were admitted quickly while some of the others were left too late before in-patient treatment was started.

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DESACETYLMETHYLCOLCHICINE IN TREATMENT OF MYELOID LEUKAEMIA

BY

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AND

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In 1953 Moeschlin and colleagues reported that desacetylmethylcolchicine ("colcemid") had beneficial effects on a group of patients with chronic myeloid leukaemia, while some encouraging results were also noted in a few cases of acute myeloid leukaemia and in two patients in the acute myeloblastic phase of chronic myeloid leukaemia. On the other hand, chronic lymphatic leukaemia failed to respond and might even have been made worse. The profound depressive effects on the granulocytopoiesis were accompanied simultaneously by a reduction in the size of the spleen and an increase in the red blood cell count and haemoglobin values.

Desacetylmethylcolchicine was isolated in a pure form by Santavy and Reichstein (1950) from the mixed alkaloid extract of *Colchicum autumnale* and was found to have a relatively low general toxicity, some 30–40 times less than colchicine (Schär *et al.*, 1954), which, although having a very marked inhibitory effect on cell mitosis, is too toxic for safe clinical use (Jacobj, 1890; Dustin, 1938; Bucher, 1939).

Lichtman (1954) has described in detail the effects of desacetylmethylcolchicine on the blood cellular elements in rabbits and cats, producing a diminution of total leucocyte count in two days after intravenous administration and in 12–14 days after oral treatment. With cessation of treatment the leucocytes rapidly returned to normal levels.

We have been able to repeat the observations of Moeschlin and his colleagues in a series of leukaemias and leukaemoid conditions, and are reporting here some of our results with chronic and acute myeloid leukaemias.

Dosage and Control

The initial oral dose of 3 mg. of colcemid daily was increased after three to four days to a total of 7–10 mg. daily according to the white-cell count. This dosage was continued until the leucocytes dropped to approximately 25,000 per c.mm., and was then stopped for three to four days. A daily maintenance dose of 3–5 mg. was then instituted. Daily white-cell counts, platelet counts, and haemoglobin estimations were performed until the maximal effect on the white cells had been attained; thereafter counts were done twice weekly and finally every one to two weeks.

Chronic Myeloid Leukaemia (8 cases)

Of eight patients with chronic myeloid leukaemia there was a distinct clinical improvement in six (Cases 1–6); their appetites improved, they gained weight and experienced far more energy; their spleens rapidly decreased in size and became barely palpable. In the remaining two (Cases 7

FIG. 1.—Case 6. Effects of colcemid on the total white cells and haemoglobin levels.

TABLE I.—Chronic Myeloid Leukaemia Treated with Colcemid

Case	Age and Sex	Before Treatment		After Treatment		No. of Days of Initial Treatment	Total Initial Course mg.	Max. Daily Dosage mg.	Maintenance Dosage mg.	Effects on Splenomegaly (cm. Below Costal Margin)
		W.B.C.	Hb	W.B.C.	Hb					
1	60 F	136,000	58%	4,100	71%	21	76	10	3	13 to 2
2	72 M	116,000	60%	3,900	69%	14	63	6	4	16 " 0
3	62 F	180,000	50%	5,500	64%	36	74	10	5	11 " 4
4	44 F	427,000	62%	26,000	80%	43	302	10	10	13 " 2
5	42 M	299,000	55%	13,050	70%	42	126	10	Discontinued (allergic reaction)	12 " 4
6	64 M	92,000	93%	12,000	96%	29	192	10	5	12 " 4
7	59 M	57,000	70%	6,950	73%	14	42	5	4	10 (no effect)
8	34 M	75,000		65,000		42	296	10	Discontinued (no effect)	11 to 9

Previous treatment: Cases 2, 3, 7, and 8 had had myleran; Cases 3, 7, and 8 had also had 6-mercaptopurine.

and 8), colcemid had little effect on the splenomegaly, but these two had also become resistant to "myleran" and 6-mercaptopurine, both of which had failed to influence the degree of splenomegaly. In Case 7, in spite of a reduction in the white-cell count from 57,000 to 6,950 per c.mm., there was no improvement in the clinical condition.

In Table I details of these cases are shown. Cases 2, 3, 7, and 8 had received previous medication with myleran, and Cases 3, 7, and 8 had also had 6-mercaptopurine and had become resistant to treatment; one of these (Case 8) also failed to respond to colcemid. So far, Cases 1-6 have been maintained in satisfactory clinical and haematological states for periods of four to nine months on maintenance doses of 3-10 mg. All were treated as out-patients and carried on with their normal household duties or occupations.

In Case 5, in spite of a very satisfactory remission, colcemid had to be discontinued owing to an allergic reaction, but the patient maintained his improvement after a further three months. At the height of the depressant action on the granulocytes (white cells 11,400 per c.mm.) the patient experienced difficulty in swallowing and had scrotal tenderness and some loss of scalp hair. On examination there

was a generalized congestion of the fauces and erythema of the scrotum. This rapidly subsided on discontinuing treatment, and was thought to be a sensitivity reaction to colcemid.

It is important to institute a maintenance dose as soon as the white cells have reached the desired level; failure to do so may result in a rising white-cell count that may be resistant to treatment for several weeks. Fig. 1 shows the effects of instituting a maintenance dose at the correct time, and Fig. 2 shows the effects of withholding an early maintenance dose. It is interesting to note that the second course of colcemid found necessary to restore a normal white-cell count was much greater in total dosage than that required initially—229 mg. as against 63 mg.

In spite of the dramatic effect on the total white cells, in no case did the differential picture return completely to normal. In the majority there was a considerable reduction in the percentage of promyelocytes and myelocytes, but they persisted to a lesser degree when the white cells were restored to a more normal level; in several the initial basophilia persisted.

Marrow biopsies performed after treatment showed reduced cellularity and fewer promyelocytes and myelocytes, but the overall picture still remained that of chronic myeloid leukaemia.

There was a rise in the haemoglobin values and red-cell counts, but their maxima were not reached for several weeks after the white cells had reached their maximal fall. The platelet counts in all were unaffected by the treatment, many remaining at the original high levels.

Myelofibrosis

The effects of colcemid on two patients with myelofibrosis are shown in Table II. The two cases are described separately because, although presenting like chronic myeloid leukaemia, the clinical and haematological findings suggested that these were actually examples of myelofibrosis.

Case A.—A housewife aged 64, who had had rickets in her childhood, had received x-ray treatment for chronic myeloid leukaemia before she was referred to us; attempts to obtain a marrow specimen had been repeatedly unsuccessful. Five months after x-ray treatment she was admitted to hospital complaining of severe bone pains in the limbs, loss of energy, and dyspnoea. The spleen was enlarged 13 cm. below the subcostal margin; red cell count, 3,320,000 per c.mm.; haemoglobin, 60%; platelets, 130,000 per c.mm.; total leucocyte count, 56,400 per c.mm. (polymorphs 4.5%, lymphocytes 2%, monocytes 0.5%, eosinophils 0.5%, basophils 0.5%, "blasts" 3%, promyelocytes 3.5%, myelocytes 11.5%, metamyelocytes 3%, atypical cells 71%). The atypical cells resembled normoblasts but were found to be peroxidase-positive. Attempts to obtain marrow from the sternum and iliac crest were repeatedly

FIG. 2.—Case 2. Effects of colcemid on the total white cells and haemoglobin levels.

TABLE II.—*Myelofibrosis Treated with Colcemid*

Case	Age and Sex	Before Treatment		After Treatment		Duration of Initial Treatment (Days)	Total Dose (mg.)	Maintenance Dose (mg.)	Effects on Splenomegaly (cm. Below Costal Margin)
		W.B.C.	Hb	W.B.C.	Hb				
A	64 F	56,400	60%	7,200	56%	3	3	1	13 to 8
B	40 F	75,000	62%	26,100	56%	5	15	2-3	15 „ 12

unsuccessful: the bones were found to be extremely hard, but x-ray films of the skeleton showed no detectable abnormality.

Colcemid was administered cautiously in a dose of 1 mg. daily, and after a total dosage of 3 mg. the white cells were 7,200 per c.mm., red cells 3,010,000 per c.mm., haemoglobin 54%, and platelets 125,000 per c.mm. The differential count showed a persistence of the atypical granulocytes: polymorphs 5.5%, lymphocytes 1%, monocytes 0.5%, eosinophils 1%, basophils 0.5%, "blasts" 2%, promyelocytes 2%, myelocytes 9%, atypical cells 78.5%. Transfusions were given and the haemoglobin eventually rose to 81%, and the loss of energy and dyspnoea subsided. The bone pains were controlled with phenylbutazone 200 mg. twice daily. She has been maintained in this improved clinical state for six months on a daily dose of colcemid 1 mg. The white-cell count has been kept within normal limits, but the abnormal differential has remained more or less unchanged.

Case B.—A housewife aged 40 was referred to us with a history of sudden haemoptyses and was found to have anaemia and considerable splenomegaly (15 cm. below the subcostal margin). A blood count showed: red cells, 4,550,000 per c.mm.; haemoglobin, 62%; platelets, 305,000 per c.mm.; white cells, 75,000 per c.mm. (polymorphs 54%, lymphocytes 11%, eosinophils 3.5%, basophils 4%, myeloblasts 13.5%, promyelocytes 1.5%, myelocytes 8%, metamyelocytes 4.5%); there were 6 nucleated red cells per 200 white cells. The marrow biopsies in several different bones were repeatedly unsuccessful; with the use of considerable force the needle entered the marrow cavity, but no marrow was ever aspirated. Radiological examination of the skeleton and chest was negative. After a total dosage of 15 mg. of colcemid, the white-cell count fell to 26,100 in five days (polymorphs 31.5%, lymphocytes 8.5%, monocytes 0.5%, eosinophils 3%, basophils 17.5%, "blasts" 14%, promyelocytes 4%, myelocytes 14%, metamyelocytes 7%); haemoglobin, 56%; red cells, 4,540,000 per c.mm.; platelets, 300,000 per c.mm. The patient felt improved in herself, had far more energy, and there were no further bleeding episodes. On a daily maintenance dose of 2-3 mg. this clinical improvement has been maintained for five months, the total white cell count has been kept within normal limits, but the abnormal differential count has remained unchanged.

Chronic Lymphatic Leukaemia

Case X.—A man aged 63 presented with generalized lymphadenopathy, splenomegaly (5 cm. below costal margin), and blood and marrow pictures of chronic lymphatic anaemia. The blood picture before treatment was red cells, 3,670,000 per c.mm.; haemoglobin, 83%, white cells, 224,000 per c.mm. (polymorphs 5%, lymphocytes 91%, lymphoblasts 3%, metamyelocytes 1%).

Colcemid, 3 mg., was given daily, and after six days' treatment the white cells had risen to 326,000 per c.mm., while the differential count showed 17% lymphoblasts. His general condition deteriorated with pyrexia, anorexia, and malaise. Treatment was discontinued and within seven days the "blasts" disappeared from the peripheral blood and the white-cell count dropped to its initial level, while his clinical condition slowly improved.

There is no doubt that colcemid aggravated the condition, and if treatment had not been discontinued an irreversible acute leukaemic phase might well have persisted. This experience is similar to that of Moeschlin *et al.* (1953), and we feel that colcemid should not be given to patients with lymphatic leukaemia.

Acute Myeloid Leukaemia

In Table III Cases I, II, and III had acute myeloblastic leukaemia which had failed to respond to other forms of therapy, and Case IV had received no previous treatment. Cases V and VI had suffered from long-standing chronic myeloid leukaemia which had developed an acute myeloblastic phase.

Colcemid was given in doses of 3 mg. daily and increased to a maximum of 5 mg. a day, while supportive therapy with transfusions and antibiotics was also given.

Colcemid had little effect on the clinical condition in Cases I-III; there was no improvement in general well-being and no effect on the bleeding diathesis. However, in all there

TABLE III.—*Acute Myeloid Leukaemia Treated with Colcemid*

Case No.	Before Treatment		After Treatment		Time taken (Days) for Blood Changes in the Previous Column	Previous Treatment	Duration of Leukaemia from Start of Treatment and Present Clinical Condition
	W.B.C.	"Blast" Cells	W.B.C.	"Blast" Cells			
I	37,100	95%	26,000	49%	14	6-Mercaptopurine, Cortisone A.C.T.H. gel	Died 3 months
II	18,100	13%	7,400	30%	17	"	" 3 "
III	24,000	54%	7,950	32%	27	"	" 5 "
IV	9,200	69%	2,400	19%	14	None	" 3 "
V	148,000	38%	253,000	32%	31	Myleran, 6-Mercaptopurine	Still living 4 months. Very poor condition
VI	57,000	42%	90,000	32%	21	Myleran	Still living 5 months. Very poor condition

was a fall in the total white-cell counts and a decrease in the number of myeloblasts. The red cells and platelets were reduced in numbers, and this would probably have been more pronounced had transfusions not been given.

Colcemid did not have any beneficial effect in Cases V and VI; in fact, their white-cell counts increased and their clinical condition deteriorated.

Discussion

The results of treating chronic myeloid leukaemia with colcemid are encouraging. It appears that this compound is a more selective granulocyte depressant than other chemotherapeutic agents. The disadvantage of myleran in producing thrombocytopenia and aplastic anaemia, and in some cases precipitating an acute myeloblastic leukaemia, have so far not been seen in any of this small group of cases after treatment with colcemid. This drug is more effective in the early stages of chronic myeloid leukaemia, but in one patient who had survived for four years (on a variety of chemotherapeutic agents) it was completely ineffective. The clinical effects are just as striking as the effects on the blood; with reduction of splenomegaly, improvement in appetite and increase in weight and general well-being were very notable features. From the early results with colcemid it would appear worthy of further trial in chronic myeloid leukaemia, so that its long-term effects may be compared with other well-tried forms of therapy.

In both the patients with myelofibrosis the white cells were extremely sensitive to colcemid and dropped to low levels in three and five days respectively. This is in sharp contrast to the effects on the white cells in the more typical chronic cases of myeloid leukaemias.

The results of treating acute myeloid leukaemia and the acute phase of chronic myeloid leukaemia were disappointing. In spite of some reduction in the number of myeloblasts in the differential counts clinical deterioration continued, and in no case was a complete or even temporary remission obtained.

Summary

The effects of desacetylmethylcolchicine ("colcemid") on some cases of chronic myeloid leukaemia, myelofibrosis, chronic lymphatic leukaemia, and acute myeloblastic leukaemia are described.

Colcemid is of greatest value in chronic myeloid leukaemia, having a distinct depressant action on the

granulocytes and producing rapid reduction of splenomegaly and a marked clinical improvement in six of eight such treated cases.

The disadvantage of many other agents such as myleran in producing thrombocytopenia and aplastic anaemia was not seen in cases of chronic myeloid leukaemia treated with colcemid.

The effects of colcemid on myelofibrosis are considered.

Colcemid would seem to be contraindicated in the treatment of chronic lymphatic leukaemia, and evidence suggests that it may even produce an acute change.

Colcemid has little or no beneficial effects on acute myeloblastic leukaemia.

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TEN-YEAR RECOVERY FROM CHRONIC LYMPHOCYTIC LEUKAEMIA

BY

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Reports of recovery from leukaemia are extremely rare. I wish to present the case of a patient who undoubtedly suffered from chronic lymphocytic leukaemia eleven years ago, but has since recovered both clinically and haematologically and has so far survived for ten years. I wish to stress that the point here is not the time of survival. Many patients have survived for ten and more years, but they have always shown signs of the disease, at least as far as an abnormal blood picture.

Case Report

The patient, a female textile worker, was born in 1882. In April, 1940, she had a severe attack of faucial diphtheria with pharyngeal palsy, diaphragmatic palsy, head-drop, and brachial palsy. There was nothing else relevant in her past history.

When seen on July 7, 1943, she complained of lassitude, dyspnoea, sweating, cramps in the legs, and indigestion for about one year. For the same period she had had two lumps in the left armpit.

Examination showed enlarged cervical, supraclavicular, axillary, and inguinal lymph nodes. They were firm, discrete, and quite painless. The spleen extended as far as the left iliac fossa, the notched medial border reaching the umbilicus. It was not tender. The sternum and tibiae were tender on tapping. There were some bluish nodules under the nail-bed of some toes. The urine showed a trace of albumin. There was no excess of urobilinogen or urobilin, and nothing abnormal in the deposit. Blood: R.B.C., 3,480,000; Hb, 70%; C.I., 1; W.B.C., 224,000 (polymorphs 3,360, lymphocytes 219,520, monocytes 1,120). The lymphocytes were fairly mature cells bigger than normal. The stain was taken well by the red cells. There were no nucleated red cells.

The patient was admitted for x-ray therapy, eight doses of 50 r each being given to the spleen. Thereafter the margin of the spleen was just palpable below the ribs, and the W.B.C. numbered 17,100, with 13,766 lymphocytes.

She began to lose her tiredness, dyspnoea, and abdominal pain, and started to feel well. The lymph nodes became gradually smaller, without, however, returning to normal size. The spleen was firm and painless and remained palpable three fingerbreadths below the left costal arch. Serial blood counts (see Table I) showed normal haemoglobin and red cells, with slightly raised total leucocytes, of which 75–80% were lymphocytes.

It was decided to give a further series of x rays to the cervical and axillary glands, and 50 r to four fields twice weekly to a total of 400 r was applied in May, 1944. Thereafter the glands were smaller, soft, discrete, freely mobile, painless, and about the size of a pea. The inguinal glands were no longer palpable. The size of the spleen was unchanged. The patient felt well in herself and did her housework and shopping.

In February, 1945, she developed a lower respiratory infection, the first of many more to follow. She made a slow recovery on symptomatic treatment, the blood picture being unchanged. After this the margin of the spleen could only just be felt below the ribs. The glands were unchanged in size. Further serial blood counts throughout 1945 and 1946 were normal (see Table I). In January, 1947, she again developed bronchopneumonia. In April the blood picture returned to normal. Cervical and axillary glands were palpable, and the spleen could not be felt. At the end of June, 1947, she again developed bronchitis, and a further bronchopneumonic attack occurred in December, 1947, and again in June, 1948. No glands could be felt anywhere, nor was the spleen palpable in December, 1948. In March, 1949, she started once more to cough and was feverish. She again had pneumonia in April, 1950, in January, 1951, and in April, 1952. She had a *Haemophilus influenzae* infection in January, 1953. In January, 1954, she developed erysipelas of the right cheek and forehead.

A blood count in July, 1954, revealed a hypochromic anaemia (Hb 65%). Seven weeks later, after iron medication, the haemoglobin was 83%.

Cases from the Literature

It is difficult to find sufficiently well-documented cases in the literature for comparison. Forkner (1938) quotes quite a number of cases, but most of these do not bear close scrutiny. Naegeli (1931), referring to chronic lymphocytic leukaemia, states that "published cures relate probably always to lymphatic reactions." Heilmeyer and Bege-mann (1951) in the latest German textbook do not even mention cure. Kolmer (1949) states that true leukaemia is invariably fatal, alleged recovery being due to errors in diagnosis. Wintrobe (1951) merely states that there are a number of reports of cure, but does not give his own opinion. So much for the rarity, even denial, of the possibility of recovery.

One case of recovery was described by Schiassi (1933).

A man aged 20 developed right pleurisy in 1911. In 1923 he developed left pleurisy with fluid. An enlarged spleen was found. A blood count in 1924 showed 200,000 leucocytes, of which 40% were immature granulocytes. Chronic myelocytic leukaemia was then diagnosed and a series of x-ray treatments were given. On his discharge in December, 1924, the leucocytes numbered 25,200, with 10% immature granulocytes. The spleen and liver were reduced to nearly normal limits. He returned to work. In July, 1928, he suffered from lassitude, loss of appetite, and pains in the right leg. He had 120,000 leucocytes (12% immature). Further x-ray therapy was given and the leucocytes fell to 12,400 on discharge. In December, 1931, he again felt weak and had pain in the left hypochondrium. The spleen and liver were not palpable. He had 18,740 leucocytes, with some myelocytes. In February, 1933, he had a haemoptysis. There were no palpable lymph nodes anywhere. The liver and spleen could not be felt. There was diminished air entry over the left lower chest and an x-ray film showed pleural thickening at the left base. The lung