

# blood

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## ON THE INFLUENCE OF STILBAMIDINE UPON MYELOMA CELLS

By I. SNAPPER, M.D., AND B. SCHNEID, M.D.

ONE of us<sup>1</sup> has reported that in certain cases of multiple myeloma, considerable improvement of the clinical condition can be obtained by intravenous or intramuscular injections of stilbamidine (diamidino-stilbene di-isethionate).<sup>\*</sup> It is necessary that the patient follow a diet low in animal protein. A favorable result has been observed in 9 out of 10 patients. During this treatment with stilbamidine, histological changes can be observed developing in the myeloma cells.

The basophilic cytoplasm of myeloma cells is usually vacuolated and, on the whole, is free of granules or other inclusions. From time to time a few azurophilic granules and tiny azurophilic rods, resembling Auer bodies, are found. Exceptionally these azurophilic inclusions grow to a larger size.

During a course of injections of stilbamidine large basophilic granules appear in the cytoplasm of the myeloma cells which are without difficulty visualized in bone marrow smears by Wright or Giemsa stains. These granules have first been observed after the treatment has lasted 3 to 4 weeks. The amount of stilbamidine administered up to the time when the granules appear has varied between 1875 and 3600 mg. In the beginning the granules have a faint resemblance to swollen cocci. When the treatment is continued the granules become confluent, so that after several weeks of treatment large deeply blue precipitates, resembling inclusion bodies, are found in the cytoplasm of most myeloma cells (fig. 1).

Supravital staining of the myeloma cells of untreated myeloma cases with Janus green and neutral red reveals the presence of a considerable number of green staining mitochondria. In the myeloma cells of myeloma cases treated with stilbamidine the cytoplasm contains not only green mitochondria but also large red globules. Although it cannot be proved that these red granules visualized by the vital stain are identical with the blue granules found in the Wright stain, it may be stressed that both types of granules develop at the same time.

The cytoplasm of myeloma cells stains deeply red with pyronine if Unna's phenol methylgreen pyronine stain is used. In the cytoplasm of the untreated myeloma cases this stain does not reveal the presence of any granules. In the patients in whom stilbamidine treatment has given rise to the development of the granules mentioned above, the Unna stain shows the presence of bright red granules in the red cytoplasm.

The granules which develop in the myeloma cells under influence of the stilbamidine treatment are not metachromatic because they do not stain with Unna's polychrome methylene blue. The granules do not show positive oxydase reactions.

In 7 out of 9 cases of multiple myeloma treated with stilbamidine, these inclusion bodies were consistently present and could be found in 80 to 90 per cent of the myeloma cells of the bone marrow. In none of the other bone marrow elements

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<sup>\*</sup> Manufactured by May and Baker, Dagenham, London.

could comparable granules be demonstrated. In one of these 7 patients myeloma cells could be found in the peripheral blood. During the stilbamidine treatment these cells also presented the basophilic granules mentioned.

It is easy to distinguish these basophilic bodies from the large azurophilic inclusions which exceptionally are found in the myeloma cells of untreated myeloma patients. The azurophilic inclusions always appear reddish blue in Wright or Giemsa preparations. They do not take the pyronine stain, and they cannot be visualized by neutral red in the vitally stained preparations.

In highly interesting *in vitro* experiments, Kopac<sup>2</sup> demonstrated that stilbamidine dissociates protamine ribonucleate and releases the protamines from these compounds. This mechanism may well be responsible for the changes visualized in the

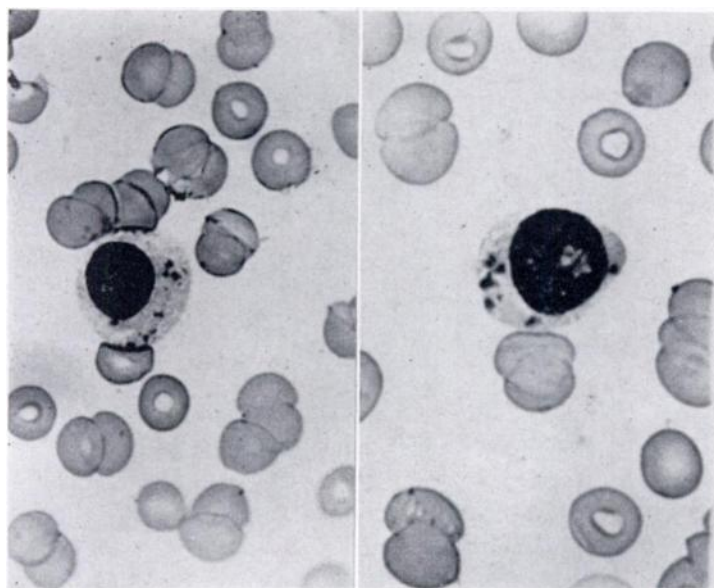


FIG. 1. BONE MARROW SMEAR OF A PATIENT WITH MYELOMA TREATED WITH STILBAMIDINE

Myeloma cells contain basophilic inclusions which are stained deeply blue with Wright stain.

myeloma cells under influence of stilbamidine. Evidence available indicates that ribose nucleic acid forms one of the main constituents of the basophilic inclusion bodies, described above.\*

#### SUMMARY

Injections of stilbamidine cause morphological changes in myeloma cells. During this treatment large basophilic granules appear in the cytoplasm which show a tendency to become confluent. These granules stain red with pyronine and can be

\* As far as we can see, the myeloma cells containing inclusion bodies do not deteriorate ultimately. However, in view of the fact that these bodies represent precipitates of ribose nucleic acid, the metabolism of the cell must have been thrown out of gear. Personally, we have the feeling that only the extension of the myeloma areas is inhibited. This would explain the cessation of pains. An actual cure, at least for the time being, we have not observed.

visualized in the supravital stain with neutral red. One of the main constituents of these inclusions consists of ribose nucleic acid.

These morphological changes seem to be limited to myeloma cells, since in none of the other bone marrow elements do comparable granules or inclusions develop.

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