

CHEMOTHERAPY OF MULTIPLE MYELOMA; THE USE OF ANTIMONY

(PRELIMINARY REPORT)*

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MULTIPLE myeloma is a neoplastic, infiltrative disease of the bone marrow. The histological origin of the myeloma cells, whether of lymphatic, myeloid or other origin, is still a matter of discussion. Nor is the position of multiple myeloma among other neoplastic diseases, in particular its relationship to leukemia, sufficiently clarified. It shares with the other neoplastic diseases both the mystery of its origin and the lack of any effective treatment.

However, there is one characteristic which distinguishes myeloma from other neoplastic diseases, namely the peculiar abnormalities in its protein metabolism. The main biochemical features of multiple myeloma are the Bence-Jones proteinuria, discovered as early as 1845 only a few years after the first case of multiple myeloma had been described, and the hyperproteinemia found a half century later and finally identified as being essentially due to hyperglobulinemia. This hyperglobulinemia is the basis for many laboratory tests characteristic of multiple myeloma, such as rouleaux formation, rapid sedimentation rate of red cells, formol gel test, etc.¹

In addition to multiple myeloma, there are at least 3 other diseases likewise characterized by the presence of hyperproteinemia and hyperglobulinemia, but unlike multiple myeloma these diseases are of well established etiology. They are kala-azar, lymphogranuloma venereum, and schistosomiasis. These diseases have varied etiologic agents: protozoan Leishman-Donovan bodies in the first instance, a filtrable virus in the second, and metazoan helminthes in the third.

Despite the wide range of etiologic agents in these diseases, they have two common denominators: (1) the frequent occurrence of hyperglobulinemia, and (2) the favorable response to the same therapeutic agent, namely to antimony compounds.²

The therapeutic action of antimony has not been clearly established. However, since its activity is largely confined to the above mentioned diseases, notwithstanding their various etiological agents, we may assume that its effects are linked in some way with the biochemical characteristics which the 3 diseases have in common, that is, the hyperglobulinemia.

Based on the assumption that antimony acts on diseases with hyperglobulinemia, it was a natural step to assume that the drug might be found therapeutically effective in another disease with hyperglobulinemia, namely in multiple myeloma.

The experimental treatment of multiple myeloma with antimony was begun

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in the spring of 1943 and has been continued with some interruption to the present. Early in 1945 Snapper began to treat patients with multiple myeloma with stilbamidine, another drug recently shown to be effective in kala-azar, also on the basis of the occurrence of hyperglobulinemia in both diseases.³

The dosage and the preparations used by us have been repeatedly changed during the work. At first we used preparations of tartar emetic which, because of its toxicity, could be administered only in small doses; later less toxic antimony compounds were used and at present neostibosan is being given. A full course of treatment consists in the injection intravenously of 15 Gm. of the latter preparation in divided doses of 0.3 Gm. given at suitable intervals. Special precautions, including frequent urine and blood examinations, are necessary in cases showing renal involvement.

This paper is a preliminary report based on our experience with this method of treatment on 7 patients with multiple myeloma. In evaluating the influence of antimony on multiple myeloma it is necessary to realize the possibility of occasional spontaneous remissions in this disease, as well as of a prolonged course over a period of years with a relative freedom from symptoms, and the occasional sensitivity to radiation with amelioration of pain in some cases.

This occurred in one of the first patients (case no. 2) treated with antimony, who, in the period before treatment showed a very prolonged course with frequent symptomatic remissions including spontaneous healing of pathological fractures. At the time treatment was instituted, multiple painful external tumors were present over the clavicle, ribs, and arms. The first course of antimony thio-glycollamide was followed by a course of x-ray therapy, since the latter had relieved pain on previous occasions. The visible tumor masses regressed promptly following this combined treatment. However, similar lesions soon appeared at different sites of the skeleton, some of them only to disappear again following another course of x-ray therapy; the pain was also greatly relieved.

The remarkable radiosensitivity of the tumor masses seen in this particular patient following a course of antimony treatment could not be attributed with certainty to the drug. This case, already briefly reported,⁴ will be the subject of a separate publication in which the difficulties in evaluating treatment of multiple myeloma will be discussed at length.

The results obtained in another patient (case no. 4) were more conclusive. Large external masses over the anterior and posterior surface of ribs were present together with numerous punched out areas in the bones. The visible tumor masses had been noticed by the patient about 2 years prior to admission, and were progressively increasing in size. The patient received six x-ray treatments, but without relief of pain or reduction in the size of the tumor masses. On admission to the hospital in 1945, a first full course of neostibosan treatment, followed by x-ray therapy applied to the site of the tumor masses, was given. At the completion of neostibosan injections, and before further x-ray treatment, the visible tumors were found to be decreased in size, and they completely disappeared soon after the subsequent x-ray therapy. To date, 8 months after this treatment, no external tumor masses have reappeared.

Examinations of the bone marrow were repeated at frequent intervals, both during and after the course of treatment; both sternal and iliac bone aspirations were studied. We are aware of the fact that numerical variations of the plasma cell content of bone marrow aspiration may occur on repeated examinations, even when simultaneously performed at different sites. It is nevertheless interesting to

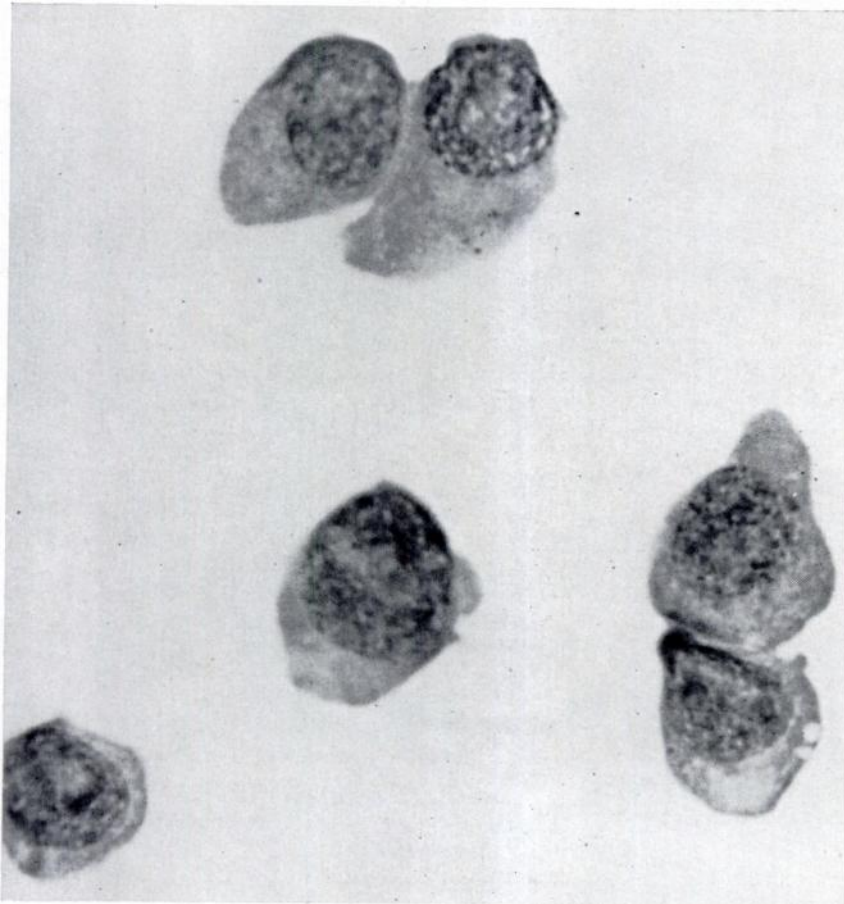


FIG. 1. Case 4. Plasma cells in the bone marrow after ten injections of 0.3 Gm. neostibosan. Occasional granules are seen in the plasma cells.

note that following antimony treatment the percentage of myeloma cells in the differential count was frequently found to be diminished, and the number of normal myeloid and erythroid elements increased. Another index of the degree of myelomatous infiltration of the bone marrow would be the degree of anemia which is almost certainly due to displacement of the hematopoietic tissue by the myeloma cells. The observations concerning the influence of antimony treatment on the anemia of multiple myeloma are now being conducted.

Changes in the morphologic appearance of the plasma cells were more significant than the quantitative variation. The appearance of metachromatic, basophilic granulation in the cytoplasm of myeloma cells in 2 of the 7 cases treated with antimony, constituted the most conspicuous change. These granules were seen in greater numbers only after repeated courses of antimony injections, and were usually lacking before completion of the full course of treatment. The photomicrographs shown in figures 1 and 2 reproduce the granulated myeloma cells in a

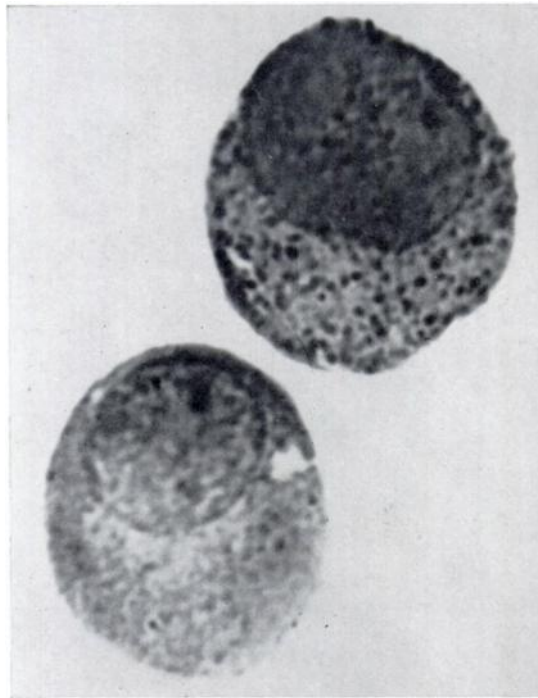


FIG. 2. Case 4. Plasma cells in the bone marrow after two courses of neostibosan injections. Plasma cells containing numerous granules.

patient receiving antimony (case no. 4). It is noteworthy that no other bone marrow elements were affected in this way by the antimony treatment.

In some cases, the plasma cells, following a course of antimony, assumed an appearance resembling that of a medium size lymphocyte.

No definite changes were observed in the hyperglobulinemia in patients receiving antimony.

The case (no. 6) of M.K., a 53 year old woman will be cited as an example of a striking relief of pain following combined antimony and radiotherapy. This patient's chief complaint was very severe pain in the back for the past year. The diagnosis of multiple myeloma was made on the basis of bone marrow findings and x-ray studies of the bones; there was also a moderate hyperglobulinemia,

but no Bence-Jones proteinuria. The patient was given (October 11, 1946 through October 26, 1946) a full course of neostibosan, followed by x-ray treatment. Progressive relief of pain was seen in the course of this treatment. This patient, who was bedridden and unable to turn in bed, is now being fitted for a brace which will enable her to get out of bed; the analgesics which the patient was receiving are being withdrawn.

In general, our observations on antimony are strikingly similar to those of Snapper, using stilbamidine, a drug containing no antimony.

Brief summaries of the case reports of the 7 patients treated with antimony follow:

CASE NO. 1

Patient R. S. (Hospital admission no. 362573) was a 58 year old woman, first seen on August 6, 1943. She complained of low back pain of 2 months' duration. Physical examination revealed tenderness over the spinous processes of L4 and L5 and the upper sacrum. The blood count showed hemoglobin 31 per cent, red blood cells 1,900,000 and white blood cells 6,100 per cu. mm. The differential count was normal except for an occasional atypical plasma cell which contained one or more nucleoli. The possibility of plasma cell multiple myeloma was at once suggested by the appearance of these cells. Sternal marrow aspiration confirmed the diagnosis of myeloma, revealing 56 per cent plasma myeloma cells.

Other blood studies were: urea nitrogen 64 mg. per 100 cc., phosphorus 5 mg. per cent, calcium 10.4 mg. per cent, total protein 7.3 Gm. per cent, globulin 4.4 Gm. per cent, alkaline phosphatase 4 King-Armstrong units, sedimentation rate 18 mm. in 8 minutes. The urea clearance was 11 per cent. The blood serum showed an immediate positive formol gel reaction. Using the ordinary heat test at pH 5 the urine was found to contain large quantities of Bence-Jones proteoses and to be consistently free of albumin. There were occasional hyalin and granular casts. Urinary concentration tests showed a specific gravity of 1.012 to 1.015. Roentgenographic examination of the skull showed numerous circular punched out lesions throughout the bones of the calvarium. There were numerous areas of bone destruction of the lower ribs, lumbar vertebrae, and pelvis and a pathological fracture of the body of the first sacral vertebra.

On August 20, 1943 and on the two following days the patient received intravenous injections of 10 cc. of 1 per cent tartar emetic. The injections had to be stopped because of a shocklike reaction following the third injection. The patient stated that during the few weeks following the injections, she was able to move more freely and perform some housework. However, in the last week of September she suddenly developed signs of paresis of the low extremities and severe backache. She was admitted to Mount Sinai Hospital where collapse of several lumbar vertebrae was found with evidence of spinal compression. The course was progressively downhill and she died on October 1, 1943. A postmortem examination was not obtained.

CASE NO. 2

Patient A. W. was a 17 year old boy (Hospital admission no. 105534) with a history of pain in the left hip for 3 years. In June 1942 he sustained a pathological fracture of the left hip. The diagnosis of multiple myeloma was made on the basis of bone marrow studies which showed the presence of 28 per cent plasma cells. The diagnosis was substantiated by the presence of multiple punched out areas in x-ray films of the skull and ribs and long bones. Urine examinations showed the presence of Bence-Jones protein. The blood proteins were normal, as well as blood phosphorus, calcium and phosphatase.

Biopsy of a lesion in the skull, localized in the x-ray, was performed on March 8, 1943. The pathological report was plasma cell myeloma.

In 1944 there were noted, in addition to the bone lesions seen in the x-ray films, multiple tumor masses over the clavicle and the ribs; also on the anterior surface of the ribs and over the sternum. The lesions ranged from pea size to the size of a large fist. It was noted that some of these lesions regressed spontaneously.

Patient received intensive radiotherapy to the various affected areas.

The first course of x-ray treatment at Montefiore Hospital was given to the lesion in the left tibia. He received 6250 R to that area given through 3 different portals. Subsequently, he received similar treatments to the various affected parts including the skull, right hip, right upper arm, right forehead, right mastoid area, right clavicle, left clavicle, left knee, etc. Marked relief of pain was observed, although x-ray studies showed definite progression of the lesions. He also received radiotherapy to the left shoulder, chest, lower back, lower abdomen, and right thigh, all with considerable relief of pain but with no change in the appearance of the lesions on x-ray.

Treatment with antimony was started on April 25, 1944. Only two intravenous injections of 5 cc. of 1 per cent tartar emetic were given. These were discontinued because of a shocklike reaction. Antimony was resumed on September 15, 1944 with daily intravenous injections of 20 cc. of 5 per cent antimony thioglycollamide continued through October 9, 1944. This course of treatment was followed by another course of radiotherapy. A rapid regression of a huge mass over the sternum and of the smaller tumors over the clavicles was noted after this combined treatment. However, in view of the spontaneous regression of some other visible tumors, previously observed in this patient, the value of the treatment was difficult to appraise.

In the fall of 1944, the patient developed signs of uremia, spinal compression with appearance of a neurogenic bladder, and pylonephritis developed. The patient died in December 1945 of uremia. Autopsy showed multiple myeloma, with myeloma kidney.

CASE NO. 3

Patient A. H. (Hospital admission no. 39350), a 64 year old male, was admitted to the hospital in November 1944 for pain in the back and right leg of two months duration. Physical examination was negative except for percussion tenderness over the lumbar spine and over the right thigh. The diagnosis of multiple myeloma was made on the basis of sternal marrow aspiration which revealed 51 per cent plasma myeloma cells in differential count. X-rays of the bones showed extensive destruction of the L1 and L2 vertebrae and marked degree of general decalcification of the skeleton. Blood studies showed: total serum protein 12.4 Gm. per cent, albumin 3.4 Gm. per cent, globulin 9.0 Gm. per cent, calcium 10.2 mg. per cent, phosphorus 4.3 mg. per cent, alkaline phosphatase 0.2 Bodansky units, hemoglobin 10.5 Gr. per 100 cu. cm., red blood count 3,500,000 per 1 cu. mm., white blood count 5,500 with a normal differential. Urine examination showed traces of albumin but was negative for Bence-Jones protein.

Patient was given 4 injections of 5 cc. of 1 per cent tartar emetic intravenously (May 30, May 31, June 2, June 3, and June 4, 1945). Because of shocklike reaction which followed, these were discontinued. Radiotherapy was then given over lumbo-sacral area and over the right mid-thigh. In July marked relief of pain was noted. The serum protein at that time showed: total protein 7.0 Gm. per cent, albumin 2.9 Gm. per cent, globulin 2.1 Gm. per cent, alkaline phosphatase 3.7 Bodansky units. However, in October 1945 the patient developed pneumococcal pneumonia of the entire left lung to which he succumbed in spite of intensive penicillin treatment. Autopsy revealed plasma cell myeloma involving bone, spleen and lymph nodes.

CASE NO. 4

Patient D. C. (Hospital admission no. 110504), a 47 year old male, was admitted in April 1946 with a history of pain in the lower left chest for the last 2 years and pain in both hips for the last year with a loss of 25 pounds during this time; also progressive general weakness.

About 2 years ago the patient noted the appearance of two masses in the outer part of the left chest and in the left axillary region which have been progressively increasing in size in spite of x-ray treatments given about a half year ago. On admission the mass in the left axilla measured 10.5 cm. length, 8 cm. wide and 2 cm. deep. The mass over the left chest measured 7 cm. x 6.5 cm. x 3 cm. Blood count showed: hemoglobin 60 per cent, red blood count 3,150,000, white blood count 9,800, normal differential. Blood chemistry determinations: total serum protein 11.8 Gm. per cent, albumin 3.1 Gm. per cent, globulin 8.7 Gm. per cent, calcium 10.6 mg. per cent, phosphorus 3.8 mg. per cent, alkaline phosphatase 6 Bodansky units, urea nitrogen 8.9 mg. per cent. The urine was negative for Bence-Jones protein, sugar and albumin. X-ray studies showed multiple areas of destruction in the frontal and parietal bones of the skull, and bone destruction in the eighth and tenth rib and pathological fracture of ribs in the axillary region. Shadows

of the 2 above mentioned visible masses were seen. There was also compression of the fifth lumbar vertebra. Sternal marrow aspiration showed 38 per cent plasma myeloma cells.

On April 5, 1946 the patient was started on a course of neostibosan treatment consisting of a daily intravenous injection of 0.3 Gm., until the total amount of 15 Gm. was reached. On May 17, on completion of the first course of treatment the visible tumors had decreased in size measuring: 4.5 cm. x 4.0 cm. x 0.5 cm. over the left posterior thorax, and 6.5 cm. x 8.0 cm. x 3.0 cm. in the left axilla. A course of neostibosan treatment was repeated twice again, in May and August 1946. The last treatment was followed by a course of radiotherapy. At the end of August 1946, following this combined neostibosan and x-ray treatment both visible tumor masses had completely disappeared. At that time the patient stated that there was improvement of his general condition and considerable relief of pain. Urine had been negative for Bence-Jones protein throughout the patient's stay in the hospital. Blood urea nitrogen after treatment on May 17 was 10 mg. per cent. The serum protein showed some decrease.

TABLE 1.—Serum Protein in Case 4

Date	Total Protein	Albumin	Globulin
	Gm.	Gm.	Gm.
May 17, 1946.....	9.9	3.1	6.8
July 3.....	8.3	2.3	5.8
Aug. 14.....	10.6	3.7	6.9
Oct. 23.....	7.1	2.1	4.9
Jan. 20, 1947.....	7.3	2.0	5.3

Bone marrow studies repeated on August 14, 1946 and October 26, 1946 showed a diminished number of plasma cells (16 per cent and 23 per cent respectively). Basophilic granulation was seen in the cytoplasm of the plasma cells.

In September 1946 the patient was allowed to walk but sustained pathological fracture of the hip and was immobilized in bed with application of traction. This patient is still in the hospital under observation.

CASE NO. 5

Patient M. W. (Hospital admission no. 110282), a 54 year old colored woman, was first seen on June 15, 1946 with a history of numbness in the hands for 2 years followed by pain in the back, elbows, knees and wrists. X-ray examination of the bones showed areas of bone destruction in both scapulae and in several of the ribs, clavicles, humeri and both radii. The urine test for Bence-Jones protein was positive. Blood chemical determinations on admission showed: total protein 7.0 Gm. per cent, albumin 5.0 Gm. per cent, globulin 2.0 Gm. per cent. The hemoglobin was 10 Gm. per 100 cc., red blood count 3,120,000 per cu. mm. and white blood count 6,000 per cu. mm., with normal differential. Bone marrow studies were characteristic of multiple myeloma, showing 20 per cent plasma cells.

Patient was given a course of neostibosan from June 14 through July 7. On August 30, 1946 another course of neostibosan treatment was started and was followed by a course of radiotherapy. By November 5, 1946, the patient's back pain was greatly relieved, but she continued to complain of stiffness in the hands and wrists. On July 12, 1947, the total blood protein was 5.8 Gm. per cent with albumin 3.2 Gm. per cent and globulin 2.6 Gm. per cent.

The patient is still in the hospital.

CASE NO. 6

Patient M. K. (Hospital admission no. 110969), a 53 year old woman, was admitted on August 22, 1946 for complaints of severe pain in the lower back and right thigh of 18 months duration and inability to walk since November 1945.

Physical examination revealed gibbus of D-10 and percussion tenderness over lower thoracic spine

and iliac crest. X-ray studies showed numerous small radiolucent areas throughout the calvarium, partial collapse of upper cortical plate L1, pathological fracture of L3.

Laboratory examinations showed total serum protein 7.5 Gm. per cent, albumin 3.9 Gm. per cent, globulin 3.6 Gm. per cent, hemoglobin 11.5 Gm. per 100 cc., red blood count 3,700,000 per cu. mm., white blood count 5,000 with normal differential. Bone marrow aspiration showed 50 per cent plasma cells typical of multiple myeloma. Urine was negative for Bence-Jones protein.

A first course of neostibosan was given from September 3 to September 20; a second course of neostibosan from October 11 through October 26, 1946, followed by radiotherapy. At the start of treatment, the patient was completely immobilized and unable to make the slightest movement because of pain. By November 26, 1946 the patient had considerable relief of pain; by December 26 she was able to move about freely in bed. By mid-February 1947, opiates and demerol previously necessary for relief of pain could be withdrawn. The patient is learning to walk with the aid of Taylor's brace. Repeated bone marrow aspiration of January 15, 1947 showed 28 per cent plasma cells.

Patient is still in the hospital.

CASE NO. 7

Patient A. C. (Hospital admission no. 11030), a 70 year old woman, was admitted on September 6, 1946 for pain in the neck of one year's duration, for the last months becoming so severe as to totally incapacitate the patient; also pain in the right thigh. The neck was extended and attempts at flexion met with cries of pain.

Laboratory studies showed: hemoglobin 35 per cent, red blood count 1,500,000, white blood count 5,000, with normal differential. Total serum protein 9.2 Gm. per cent, albumin 4 Gm. per cent, globulin 5.2 Gm. per cent, urea nitrogen 34 mg. per cent.

Bone marrow studies showed 58 per cent plasma cells in the sternal aspiration and 75 per cent in iliac crest aspiration. The urine was positive for Bence-Jones proteins. Because of severe pain in the neck a plaster collar was applied on September 16. Neostibosan treatment was started at the same time. A very marked relief of pain was obtained in a few days, so that the collar was removed. The pain in the neck has failed to recur. The pain in the back has also disappeared. The relief of the pain was so marked that no radiotherapy was given.

Because of persistent anemia with a hemoglobin below 50 per cent several blood transfusions were given to this patient.

Another course of neostibosan treatment was given from January 7, 1947 through January 22, 1947 at which time the patient showed difficulty in hearing which persisted for a month after the treatment had been stopped. On January 31, 1947, determinations of blood showed: total protein 7.1 Gm. per cent, albumin 3.1 Gm. per cent, globulin 3.5 Gm. per cent, urea nitrogen 21 per cent.

SUMMARY

This is a preliminary report on the treatment of 7 patients with multiple myeloma with antimony compounds. The therapeutic trial was based on the fact that multiple myeloma is frequently associated with hyperglobulinemia, a characteristic shared with other diseases in which antimony had been found therapeutically effective.

The results obtained thus far are insufficient to warrant conclusions, although they indicate a possible influence of antimony on myeloma tissue. This influence is seen mainly as an increased radiosensitivity when patients are subsequently treated with x-rays.

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