Approximately 40% of the infants admitted to the unit required intravenous therapy. This could have been administered only in a hospital with the necessary facilities. The success of treatment is therefore dependent on: (1) recognition of dehydration in its early stages and admission to hospital of all but the mildly dehydrated; (2) correct assessment of the degree of dehydration in relation to the requirements of treatment; (3) a team of trained and experienced staff to carry out the necessary treatment. These requirements are best fulfilled by the establishment of self-contained hospital units for the treatment of enteritis.

The recognition of dehydration in its early stages is within the province of all medical practitioners, and the need for early treatment should be more widely appreciated. The assessment of the degree of dehydration and the treatment required in each case is essentially dependent on clinical judgment gained through practical experience. The successful application of these methods of treatment depends upon the training of the medical and nursing staff of the unit.

The figures shown in Table III lend support to this view. The fall in fatality rates after the first six months of 1945 appears to be directly related to the training of the nursing staff, since the technique of treatment was the same throughout the two years and the degree of severity of the cases did not vary from one year to the next. The distribution in age groups did not vary significantly in successive periods, nor during the first six-months period was there any preponderance of the younger age groups, in which a higher fatality rate might be expected. Owing to necessarily frequent changes of staff, in approximately six months most of the nurses in the hospital had worked in the enteritis unit and had become familiar with the routine management and treatment established there. Thereafter, although shortage of staff became a serious problem, all the available nurses were acquainted with the nursing and treatment of the dehydrated infant and were able to maintain the high standard of care necessary for these babies.

In this series 112 infants relapsed with dehydration. Since the nature of the infecting organism or organisms in diarrhoea and vomiting is not yet known, it is not possible to say what proportion of these relapses was due to cross-infection or to re-infection. The possibility of such an occurrence, especially in an open ward, must, however, be borne in mind. The observations in a previous series (Alexander and Eiser, 1944) are of interest in this connexion. In that series the infants were nursed in two different wards—an "open" barrier ward and a single-cell barrier ward. The technique of nursing and treatment were identical, and the numbers of admissions and dehydration rates on admission were the same for both wards. Yet the relapse rate in the open barrier ward was four times as great as that in the single-cell ward.

It seems advisable, therefore, that bed-isolation and barrier nursing should be rigidly enforced in enteritis units, which should, whenever possible, be accommodated in wards of single rooms or cells. By the establishment of such units, staffed by trained medical officers and nurses, much may be done to reduce the number of infants still dying of diarrhoea and vomiting.

Summary

The organization of a hospital unit for enteritis of infants is described and the treatment is outlined.

The results of treatment for the years 1945 and 1946 are detailed: 456 infants under the age of 1 year were treated in the unit during this period; 258 (56.6%) of these infants were dehydrated during the course of their illness. There were 22 deaths, giving a case mortality of 4.8% for all cases, or 8.5%

for infants who were dehydrated. There were no deaths among infants who were not dehydrated. Parenteral infections were found on admission in 238 cases (52.2%).

The association between parenteral infections and dehydration is low, and this series does not support the view that parenteral infections are a major factor in the causation of diarrhoea and vomiting. The need for careful search for parenteral infections is, however, stressed from the point of view of treatment.

The importance of prevention or early correction of dehydration, the necessity for intravenous therapy in severe cases, and the need for prevention of cross-infection are emphasized. This implies the provision of adequate facilities and a staff of medical officers and nurses experienced in the technique of barrier nursing and the treatment of dehydration in infants.

It is suggested that these requirements are best fulfilled by the establishment of self-contained hospital units for the treatment of enteritis.

My acknowledgments are due to Dr. E. H. R. Harries (late medical superintendent of the North-Eastern Hospital) and to Dr. Robert Swyer, acting physician-superintendent, for facilities to carry out this work. I am greatly indebted to the resident medical officers and to the nursing staff for their enthusiastic co-operation and to Mr. L. G. C. Maslen for all laboratory work. I wish to thank Mr. B. Benjamin, statistician to the L.C.C. Public Health Department, for help with the statistical analyses.

REFERENCES

- Alexander, M. B., and Eiser, Y. (1944). *British Medical Journal*, **2**, 425.
Campbell, R. M., and Cunningham, A. A. (1941). *Arch. Dis. Childh.*, **16**, 211.
Gamble, J. L. (1947). *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*. Harvard University Press, Cambridge, Mass.
Garrod, A. E., Batten, F. E., and Thursfield, H. (1947). *Diseases of Children*, 4th ed., edited by D. Paterson and A. Moncrieff, Vol. I. Arnold, London.
Harries, E. H. R., and Mitman, M. (1947). *Clinical Practice in Infectious Diseases*. 3rd ed. Livingstone, Edinburgh.

MULTIPLE MYELOMA TREATED WITH STILBAMIDINE AND PENTAMIDINE

BY

ANGUS E. BREWER, M.R.C.S., L.R.C.P.

Clinical Pathologist, Hampstead General Hospital

Von Rustizky (1873) was the first to describe the disease of multiple myeloma, the name of plasma-cell myeloma being proposed 27 years later by J. H. Wright (1900). Macintyre (1850) had already described a case of multiple bone tumour, calling it mollities ossium, which had a peculiar "animal matter" in the urine that became evident on gentle heating and disappeared on further heating. He sent the urine to Bence-Jones (1848) for examination, and the substance subsequently became known as Bence-Jones protein. About the same time Dalrymple (1846) gave a clear description of the bony changes in a case he reported on as mollities ossium.

Life insurance tables give the incidence of multiple myeloma as 0.03% of all malignant growths or 3% of all bone sarcomas, but recent collections of cases published suggest that the figures may be higher. Thus Batts (1939) found 40 cases in 200 primary malignant tumours of bone, and Bayrd and Heck (1947) saw 18 in a period of six months. Improved methods of pathological investigation and the attention drawn to the disease by publications have no doubt been largely responsible for the increased number of cases diagnosed.

Multiple myelomatosis is usually described as a fatal disease of middle life, occurring twice as often in males as in females and characterized by multiple tumours growing from the marrow and eroding the bone in a characteristic

manner. It is quite apparent, however, that the condition (see Cases 1, 2, and 6 below) may present as a more diffuse pathological process of the marrow without tumour formation and without the typical areas of rarefaction in the bones (Bayrd and Heck, 1947).

All authorities agree that most cases are not recognized until in a fairly advanced stage of the disease and that the clinical manifestations are very variable and entirely non-specific in origin, although some form of pain as a presenting symptom is fairly constant. Batts found a palpable tumour in 45%, characteristic x-ray pictures in 60%, Bence-Jones protein in 50%, and circulating myeloma cells in 3% of 40 cases.

Morissette and Watkins (1942) stress the importance of the blood count as an aid to diagnosis. In 56 cases out of 100 they found myeloma cells in the peripheral blood, and stated that anaemia with eosinophilia and lymphocytosis was frequent. They made particular mention of the apparent "greasiness" of the blood smears, presumably due to the increased serum globulin. Sternal puncture appears to offer the most reliable early information, and increase in the raised serum globulin is valuable corroborative evidence.

Until recently treatment, which consisted mainly of x-ray therapy, was entirely palliative, being an attempt to lessen the continual pain. Geschickter and Copeland (1936) state that the average period of survival is two years and that it is uninfluenced by treatment. Ghormly and Pollock (1939) gave the average duration after diagnosis as one year. In 1945 Snapper and his colleagues began treatment with stilbamidine and pentamidine, drugs which had been used successfully since 1939 in the treatment of kala-azar (Adler and others, 1939). The trial of these drugs in the treatment of plasma-cell myeloma was provoked by the fact that in this disease, as in kala-azar, there is an increase in the serum globulin.

Snapper's results were encouraging. In all his cases the pain was favourably influenced. Of 15 patients treated up to January, 1947, 11 could walk on discharge from hospital, although relapses occurred and four have since died. The marked clinical improvement was accompanied by healing of fractures and some recalcification, although an anatomical cure of the disease was not obtained, as myeloma cells could always be found in the marrow.

Method of Treatment

Snapper's (1946a) method was followed, the patients being given a low-protein diet, as animal protein appears to block the effect of the drug. Stilbamidine hydrochloride (May and Baker) was used, made up in 0.15-g. ampoules as a yellow powder. Five millilitres of distilled water and 1 ml. of 2% "proctocaine" were added and the injection was given intramuscularly. The first injection contained 0.05 g. of stilbamidine; the second, containing 0.1 g., was given the following day, and subsequent injections of a full ampoule (0.15 g.) were given daily or every other day. Pentamidine was employed similarly in the terminal phases of two fatal cases (Nos. 4 and 5).

To combat vasomotor reactions 1/100 gr. (0.65 mg.) of atropine was dissolved under the tongue half an hour before the injections were given. Adrenaline, which was kept at hand in case of a severe fall in blood pressure, was never found necessary.

Case 1

A flabby, fat, short, pale-looking man aged 66 was admitted as a hypertensive with marked albuminuria and angina of effort and the probability of a recent coronary thrombosis when the systolic blood pressure fell from 200 to 130. His only complaint apart from anginal pain was of increasing weakness.

Blood examination showed a normocytic normochromic anaemia (Hb 45%) and a leucocyte count of 10,000, with 15% monocytes and a marked neutrophil shift (2% myelocytes, 3% juveniles). Since the cause of the blood changes remained obscure a sternal puncture was done, and this revealed 15% myeloma cells. The red cell series with normoblastic maturation was reduced (12%). The granulocyte series was also reduced (45.5%), and showed some atypical and microcytic forms, with an increase in eosinophils. Lymphocytes (18%) and monocytes (6.5%) were on the high side. Urine examinations, which had previously shown proteinuria with casts, now revealed a considerable quantity of Bence-Jones protein. Serum protein showed an increased globulin (4.29 g.), but the serum phosphatase and calcium were normal. Radiographs of the bones showed no characteristic picture, although a faint patchy rarefaction in the parietal bones could be made out.

A course of stilbamidine was begun, but after a total dosage of 0.45 g. over six days the patient died in uraemia.

Necropsy revealed a hypertrophied and dilated heart, very marked atheroma, and pronounced nephrosclerosis. In the sternum, ribs, and femur the marrow had a mottled appearance with areas of actual haemorrhage set in a background of reddish-pink hyperplastic marrow. There was no macroscopic evidence of bony erosion.

Case 2

A tall, well-built but thin man consulted his doctor about thrombosis in the left calf which followed unaccustomed exercise. He also confessed to increasing weakness and loss of colour over the previous nine months. He developed a fever without any definite signs and complained of some indefinite pains in the right side of the chest. Treatment with sulphadiazine and penicillin was without effect.

On admission to hospital he was found to have a normocytic normochromic anaemia (Hb 44%) and a marked leucopenia (1,000 per c.mm.), the neutrophils showing a pronounced degenerative and toxic shift. Sternal puncture disclosed 24% myeloma cells. The red cell series showing normoblastic maturation was relatively increased (23%); the granulocyte series (17.25%) was greatly reduced and showed numerous toxic and degenerative cells. Lymphocytes (26%) and monocytes (4%) were increased. The urine was normal at all times. The serum globulin was considerably raised (5.6 g.). The serum calcium and serum phosphatase were normal. A radiograph showed only some very indefinite areas of possible rarefaction in the skull.

Transfusions were given to raise the haemoglobin to 76% and a course of stilbamidine was begun. The patient died after 1.15 g. had been given over eleven days. Permission for a necropsy was not obtained.

Case 3

A well-built woman aged 62 complained of vague epigastric and subcostal pain, which was diagnosed as indigestion. A few months later she developed pain and stiffness of the right hip and right shoulder and was treated for rheumatism. A tender firm subcutaneous swelling then appeared over the right clavicle and a radiograph revealed a pathological fracture with the typical appearance of plasma-cell myeloma, such changes also being apparent in the pelvis and both scapulae.

The blood count showed a microcytic hypochromic anaemia (Hb 74%) and a leucopenia (3,200 per c.mm.). Sternal puncture revealed 15% myeloma cells. The red cell series (22%) showed normoblastic maturation with some microcytes; the granulocyte series (36.5%) was reduced, and the lymphocytes (17%) were on the high side. The serum globulin was considerably raised (4.3 g.). The serum calcium (11.8 g.) and the serum phosphatase (41 units) were also raised. The urine was normal.

A total of 4.5 g. of stilbamidine was given over three months with much improvement. The patient was able to get about for short distances and had very considerable relief of pain. There was some recalcification of the clavicular fracture, but the swelling remains unchanged. Radiographs showed no new lesions, although those in the pelvis seemed slightly larger. A dissociated trigeminal anaesthesia appeared six months after treatment started and three months after it ceased. It has now completely resolved.

Case 4

A well-built woman aged 42 consulted her doctor for an aching pain in the middle and lower parts of the back. It had been present for some months. She had recently noticed some breathlessness on exertion and an increasing weakness. Physical examination did not reveal any cause for these symptoms.

The blood count disclosed a macrocytic anaemia (Hb 41%) and a leucopenia (3,800 per c.mm.) due to a reduction in neutrophils, the latter showing a marked shift. There were 3% of myeloma cells in the blood smears, which were particularly "greasy." At the same time a routine radiograph of the chest showed an expanding and bone-destroying tumour of the seventh rib posteriorly. Radiographs of the rest of the skeleton did not reveal any other lesions. A sternal puncture showed 61.5% myeloma cells, with the red cell series (3%) and the neutrophil series (20%) greatly reduced, findings which indicated extensive and widespread involvement of the marrow in spite of the fact that only one small tumour was apparent on the x-ray film. The serum globulin (5.6 g.) and alkaline phosphatase (26 units) were considerably raised. The urine was normal.

After a transfusion a course of deep x-ray therapy was given without any improvement and the pain became worse. A total of 4 g. of stilbamidine was then given over a period of two months; this resulted in complete alleviation of pain, although the general condition continued to deteriorate and the urine now contained protein and casts. Bence-Jones protein was never found. Over the next two months 3.8 g. of pentamidine was given, but the patient went steadily downhill and died from complete aplasia of the marrow due to replacement by myeloma tissue and renal failure. There were generalized haemorrhages and purpura.

Case 5

A stocky well-built Greek complained in January, 1946, of intermittent epigastric and subcostal pain. He was investigated for peptic ulcer in hospital, but no definite diagnosis was made. Over the next year the pain became much worse, was more extensive and continuous, and was accompanied by increasing weakness.

In June, 1947, the blood count showed an extensive leucocythroblastic anaemia (Hb 36%) with 3% myeloma cells in the differential count. A sternal puncture revealed 86% myeloma cells, with very scanty red cell series (less than 1%) and white-cell series (13%). The serum globulin was raised (3.7 g.). The urine contained albumin, casts, and pus, although Bence-Jones protein did not appear until the very terminal stages.

A radiograph of the skeleton taken in June, 1947, showed advanced generalized myelomatosis with considerable collapse of the spine and many fractures. Support was given by a spinal jacket and he received a course of x-ray therapy without any improvement or relief of pain.

Stilbamidine therapy was started on Oct. 11 and totalled 8.6 g. over a period of three months, combined with transfusions, folic acid and iron, and penicillin for bronchopneumonia. Apart from improvement in the pain, the patient gradually became worse and died on Jan. 12, 1948. During the last two weeks 2.1 g. of pentamidine was given, also without improvement.

Necropsy revealed the ribs, sternum, and vertebrae to be almost entirely replaced by myelomatous tissue. In the long bones the marrow cavities were enlarged and filled with such tissue. There were very numerous pathological fractures. Sections and smears showed masses of myeloma cells, about 7% containing inclusion bodies (see below). Both kidneys showed pyelonephritis. Sections of the kidneys and the liver revealed myelomatous infiltration.

Case 6

A large well-built man aged 63 was admitted with generalized purpura, haematuria, epistaxis, melaena, and a right testicular haematoma. Generalized aching pains had been present for the last few months, had become worse in the last few weeks, and were now accompanied by some loss of feeling in the

hands and feet. Marked arteriosclerosis and some chronic bronchitis were present. The central nervous system, apart from rather weak jerks, showed no abnormality.

Blood examination showed a normal red cell count, a thrombocytopenia, a leucocyte count of 10,000 per c.mm., with a marked neutrophil shift and an eosinophilia (23%), and the presence of scanty myeloma cells. A sternal puncture revealed 9% myeloma cells with 4% plasma cells. The red cell series (14%) and the neutrophil series (31%) were reduced; eosinophils (18%) were increased. The serum globulin (7.8 g.) was greatly raised. The serum calcium (11.8 mg.) and plasma alkaline phosphatase (16.9 units) were slightly increased. The urine contained protein with some granular casts, but no Bence-Jones protein. A radiograph of the skeleton failed to show any abnormalities. A total of 4.2 g. of stilbamidine was given over two months. Clinical improvement was at first limited to disappearance of the purpura, but on completion of the treatment the patient could get about fairly well and said that his pains were not as bad.

Effects of Treatment

Clinical.—Case 3 has shown definite improvement with relief of pain and could get about for short distances twelve months after the diagnosis was made and approximately two years from the time of the first symptom. Case 6 has shown some improvement and is fairly mobile six months after the diagnosis and twelve months from the time of the first symptom. In Cases 4 and 5 the patients, who had very extensive marrow involvement before treatment, died after a period of some months without showing any improvement except for the relief of pain. In Cases 1 and 2 the patients died suddenly after a few injections of stilbamidine, the first from renal failure and the second from agranulocytosis.

On Myeloma Cells.—Snapper and his colleagues demonstrated the development of basophilic inclusion bodies in the cytoplasm of myeloma cells in patients receiving stilbamidine. These bodies appeared to be compounds of stilbamidine and ribose nucleic acid. It is suggested that the ribose nucleic acid becomes dissociated from its protein in the ribose nucleic complex and attached to the stilbamidine to form a substance which appears within the cytoplasm of the cell as deeply basophilic granules. These granules ultimately coalesce to form inclusion bodies. Such inclusion bodies were demonstrated in Cases 3, 4, and 6 (Figs. 1 and 3). Case 5 never developed them in spite of the

FIG. 1.—Two typical myeloma cells, one containing at least 12 well-formed inclusion bodies and the other three earlier and less distinct bodies. ($\times 850$.)

large dosage and the length of treatment. Cases 1 and 2 ended fatally before there was time for them to develop. A reduction in the number of myeloma cells was obtained by sternal puncture in Case 3 (15% to 3%) and in Case 6 (9% to 5.5%) (Table I). In both cases the small number of myeloma cells originally present in the peripheral blood disappeared.

Biochemical.—No improvements were obtained except in Cases 3 and 6 (Table II). In Case 3 the plasma globulin, the alkaline phosphatase, and the serum calcium returned to normal. In Case 6 they showed a fall towards normal.

Haematological.—Cases 3, 4, and 6 developed a very considerable eosinophilia in the early stages of treatment (74% in Case 6). In Case 4 this persisted until death, but in

TABLE I.—Myelograms

Case No.	Myeloma Cells			Plasma Cells	Reticulum Cells	Haematocytoblast	Red Cell Series				White Cell Series									
	Primitive	Typical	Multinuclear				Pro-erythroblast	Early Normoblast	Intermediate	Late Normoblast	Blast Cells	Neutrophils					Eosins		Lymphocytes	Monocytes
												Pre-myelocyte	Myelocyte	Juvenile	Band	Segment	Early Eosin.	Eosin.		
1	0.5	14	0.5	0.5	0.5	0.5	0.5	2	12	5	1	3	13	14	15	18	1	1	10	2
2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
3	(a)	20	2	3	1	1	3	3	7	10	0.75	1	7	9	8	14	3	3	18	6.5
4	(b)	2.5	11	1.5	6	0.5	1	3	11	7	0.5	2	4	1.5	2	4	2.5	1.5	26	4
5	..	V.S.	2	1	3	0.5	1	7	16	9	2	1	6.5	6	5.5	14.5	1	1.5	17	2.5
6	(a)	2.5	50	9	4	1	V.S.	V.S.	1	2	V.S.	2.5	12	10	7	9	1	1	13	2
7	..	3	82	1	2	0.5	V.S.	V.S.	V.S.	V.S.	V.S.	0.5	2	2	6	8	1	1	10	1
8	(b)	—	9	Occ.	4	0.5	0.5	1	5	7.5	0.5	2	12	8	4	1.75	V.S.	V.S.	2.5	0.25
9	..	0.5	5	—	4	0.5	0.5	2	4.5	11	0.5	1.5	18	8	3	11	6	10	14	2

(a) = before treatment. (b) = after treatment. V.S. = Very scanty

TABLE II.—Biochemical Findings

Case No.	Serum Proteins (G. per 100 ml.)					Blood Urea (mg./100 ml.)	Plasma Alk. Phos. (Units)	Serum Calcium (mg./100 ml.)
	Total	Alb.	Glob.	Glob. as % Total	A : G Ratio			
1	9.14	4.9	4.24	46	1.15 : 1	60 rising to 270	10.6	10.5
2	9.38	3.77	5.61	60	0.7 : 1	40	9.7	10.7
3 (a) .. .	7.7	3.4	4.3	56	0.7 : 1	38	41	11.8
(b) .. .	7.25	5.4	1.85	26	4 : 1	36	9	9
4	8	2.4	5.6	70	0.43 : 1	—	24	10.4
5	7.3	3.6	3.7	51	1 : 1	35 rising to 100	—	—
6 (a) .. .	11	3.2	7.8	71	0.4 : 1	45	16.7	11.8
(b) .. .	10.2	3.5	6.7	65	0.5 : 1	35	14	11

TABLE III.—Blood Counts

Case No.	Hb%	R.B.C.	C.I.	M.C.V. (c. μ)	Remarks	Leuco-cytes	Neutrophils				Eosins.	Lymphos.	Mono-cytes	Myeloma cells	Remarks
							Segment	Band	Juvenile	Myelocyte					
1	45	2.5	0.9	89	Size, shape, and staining normal	10,000	36	17	3	2	3	24	15	—	Blood film greasiness with rouleaux formation +
2	44	2.3	0.96	91	"	1,000	24	22	—	—	2	43	9	—	Greasiness with rouleaux formation + +
3 (a)	74	4.9	0.77	78	Microcytic and hypochromic	3,200	25	11	2	1	2	48	11	2	Greasiness with rouleaux +. Developed eosinophilia in treatment
(b)	81	4.7	0.86	88	Size, shape, and staining normal	3,600	37	10	—	1	9	36	6	—	No greasiness or rouleaux formation
4	41	1.9	1.1	105	Macrocytic and normochromic variation +	3,800	21.5	23	2	0.5	1	42	7	3	Greasiness with rouleaux + + +. Developed 36% eosinophils in treatment
5	36	2.2	0.8	89	Variation in size, shape, staining + + +	4,400	29	22	3	1	5	32	5	3	Greasiness with rouleaux + + +. Developed 20% eosinophils in treatment
6 (a)	90	5.0	0.9	90	Size, shape, and staining normal	10,000	46	7	2	1	23	18	3	Scanty	Greasiness with rouleaux +. Developed 74% eosinophils in treatment
(b)	90	5.2	0.8	86	"	7,000	53	9	—	—	8	22	8	—	Thrombocytopenia improved from 80 to 120,000

(a) = before treatment. (b) = after treatment.

Cases 3 and 6 fell towards normal at the end of treatment and has remained at approximately 8% since. No improvements in the general blood picture were obtained except in Cases 3 and 6 (Table III).

Toxic.—These were not marked. All cases except two complained of nausea following the injection, and actual vomiting occurred in Cases 1, 5, and 6. A dissociated trigeminal anaesthesia occurred in Case 5, but was followed by complete recovery.

Local.—Complaints of pain at the site of injection varied but did not appear to be a distressing factor except in Case 6, in which in spite of the use of a local analgesic the injections came to be anticipated with dread.

Description of the Abnormal (Myeloma or Plasma) Cells Found in the Marrow

The origin of the cells found in multiple myeloma has been greatly disputed, and descriptions given have

incriminated most of the early cells found in marrow and in particular myelocytes, erythroblasts, lymphoblasts, and reticulo-endothelial cells.

The myeloma cells found in these cases were divided into three types—blast cells (Fig. 5), typical myeloma cells (Figs. 2 and 3), and multinuclear cells (Fig. 4)—and the following descriptions are given with the suggestion that the typical myeloma cell resembles a cell intermediate between a blast type (plasma blast) and an adult plasma cell and compares in cellular age and position with the myelocyte.

The typical myeloma cell was oval in shape and about 16 μ in its largest diameter, and had a round nucleus situated towards one pole and occupying half the cell space. The nucleus was confined by a definite nuclear membrane and the distinction between its parachromatin and chromatin was marked, the latter appearing as stippling or as larger aggregations arranged irregularly but not infrequently leaving a pale central zone which gave the

impression of a dispersing nucleolus. The cytoplasm stained irregularly, giving a foamy appearance. As a rule deeply basophilic, it had a definite and distinctive purplish tint (Jenner-Giemsa stain), often contained a number of azure granules, and was sometimes vacuolated.

The primitive or blast type (Fig. 5) was about $26\ \mu$ in diameter. A definite nuclear membrane enclosed a nucleus which occupied three-quarters of the cell space and possessed one large nucleolus with sometimes up to three small nucleoli in addition. The chromatin assumed a definite

FIG. 2.—Early stage in development of typical myeloma cell: disappearance of nucleoli and condensation of nuclear chromatin. Outline of the foamy cytoplasm distorted by spreading. ($\times 965$.)

FIG. 3.—Typical myeloma cell containing stilbamidine inclusion bodies. Pale central nuclear zone surrounded by coarse chromatin masses. ($\times 965$.)

FIG. 4.—Multinucleated myeloma cell. ($\times 965$.)

FIG. 5.—Blast type of myeloma cell containing three nucleoli. ($\times 850$.)

stippled pattern. The cytoplasm presented the same features as described in the typical myeloma cell but did not contain granules or vacuoles nor stain so deeply.

The multinuclear cells usually contained two nuclei but occasionally had four or more, and varied in size from 20 to $40\ \mu$. The nuclear and cytoplasmic characteristics were identical with those described in the typical myeloma cell.

In all cases the myelogram showed an increase in the number of normal plasma cells—i.e., plasma cells indistinguishable morphologically from those found in normal marrow.

Comments

The fact that stilbamidine has such a favourable influence on the pain of multiple myeloma constitutes an advance in the treatment of this malignant disease. The method of administration by intramuscular injection is simple and not usually accompanied by severe local or general reactions provided the precautions outlined are taken. In addition stilbamidine seems to have a specific effect upon the protoplasm of some myeloma cells which is evident in fixed stained preparations. While this effect does not bring about complete disappearance of the cells there is evidence that it hinders their increase and dissemination, allowing local healing reactions to take place. The fact that no other cells but myeloma cells are affected suggests that the protoplasm and protein metabolism of the latter differs from that of other cells. Snapper (1946a) states quite definitely that stilbamidine has no effect in other malignant diseases such as leukaemias and Hodgkin's disease.

Two prime factors seem to influence the success of treatment: (1) the initial blood count findings, which are a reflection of the state of the marrow, and (2) the extent of renal involvement.

Those cases which presented with a serious anaemia did not improve. The malignant process was evidently too widespread and had replaced too much normal marrow to permit recovery of haemopoiesis. It seems likely that not enough stilbamidine could be given to have an effect on all the myeloma cells. For example, in Case 5, which received 8.6 g. , inclusion granules were demonstrated in only 7% of the myeloma cells, and this figure did not vary significantly whether the tissue examined was from the ribs, sternum, vertebrae, or femur.

The one patient showing extensive renal involvement (Case 1) died in uraemia after only six injections, suggesting that the stilbamidine had provoked an unfavourable renal reaction.

Snapper (1946a) stated that stilbamidine gave its best results in patients with widespread but not large osteolytic lesions and with normally functioning kidneys. Detailed information on the blood counts and marrow findings was not given.

Summary

Reference is made to some of the literature on multiple myeloma, the difficulty of early diagnosis, and the help that pathological investigation may give.

A detailed description is given of six cases and their treatment with stilbamidine by Snapper's method. (Two cases also had pentamidine). Four of the cases were fatal and two have made some clinical recovery. These results do not compare very favourably with those of Snapper, who reported seven out of fifteen showing continued improvement.

The outstanding clinical feature of treatment with stilbamidine is the relief from pain.

The morphological features of the abnormal cells found in the marrow and the appearance of inclusion bodies in their cytoplasm as the result of treatment are described.

My thanks are due to Dr. H. V. Morlock, Dr. Harold Davis, Dr. Lindsey Batten, Dr. K. Blatchley, Dr. Gray Thomson, and Dr. Z. Leitner for the opportunity of studying these cases, to the laboratory and nursing staffs for their co-operation, and to Mr. J. H. Hunter for the photomicrographs.

REFERENCES

- Adler, S., and others (1939). *Ann. trop. med. Parasit.*, **33**, 313, 327.
 Batts, M. (1939). *Arch. Surg.*, **39**, 807.
 Bayrd, E. D., and Heck, F. J. (1947). *J. Amer. med. Ass.*, **133**, 147.
 Bence-Jones, H. (1848). *Philos. Trans.*, p. 55.
 Dalrymple (1846). *Dublin J. med. Sci.*, **2**, 85.
 Geschickter, C. E., and Copeland, M. M. (1936). *Tumors of Bone*. New York.
 Ghormly, R. K., and Pollock, G. A. (1939). *Surg. Gynec. Obstet.*, **69**, 648.
 ———, Hall, L. B., and Beizer, L. H. (1942). *Ibid.*, **74**, 242.
 Macintyre, W. (1850). *Med.-chir. Trans. Lond.*, **33**, 211.
 Morissette, L., and Watkins, C. H. (1942). *Proc. Mayo Clin.*, **17**, 433.
 Snapper, I. (1946a). *J. Mt Sinai Hosp.*, **13**, 119.
 ——— (1946b). *Blood*, **1**, 534.
 ——— (1947). *Ibid.*, **2**, 311.
 ——— et al. (1947). *J. Amer. med. Ass.*, **133**, 157.
 Von Rustizky, J. (1873). *Dtsch. Z. Chir.*, **3**, 162.
 Wright, J. H. (1900). *Johns Hopk. Hosp. Rep.*, **9**, 359.

The Executive Board of WHO has authorized the Director-General to sign a preliminary agreement, as soon as 14 of the American Republics have deposited their instruments of ratification of the WHO constitution, between WHO and the Pan American Sanitary Organization providing for the ultimate establishment of that organization as the WHO regional organization for the western hemisphere. The Executive Board has also recommended that WHO establish contacts with the following international non-governmental organizations: International Union against Venereal Diseases, International Union against Tuberculosis, International Union against Cancer, World Federation for Mental Health, International Committee of the Red Cross, International Hospital Federation, International Academy of Forensic and Social Medicine, International Leprosy Association, International Association for the Prevention of Blindness.