. Lawrence, J. H., and Rosenthal, R. L.: Multiple myeloma associated with polycythemia. Report of four cases, Am. J. M. Sc. 218: 149–154, 1949.