RECENT STUDIES OF MULTIPLE MYELOMA: STERNAL AND RIB PUNCTURE AND THE RESULTS OF TREATMENT WITH STILBAMIDINE

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MULTIPLE MYELOMA is commonly known as a malignant disease characterized by bone pain, deformity and abnormal fragility of the osseous system, cachexia, and Bence-Jones proteinuria. The tumors tend to be multiple. They are found most frequently in the spine, ribs, skull, bones of the shoulder girdle, pelvis, sternum and upper ends of the humeri and femora, where active blood formation occurs in the adult.

In 1845, Bence-Jones found an unusual protein in the urine of a patient who complained of pain in the ‘chest, back, and loins.’ This protein, which coagulated at 55 to 60 C. and redissolved upon boiling, has since been known by the name of the discoverer. Von Rustizky, in 1873, first described a condition with multiple tumors of the bones which consisted of proliferating elements of bone marrow, under the title ‘Multiples Myelom.’ Kahler associated Bence-Jones proteinuria with multiple myeloma in 1889. The term Kahler’s disease is frequently used as a synonym for this condition.

The pathology of multiple myeloma has been considered to be that of a neoplasm of the bone marrow in which the cytology varies depending upon the type of marrow cell involved. There is a diffuse proliferation of the malignant cells within the marrow. Atkinson has summarized 643 cases of multiple myeloma. Of these 207 were classified as plasmacytoma, 27 myeloblastoma, 24 myelocytoma, 16 lymphocytopoia, 5 erythroblastoma, 32 mixed, and 332 were unclassified. More recently, since the advent of the use of sternal marrow aspiration for diagnosis, reports on multiple myeloma have been almost entirely of the plasma cell type and there has been a definite trend to regard this disease as of plasma cell origin only.

The laboratory findings useful in diagnosis may be listed as follows: Bence-Jones proteinuria; hyperglobulinemia; excessive rouleaux formation of erythrocytes with clumping in Hayem’s solution, and rapid sedimentation rate; osteoporosis by x-ray; hypercalcemia with normal or moderately elevated alkaline phosphatase and serum phosphorus values; anemia; myeloma cells* in the peripheral blood; and myeloma cells in marrow aspiration. The latter finding has come to be regarded as pathognomonic of this disease. A positive marrow aspiration or surgical biopsy is necessary to establish the diagnosis.

The course of multiple myeloma is progressively fatal over a period of a few years. From the Department of Medicine, Albany Medical College, Albany, New York.

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* The term myeloma cell in this article is used interchangeably with plasma cell to denote the series of dysplastic plasma cells observed in the bone marrow in multiple myeloma.
months to six years or longer from the time the diagnosis is made. Treatment has
been palliative. Roentgen therapy, nitrogen mustard, and radioactive phosphorus
have shown no curative value. Snapper\(^7\) has introduced an interesting new
chemotherapeutic agent in the treatment of this disease. He has apparently ob-
tained relief of pain repeatedly in patients with multiple myeloma by the use of
stilbamidine and pentamidine. Stilbamidine has proved very effective in treating
visceral leishmaniasis. Because this disease and multiple myeloma are accompanied
by hyperglobulinemia, it was reasoned empirically that stilbamidine might be of
value in both. Kopac\(^9\) has indicated that stilbamidine may act on nucleoproteins
by demonstrating, in vitro, dissociation of protamine-ribonucleate complexes, the
stilbamidine releasing protamine and simultaneously binding nucleic acids. Snapper
has shown that following treatment of patients with multiple myeloma with
stilbamidine, on a low animal protein diet, large basophilic inclusion bodies ap-
peared in a high percentage of the myeloma cells. These were produced only in the
presence of hyperglobulinemia or Bence-Jones proteinuria and appeared in 12 of
13 patients with increased blood globulin.\(^10\) He has demonstrated that these in-
cclusion bodies contained ribose nucleic acid, by studying the action of ribonu-
lease on the granules and by the use of the quartz microscope.\(^11\) Stilbamidine was found
by analysis in myeloma tissue obtained at postmortem examination eight days after
completion of a course of this drug. He has advanced the theory that stilbamidine
reacts with the cytoplasmic nucleoproteins of myeloma cells only, and not with
nucleoproteins of other cells. A high protein diet, according to Snapper’s theory,
interferes with this reaction. He has suggested that pain is relieved because mye-
loma cell proliferation is arrested. Lack of expansion of osteolytic lesions for some
time after cessation of treatment was demonstrated in some patients. This occurred
despite the fact that the percentage of myeloma cells in the marrow smears was not
shown to decrease. No changes in the myeloma cells were found after treatment
with pentamidine, although relief of pain was obtained.

A feeling of formication about the face was common accompanying the injec-
tions of stilbamidine. A high incidence of dissociated anesthesia of the trigeminal
nerve occurred two and a half to five months following treatment. This caused
considerable distress in the form of severe persistent itching in only one of Snapper’s
patients. In most cases the discomfort gradually subsided. No toxic effects were
produced on the liver or hematopoietic system. Renal failure was precipitated in
two cases and caution was advocated in treating patients with renal damage and
insufficiency.\(^12\)

Ten out of eleven patients treated only with stilbamidine by Snapper were re-
lieved of pain.\(^13\) Pentamidine was used successfully in the one case in which stil-
bamidine failed. In two cases pentamidine was ineffective but subsequent use of
stilbamidine caused the pain to disappear. Recurrence of pain required repetition
of stilbamidine treatment and it was emphasized that although progress of the
disease was temporarily checked no cure was obtained.

This article deals with a study of six cases of multiple myeloma admitted to
the Albany Hospital within a relatively short period of time. An opportunity was
presented to study myeloma cells before and after treatment with stilbamidine,
and to observe the clinical effects of this drug.
Methods

Each case received a complete hospital work-up with appropriate laboratory and x-ray studies. Sternal marrow aspiration was done in all cases before and after treatment with stilbamidine. In addition, rib marrow punctures* were performed on four occasions. Because of the great dependence placed on marrow puncture in the diagnosis of multiple myeloma, a more elaborate technic was developed which differed somewhat from that previously described. Changes in procedure consisted in using heparin solution and 1 cc. syringes for marrow aspiration. Heparin solution containing ten units per 1 cc.† was used in sufficient amount to wet the syringe only. This syringe was then utilized to aspirate 0.1 cc. of marrow fluid. The heparin prevented clotting, and subsequent steps could be carried out at the leisure of the operator. Coverslip smears were made directly from the marrow fluid without mixing. A cresyl blue wet smear and two supravital smears were then made. The fluid remaining was ejected onto a hollow slide. Marrow bits were identified by tilting the slide and these were picked up with pipets and smears repeated. The marrow mixture was then placed in a Wintrobe hematocrit tube, centrifuged, and a third set of preparations made from the buffy layer. The dry coverslip smears were subsequently stained with Wright's stain and a peroxidase-Wright's stain was done on a selected smear. This method of procedure gave three possibilities of securing a representative sample of marrow cells, and precluded the chance of missing the diagnostic picture from chance selection of material for smears, dilution with sinusoidal blood, and rapid clot formation in the aspirating syringe.

Rib puncture was performed in the scapular line. The skin and periosteum were anesthetized with procaine in a manner similar to that employed in sternal puncture. The margins of the rib were grasped between the thumb and index finger to ascertain the rib center. A sternal puncture needle 1.5 cm. or less in length was used because of the possible danger of entering the pleural cavity. The center of the rib was bored with a rotary motion of the needle and the marrow cavity entered in a fashion similar to sternal puncture. The same preparations of marrow smears were made as enumerated above.§

* Rib marrow puncture was first performed on one case suspected of rib malignancy immediately post mortem. The procedure was so simple and the results so satisfactory that it was performed later on a patient diagnosed clinically as multiple myeloma when sternal puncture was unsuccessful. A second sternal puncture, and the rib puncture which was done in an area termed pathologic by the roentgenologist, proved to contain normal bone marrow. The patient subsequently recovered. Since then rib punctures have been performed on sixteen patients and excellent marrow preparations obtained. A requisite for rib puncture is the careful palpation of the selected rib. Puncture should never be done if the rib is not easily palpable.

† Lilly's solution of sodium heparin.

‡ It was found by puncturing ribs during post mortem examinations that if considerable force were exerted, the tip of a 1.5 cm. needle could be forced through the parietal pleura of a thin person. A 1 cm. needle could not be made to penetrate completely through the rib. A very definite "give" was usually experienced when the outer thin bony plate of a rib was pierced and the marrow cavity entered. This sensation was not invariably felt however, so that aspiration was always attempted when the needle was firmly fixed in the bone. Then the needle was slowly advanced until marrow fluid was obtained or the sensation of entering the marrow cavity experienced.

§ Comparison of rib and sternal preparations have shown a similar marrow picture in 13 instances when both were done immediately following each other. Variations in amount of marrow material,
The cases of multiple myeloma were treated with stilbamidine according to Snapper's method, as follows. The stilbamidine was dissolved in 10 cc. of sterile distilled water and used immediately. Injections were given intravenously, starting with a dose of 50 mg. One hundred mg. were given the following day, and then 150 mg. daily for a total of 20 treatments which constituted the usual course. Atropine sulfate Gr. 1, 150 was given hypodermically 30 minutes before each injection to prevent or minimize immediate vasomotor reactions as recommended by Snapper. The total dosages of stilbamidine and the diets given to each patient are listed in table 2.

The clinical and laboratory findings and therapeutic results are illustrated in the following case histories.

CASE I

A. S., a 61 year old white male office worker, was admitted to the Albany Hospital on Jan. 7, 1947. He had been ill for 3 months with unexplained fever. Two weeks before his hospital admission, he developed pain in his left chest which was aggravated by cough and deep breathing. Physical examination revealed a fever of 101° and evidence of pneumonia in the left lower lobe, which was confirmed by x-ray. The liver was enlarged and tender. The heart had irregular rhythm and there was a loud, blowing, apical systolic murmur. An electrocardiogram revealed auricular fibrillation and low T waves with slurring of QRS in the standard leads indicating myocardial damage. Hemoglobin was 7.5 Gm., red blood cells 2,000,000, white blood cells 8,100, segmented neutrophils 80 per cent, lymphocytes 14 per cent, and monocytes 6 per cent. Erythrocyte sedimentation rate, Wintrobe, was 10 mm. in one hour.

The patient's pneumonia was treated effectively with penicillin and three 500 cc. blood transfusions. He developed a nonpurulent, sterile, pleural effusion. Abnormal clumping of erythrocytes was noted on routine blood counting, and because of this finding he was studied for multiple myeloma. The urine was positive for Bence-Jones protein and showed a i plus albumin. Serum protein was 11.3 Gm. per cent total, with albumin 1.6 and globulin 9.9 Gm. per cent, an A-G ratio of 0.16. Serum calcium was 11.9 mg. per cent, phosphorus 3.2 mg. per cent, alkaline phosphatase 3.9 Bodansky units, and NPN 60 mg. per cent. X-ray examinations of the skull and ribs were normal. Sternal puncture revealed marked replacement of normal marrow elements by plasma cells. These made up 91 per cent of a 100 white cell differential count. This established the diagnosis of multiple myeloma.

Treatment was carried out with stilbamidine. Eighteen injections totaling 2.7 Gm. were administered. Because of the poor nutritional state of the patient, no restriction of protein was ordered. Unpleasant effects of the injections consisted of transient prickly feelings about the mouth, eyes and ears at the time of treatment, and recurrent nausea and vomiting. These manifestations were not severe. Sternal puncture following the course of stilbamidine showed that 34 per cent of cells in the marrow smears were of the myeloma type. Azurophilic granulation was noted in the cytoplasm of some of these cells, but no basophilic inclusion bodies were found.

The patient was discharged without improvement in his general condition. He subsequently expired on May 15, 1947, 3 months from the time his treatment was concluded. No autopsy was obtained.

COMMENT

The diagnosis of multiple myeloma was only suspected in this case because of the abnormal clumping of erythrocytes noted in Hayem's solution in a routine blood count. His first presenting symptom of unexplained fever without pain was atypical. Confirmatory laboratory findings of hyperglobulinemia and Bence-Jones proteinuria were offset by negative x-ray examinations of skull and ribs. Diagnosis was established by sternal puncture. Treatment with stilbamidine without pro-
tein restriction failed to effect a remission in the course of the disease or to produce basophilic granulation in the cytoplasm of the cells although hyperglobulinemia was present.

CASE 2

R. L., a 38 year old Italian male, was admitted to the Albany Hospital on January 28, 1947, with a chief complaint of vertigo. For ten days prior to admission he had repeated, transient attacks of dizziness and weakness, and for six months had suffered from generalized headaches. There was a weight loss of 15 pounds during this period. He had had an acute infection in the right ear, three weeks before admission, which had subsided. Examination revealed moderate tenderness over the left temporal region, anterior to the ear. The Romberg test was strongly positive, with the patient falling to the right. Blood pressure was 160 mm. of mercury systolic and 100 mm. diastolic. A routine x-ray of the skull showed numerous, small, punched-out areas of decreased density (fig. 1). Further studies of the osseous system revealed evidence of active bone destruction in the 5th lumbar vertebra and some compression of the second and third lumbar segments. Laboratory examinations showed hemoglobin 13 grams; red blood cells 4,400,000; white cells 10,000, with a normal differential count; blood Wassermann negative; urine normal; total serum protein 12.1 Gm. per cent; albumin 3.7 Gm. per cent, and globulin 8.4 Gm. per cent, with an A-G ratio of 0.4; serum calcium 10.5 mg. per cent; phosphorus 3.8 mg. per cent; alkaline phosphatase 3.6 Bodansky units; NPN 39 mg. per cent; creatinine 0.9 mg. per cent. No Bence-Jones protein was found on repeated tests. Sternal puncture preparations contained 19.5 per cent plasma cells.
The patient was given a course of 20 injections of stilbamidine totaling 2.85 Gm. The diet was not restricted. He complained of burning of the skin, lacrimation, salivation, bilateral tinnitus and restlessness, as an immediate reaction to the drug administration. These complaints subsided within a few minutes following the injections. Four weeks following treatment a sternal puncture revealed a reduction of myeloma cells to 6.1 per cent. The majority of these cells, 83.8 per cent, showed large basophilic inclusion bodies in the cytoplasm which were identical with those described by Snapper. A roentgenogram of the skull indicated a definite increase in the areas of decreased density (fig. 2). Subjectively, the patient felt generally improved, and the headaches and dizziness were relieved. Five weeks after completion of his first course of stilbamidine he had a recurrence of severe generalized headaches and aching pain in the lumbar spine. A second course of the drug, consisting of 1.35 Gm, was given over a period of ten days with the patient on a low animal protein diet. Relief of symptoms occurred and he returned to light work. Seven weeks after this course of treatment he complained of numbness about the mouth involving most of the face. No neurologic changes were noted. Later, intense burning in this region occurred, particularly at night. This still persisted after six months of observation. Rib puncture on Sept. 9, 1947, six and one half months following his first treatment and four and one half months after his second course of stilbamidine, revealed 18.8 per cent myeloma cells. Basophilic inclusion bodies were still present in 54 per cent of the cells. There were 1.3 per cent plasmablasts. Skull x-ray at this time showed further increase in the osteolytic lesions (fig. 3).

**Comment**

The clue to diagnosis in this case was obtained from an x-ray of the skull taken because of the patient's complaints of vertigo and headaches. The possibility of
multiple myeloma had not been previously entertained. Further osseous lesions in the lumbar vertebrae and hyperglobulinemia were confirmatory evidence. Sternal puncture established the diagnosis of multiple myeloma.

Treatment with stilbamidine without restriction of animal protein not only produced a remission of symptoms but also caused typical basophilic cytoplasmic inclusions in the majority of myeloma cells. This occurred at a time when osteoporotic lesions in the skull were increasing in size. A severe persistent trigeminal neuropathy followed a second course of treatment. Basophilic inclusion bodies were observed in the myeloma cells obtained from rib puncture four and one half months after treatment was concluded.

**Fig. 3.** September 4, 1947, six months after first course and four months after second course of stilbamidine.

**CASE 3**

C. S. H., a 47 year old white male was admitted to the Albany Hospital on Feb. 26, 1947. He had been ill for 9 months with pain in his ribs, progressive weakness and fatigue, loss of weight, and failing vision. He was told that he was anemic four months before admission to the hospital. Examination revealed a pale, thin patient who appeared chronically ill. There was tenderness to pressure over the lower ribs bilaterally. There was a soft, blowing, apical cardiac murmur. The liver edge was palpable two fingers below the costal margin. Ophthalmic examination revealed presbyopia only.
Laboratory studies: Positive test for Bence-Jones protein and 4 plus albuminuria; hemoglobin 10 Gm., red blood cells 3,320,000; white blood cells 9,500 with a normal differential count; Wintrobe sedimentation rate 12 mm. in one hour; blood Wassermann negative; total serum protein 5.6 Gm. per cent with an A–G ratio of 2.5; NPN 30 mg. per cent; calcium 10.4 mg. per cent; phosphorus 3.2 mg. per cent; and alkaline phosphatase 4.2 Bodansky units. X-rays of the skull and ribs were reported as being normal. A second roentgenogram of the ribs showed a 'suggestion of metastatic tumor' on the lower left. Sternal puncture revealed that 17 per cent of marrow cells were of the large plasma cell type.

The patient was placed on a low animal protein diet and given a course of stilbamidine totaling 2.85 Gm. He also received two 500 cc. blood transfusions. Sternal puncture was repeated after 2.5 Gm. of stilbamidine or 16 injections had been administered. The marrow contained 43.4 per cent myeloma cells of which the great majority (82.9 per cent) contained basophilic inclusion bodies. At the conclusion of treatment hemoglobin was 9.5 Gm, red blood cells 4,160,000, and white blood cells 6,800 with a normal differential count.

This patient improved considerably. The pain in his ribs subsided, his vision improved and he gained in strength. He returned home and reported in six weeks by letter that he felt fine. Follow-up of this patient revealed that two months after treatment he was relieved of pain and felt well except for a generalized skin rash and a sore tongue. His doctor reported that there was, however, a progressive decline in his general state. Retreatment was advised but the patient had moved away and the referring doctor was unable to locate his new residence. A follow-up obtained by letter, however, written on Dec. 25, 1947, indicated that the patient was still ambulatory, but otherwise totally incapacitated by his illness.

COMMENT

This patient's symptomatology fitted the clinical picture of multiple myeloma. Bence-Jones proteinuria and anemia were the positive laboratory findings and x-rays were negative. There was no hyperglobulinemia. Sternal puncture findings were pathognomonic.

Stilbamidine treatment with a low animal protein diet plus transfusions improved this patient symptomatically and typical basophilic inclusion bodies were found in the majority of the myeloma cells, although the relative percentage of the tumor cells had definitely increased in the marrow. The treatment did not however have any sustained effect upon his general condition.

CASE 4

A. W., a 61 year old male office manager, was admitted to the Albany Hospital on Jan. 12, 1947, with the chief complaint of an infection in his nose of one week's duration. He was a known diabetic who had been well controlled with diet and insulin for 30 years.

Examination revealed impetiginous lesions of the nose and forehead, a blood pressure of 170 mm. of mercury systolic and 80 mm. diastolic, and a palpable liver felt three fingers below the costal margin.

Urinalysis was normal except for a trace of sugar. Blood hemoglobin was 10 Gm.; red blood cells, 2,930,000; white blood cells 6,900; segmented neutrophils 71 per cent; lymphocytes 27 per cent; monocytes 2 per cent. NPN was 38 mg. per cent and the blood Wassermann was negative. Total protein, taken for investigation of liver function, was 10.7 Gm. per cent with albumin 2.1 Gm. per cent, and globulin 8.6 Gm. per cent, an A–G ratio of 0.14. Because of the hyperglobulinemia, further studies were done. Urine positive for Bence-Jones protein, clumping of erythrocytes was observed in Hayem's solution, and Wintrobe sedimentation rate was 61 mm. in one hour. Sternal puncture on Jan. 23, revealed 14.2 per cent large plasma cells and a marked reduction in erythroid and myeloid cells. A second sternal puncture at a higher level showed similar findings.

A diagnosis of multiple myeloma was made, but because the patient was asymptomatic he was discharged from the hospital. Five months later he was readmitted because of a severe vaccinia. At this time, he complained of pain in his right hip, but x-ray examination of his pelvis was normal. He was again discharged but shortly afterward began to have severe pain in the left chest in the region of the
fifth to the ninth ribs. He also suffered from diplopia. X-ray examination at this time showed evidence of bone destruction in the ribs. He was readmitted on July 17, 1947, for treatment with stilbamidine because of persistent bone pain. Examination revealed weakness of the left external rectus ocular muscle, with inability to move the left eye laterally. The liver was still enlarged. The urine contained 1 to 3 plus albumin but no Bence-Jones protein. Hemoglobin was 9.5 Gm., red blood cells 3,100,000, white blood cells 6,300, segmented neutrophils 71 per cent. NPN was 42 mg. per cent, total protein 9.1 Gm. per cent, with albumin 2.2 Gm. per cent and globulin 6.9 Gm. per cent, an A-G ratio of 0.32.

The patient received a course of 20 injections totaling 2.85 Gm. of stilbamidine from July 18 to Aug. 9. The diet contained 1,600 calories with 97 Gm. of protein which was qualitatively unrestricted. Immediate reactions to the treatment were a burning about the mouth sometimes extending into the eyes, which was only momentary, and nausea and at times vomiting, which were delayed until later in the day. The diplopia and bone pain were unrelieved. Sternal and rib puncture on Aug. 12., showed a myelophthisic marrow with 6.8 m per cent myeloma cells. No basophilic inclusion bodies were observed. The patient was then placed on a low animal protein diet and a total of 1.5 Gm. of stilbamidine was administered in a course of ten injections from Aug. 15 to 27. There was no relief of pain. Puncture of the right eighth rib was performed at this time and no change in the marrow picture was found. There were no basophilic inclusion bodies in the myeloma cells.

On Sept. 10, 1947, a prefrontal lobotomy was performed for relief of pain. The patient expired post-operatively.

Autopsy confirmed the diagnosis of multiple myeloma. Infiltrations of plasma cells were noted in the liver.

**COMMENT**

The diagnosis of multiple myeloma was made during the hospitalization of this patient for impetigo and diabetes mellitus, because of the presence of hepatomegaly. The findings of hyperglobulinemia, Bence-Jones protein, clumping of erythrocytes in Hayem's solution and positive sternal puncture complete the diagnostic picture although the patient had no symptoms of the disease and x-ray studies of the bones were negative.

Treatment with a full course of stilbamidine without a low animal protein diet failed to relieve pain or effect the myeloma cells. A second course of 1.5 Gm. of stilbamidine on a low animal protein diet also did not alleviate pain or produce basophilic inclusion bodies in the myeloma cells. Failure of treatment thus occurred despite the presence of both hyperglobulinemia and Bence-Jones proteinuria.

**CASE 5**

A. V., a white farmer, 72., was admitted to the Albany Hospital on Aug. 5, 1947, because of pain in the back, left hip, and left leg of six months duration. The pain in the back and left hip occurred after a fall. About one month before admission the pain began to radiate down the medial aspect of the left leg. The pain was intermittent, sharp, and worse at night. The patient also had frequent nose bleeds since the onset of his illness.

Physical examination showed emaciation. The skin was dry and loose. Blood pressure was 158 mm. of mercury systolic and 70 mm. diastolic. There was tenderness over the fourth right rib. The liver was enlarged and could be palpated two fingers below the costal margin. There was diminished sensation to light touch along the medial aspect of the left thigh and calf. The left patellar reflex was reduced.

The urine contained 3 plus albumin and many hyaline casts, but no Bence-Jones protein. Hemoglobin was 8.5 Gm., red blood cells were 2,860,000, and white blood cells were 10,150. On Aug. 6, the white blood cells were 12,200, with segmented neutrophils 48 per cent and lymphocytes 51 per cent. The blood Wassermann was negative. Total plasma protein was 12.7 Gm. per cent, with albumin 2.3 Gm. per cent and globulin 10.4 Gm. per cent, an A-G ratio of 0.22. Serum could not be obtained and clot retraction could not be studied because the blood rapidly formed a gel and no fluid portion remained. The bleeding time was one minute and 18 seconds, coagulation time three minutes and platelet count 157,000. Clumping
of erythrocytes occurred in Hayem's solution. X-rays revealed many small oval areas of lessened density throughout the skull, and in the upper third of the left humerus. Myelogram showed bilateral deformities opposite lumbar vertebrae 3 and 4, more marked on the left, which was consistent with a displaced disc.

Spinal fluid contained 60 mgs. per cent protein, and the Wassermann test was negative. Sternal and rib punctures on Aug. 9 were diagnostic of multiple myeloma. There were 45.6 per cent plasma cells. Of these, 1.2 per cent were plasmablasts, and 4.8 per cent were young forms. There was great variation in size and appearance of the cells. Syncytial sheets of small cells with nuclei placed centrally, or nearly so, and uniformly basophilic cytoplasm were seen, which resembled basophilic normoblasts. Larger cells had typically eccentric nuclei and abundant basophilic cytoplasm characteristic of plasma cell myeloma.

The patient's condition deteriorated rapidly. On the third hospital day he was given 500 cc. of blood by indirect transfusion. On the sixth day he became drowsy, stopped taking fluids and then gradually became comatose. NPN was 72 mg. per cent. On Aug. 15, NPN was 58 mg. per cent, and plasma CO2 43 volumes per cent. Fifty mg. of stilbamidine were given intravenously, and 100 mg. the following day.

The patient expired in coma on the eleventh hospital day.

Autopsy revealed involvement of lumbar vertebrae, skull and sternum with plasma cell myeloma. An unusual phenomenon was the finding of a complete cast of the heart and larger vessels formed by a firm gel composed of blood plasma.

**COMMENT**

This was a typical, malignant type of multiple myeloma showing a fully developed symptomatic and pathologic picture. Sternal and rib puncture confirmed the diagnosis. The marrow cytology was interesting because of the presence of small myeloma cells resembling basophilic normoblasts. Treatment with stilbamidine was attempted only because of the obviously bad prognosis. Autopsy confirmed the diagnosis and a striking finding was the presence of a cast of the heart and vascular system consisting of a firm gel of the blood plasma.

**CASE 6**

E. J. B., an 85 year old single white female, was admitted to the Albany Hospital on Nov. 22, 1947. She had complained of pain in her back in the region of the lower ribs which radiated anteriorly about her chest, for four months. The pain was almost constant but varied in severity. It was aggravated by motion. She had lost weight and strength and for the month prior to admission, had suffered from anorexia, dyspnea and recurrent vomiting. Physical examination showed a very thin, dehydrated patient who was tender over the lower thoracic vertebrae. The heart was enlarged and systolic murmurs were heard over the aortic and mitral areas. The clinical impression was osteomalacia or metastatic malignancy, and arteriosclerotic heart disease.

The urine showed only a trace of albumin and tests were negative for Bence-Jones protein. Hemoglobin was 8.0 Gm., red blood cells 2,500,000, white blood cells 8,750, segmented neutrophils 71 per cent, band neutrophils 1 per cent, eosinophils 1 per cent, basophils 1 per cent, and lymphocytes 26 per cent. Wintrobe erythrocyte sedimentation rate was 66 mm. in one hour. The blood Wassermann was negative. Serum phosphorus was 1.2 mg. per cent, alkaline phosphatase 1.1 Bodansky units, serum calcium 11.3 mg. per cent, and NPN 30 mg. per cent. Total serum protein was 7.7 Gm. per cent of which albumin was 3.1 and globulin 4.5, an A-G ratio of 0.7. X-ray examinations revealed a partial collapse of the bodies of thoracic vertebrae 7, 10, 11, and 12 with marked atrophic changes in all the vertebral bodies. There were multiple small areas of localized bone destruction throughout the ribs and in both scapulae. The 6th rib was fractured in the axillary line on the left. There were multiple minute areas of lessened density distributed throughout the skull. Sternal and rib aspirations were performed on Nov. 26, and the marrow smears revealed 15.4 per cent plasma cells and 0.4 per cent plasmablasts. This established the diagnosis of multiple myeloma.

The patient was placed on a low animal protein diet and given a course of 12 injections of stilbamidine totaling 1.65 Gm. There was no reaction to the drug. She continued to have constant severe pain in the back and nausea and vomiting. Her general condition gradually grew worse and death occurred.
on the twenty-second hospital day. Autopsy revealed multiple myeloma of the plasma cell type involving the ribs, sternum and vertebrae. Smears of the sternal marrow obtained post mortem showed 21.4 per cent plasma cells and 0.4 per cent plasmablasts. No basophilic inclusion bodies were observed.

**Comment**

This patient had multiple myeloma at the extreme age of 85 years. The diagnosis was indicated by the clinical picture, x-ray findings, and hyperglobulinemia, and
was confirmed by marrow aspiration. Treatment with 1.65 Gm. of stilbamidine failed to relieve pain or produce basophilic granulations in the myeloma cells, although hyperglobulinemia was present.

**Cytology**

The cytology of multiple myeloma has recently been described by Diggs and Sirridge. Their findings were based on fifty-five cases of plasma cell myeloma. Support was given to the thesis that multiple myeloma is derived from plasma
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cells arising from primitive reticulum as a specific strain of cells. The term myeloma cell was objected to because it inferred a specific type of cell peculiar to multiple myeloma only. Our observations on the cytology of the six cases being reported were similar to those of Diggs and Sirridge.

Our cases were entirely of the plasma cell type. In general, with Wright's stain, the following characteristics were noted. The cells were oval in shape, the nuclei eccentric, round and pachychromatic but not typically "cart-wheel" or "Radkern." Variation in size occurred not only in the various patients but also in each individual case. The cytoplasm was abundant and minor differences in intensity of its basophilic substance were present in the different cases. Vacuolization of the cytoplasm was common, and a perinuclear clear zone was a prominent feature. In case 5, small cells with uniformly basophilic cytoplasm and centrally placed nuclei were noted, which resembled basophilic normoblasts (fig. 9). The usual type of plasma cell in normal marrow is shown in figure 4. A second type of plasma cell with more abundant, less deeply basophilic cytoplasm, without vacuoles and with a larger nucleus, observed in the same marrow smear, is illustrated in figure 5. The latter closely resembles the typical cells found in our cases of multiple myeloma (figs. 6, 7). Plasmablasts of large size with a definitely eccentric, large leptochromatic nucleus containing nucleoli, and comparatively little, basophilic cytoplasm, were observed in small numbers (fig. 10). The highest percentage of plasmablasts was 2.3, seen in case 2. Young plasma cells containing large, relatively immature nuclei without nucleoli, and more abundant cytoplasm than the blast form, constituted 4.8 per cent of the myeloma cells in case 5. Very large cells with multiple separate nuclei were seen in all cases. Mitotic figures were not numerous. Sheets of plasma cells were commonly observed in preparations made from marrow bits and occasionally in direct smears of unconcentrated marrow fluid (fig. 8). The plasma cells were uniformly peroxidase negative (fig. 11).

Supravital studies revealed a close similarity between the myeloma cells and large plasma cells seen in marrow smears made from patients with other conditions, and from normal marrow. The cells were large and oval, or round, with abundant cytoplasm and a distinct cell membrane. The nucleus was round and very definitely eccentric. Neutral red vacuoles of variable size were present external to the nucleus. These could be observed to enlarge as the preparations aged. Large mitochondria were a striking feature. These were interspersed in the cytoplasm but were more abundant near the nucleus (fig. 12). The usual type of plasma cell seen in normal marrow was smaller and the mitochondria and neutral red vacuoles appeared to be less numerous and of smaller size. However, a large type plasma cell was observed in one case of chronic aleukemic myelogenous leukemia treated with x-ray, which was indistinguishable from the typical plasma cell seen in the multiple myeloma patients.

After stilbamidine treatment, large basophilic inclusions were noted in the cytoplasm in the majority of the plasma cells stained with Wright's stain, in cases 2 and 3, (fig. 13, 14), while no inclusions were seen in the other four cases. No change was observed in cells stained by the peroxidase method. Although the
illustrated cell (fig. 15) shows an increased size in neutral red vacuoles by supravital stain, this was not remarkable as compared to studies made prior to treatment.

**Discussion**

The method of diagnosis of multiple myeloma in the cases reported is illustrated in table 1. The seven findings which are more pertinent to the diagnosis are listed together and collateral findings which are common to other conditions are placed in the lower section of the chart. The table shows in striking fashion an observation that is well-known, that the clinical picture of multiple myeloma is extremely variable. The only constant feature in all cases was the presence of a positive marrow aspiration. In one patient (case 3), the diagnosis was made by sternal puncture although only bone pain, Bence-Jones protein, and anemia were present. A clinical diagnosis was made prior to laboratory or x-ray studies in two cases. The clue to the diagnosis was found by the simple observation of clumping of erythrocytes
in Hayem's solution in one instance, by x-ray of the skull because of vertigo and headaches in a second, and from the finding of hyperglobulinemia while investigating the presence of hepatomegaly in a third case.

The great value of marrow aspiration in the differential diagnosis of multiple myeloma makes a satisfactory technic for this procedure extremely important. A method has been described which utilized unconcentrated marrow fluid, selected marrow bits, and a concentration of marrow cells obtained by centrifugation. The selection of marrow bits produced the most satisfactory marrow smears. Rib puncture was used successfully to complement and supplement sternal aspiration. This was found to be a simple and usually painless procedure. One important advantage is psychologic, the patient being unable to observe the details of the puncture. Caution must be used and no rib puncture should be done on a patient in whom the outlines of the rib are not definitely palpable.

The criteria upon which a diagnosis of multiple myeloma is made from marrow aspiration are not well defined. The number of plasma cells in the preparations is variable and reports have been as low as four per cent in one of the cases of Diggs and Sirridge and three per cent in the series of Rosenthal and Vogel. In normal marrow the percentage of plasma cells is usually less than 1 per cent. However, in other conditions, they may be present in greater numbers. It is felt that the con-

![Table 1.—Diagnosis of Multiple Myeloma](image)

<table>
<thead>
<tr>
<th>Case number</th>
<th>1 A. S.</th>
<th>2 R. L.</th>
<th>3 C. H.</th>
<th>4 A. W.</th>
<th>5 S. V.</th>
<th>6 E. B.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bence-Jones Protein</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hyperglobulinemia</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Clumped RBC in Hayem's</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Myeloma cells in blood</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Marrow aspiration</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Elevated NPN</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>-</td>
<td>-</td>
<td>Not done</td>
<td>-</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>Rapid RBC sedimentation</td>
<td>-</td>
<td>Not done</td>
<td>-</td>
<td>+</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>Autopsy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Patient had severe headaches with vertigo. Back pain occurred later.
† Severe rib pain developed later in the course of his disease.

* In our own studies a marrow of fatal agranulocytosis showed practically a complete replacement with plasma cells and lymphocytes.
S. PROPP, L. W. GORHAM AND S. KANTOR

Table 1.—Results of Treatment with Stilbamidine

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Stilbamidine</th>
<th>Total dose</th>
<th>Diet</th>
<th>Basophilic inclusions in cells</th>
<th>Relief of pain</th>
<th>General effect</th>
<th>Final results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A. S.</td>
<td>1/31 to 1/18/47</td>
<td>2.7</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>2. R. L.</td>
<td>2/6 to 2/26/47</td>
<td>2.8</td>
<td>Normal</td>
<td>Yes</td>
<td>Yes</td>
<td>Improved</td>
<td>Poor. Increase in myeloma cells and osteolytic lesions. Persistent burning of face</td>
</tr>
<tr>
<td>3. C. H.</td>
<td>3/3 to 3/22/47</td>
<td>2.85</td>
<td>Low animal protein</td>
<td>Yes</td>
<td>Yes</td>
<td>Neuropathy of 5th nerve</td>
<td></td>
</tr>
<tr>
<td>4. A. W.</td>
<td>7/18 to 8/9/47, 8/18 to 8/27/47</td>
<td>2.85</td>
<td>Diabetic protein 97 grams</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>5. E. B.</td>
<td>11/27 to 11/11/47</td>
<td>1.65</td>
<td>Low animal protein</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>Died</td>
</tr>
</tbody>
</table>

tent of plasma cells in the marrow in diseases other than multiple myeloma may not have been adequately studied. A factor which can not be evaluated is the admixture of sinusoidal blood in preparations made directly from aspirated marrow.* It is believed that the marrow picture is pathognomonic when the predominant cell type is the myeloma cell as described above. The presence of dysplastic cells, blasts, and young forms of the same cell line is also important. Masses of apparently proliferating cells are best found in preparations made from selected marrow bits. When the percentage of characteristic cells is low, consideration of the clinical picture as a whole is felt to be essential to the diagnosis. This, of course, is always preferred, so that marrow puncture becomes only one of the criteria upon which diagnosis is based.

The thesis that multiple myeloma tissue is derived from a dysplastic line of plasma cells originating in the bone marrow is supported by our studies. All cases in this series are of the plasma cell type and plasmablasts, immature plasma cells, and dysplastic cells are described. A series of photo-micrographs (figs. 4 to 15) offers objective evidence tending to confirm this theory.

Our observations confirm the original findings of Snapper that large basophilic inclusion bodies may be demonstrated in the cytoplasm of myeloma cells obtained

* One patient with anemia due to chronic uremia revealed 10 per cent plasma cells in smears made from marrow bits when only an occasional plasma cell was seen in direct smears.
from bone marrow aspiration, in patients with multiple myeloma on a low animal protein diet, following treatment with stilbamidine. These basophilic bodies were not present prior to treatment. The two patients in our series who showed the granules obtained relief of pain. One patient was on a low animal protein diet while the diet of the second was not restricted. The latter patient showed typical basophilic granulation and a reduction in the percentage of plasma cells in marrow aspiration smears, and at the same time had a definite enlargement of osteolytic lesions in his skull. This fails to confirm the observation of Snapper that a low animal protein diet is essential for the production of basophilic granulation in the myeloma cells. The supposition that relief of pain is produced by an arrest of myeloma cell proliferation is also not substantiated. Complete failures to relieve pain or produce basophilic granules in the myeloma cells were recorded in three of our series of patients who had hyperglobulinemia. One was on a nonrestricted diet, and one received two courses of stilbamidine, the first without and the second with a low animal diet. The third patient was on a low animal protein diet.

Reactions to treatment with stilbamidine were transient except in one patient (case 3). He developed a trigeminal neuropathy which was still causing a severe burning sensation in his face after six months of observation. No dissociation of sensation occurred. Snapper reported an incidence of 10 cases of trigeminal neuropathy in a total of 18 patients treated with stilbamidine, and explained the mechanism as due to toxic degeneration of the principle sensory nucleus of the trigeminal nerve. This caused severe and persistent itching which was disabling in character in only one of his patients. This subjective symptom ultimately disappeared in all of his patients. The objective findings of dissociated anesthesia were persistent.

Summary

1. The value of bone marrow aspiration in the diagnosis of multiple myeloma was confirmed and discussed. This procedure should be utilized in all patients suspected of having this disease.
2. The importance of a reliable technic of studying bone marrow obtained by aspiration was stressed, and a method emphasizing certain important features described in detail.
3. The theory that multiple myeloma is derived from a dysplastic line of plasma cells originating in the bone marrow was supported by this study.
4. The original observation of Snapper has been confirmed, that after treatment of multiple myeloma patients with stilbamidine, large basophilic inclusion bodies can be demonstrated in the cytoplasm of a majority of myeloma cells obtained from bone marrow aspiration and stained by Wright's stain. This was produced on a nonrestricted as well as on a low animal protein diet.
5. Relief of pain was produced in two out of five patients with multiple myeloma treated with stilbamidine. One patient who was relieved of pain was on a low animal protein diet while the diet of the second was unrestricted. In both cases basophilic inclusion bodies appeared in the myeloma cells following treatment. Stilbamidine therapy failed to alleviate pain or to produce basophilic granulation in the myeloma cells in three patients who exhibited hyperglobulinemia.
6. Relief of pain and vertigo occurred in one patient treated with stilbamidine while osteolytic lesions were observed to enlarge by roentgenological examination.

7. Trigeminal neuropathy with severe discomfort still continued six months following treatment in one patient.

8. An arrest or remission in the course of the disease was not obtained in five cases of multiple myeloma treated with stilbamidine.

REFERENCES


RECENT STUDIES OF MULTIPLE MYELOMA: STErnAL AND RIB
PUNCTURE AND THE RESULTS OF TREATMENT WITH STILBAMIDINE

SIMON PROPP, L. WHITTINGTON GORHAM and SAMUEL KANTOR