refer to the concept of the myelo-proliferative diseases which are shown in Fig. 1. These diseases could, I think, be regarded as benign neoplasms, and the grounds for this concept of myeloproliferative disease is the agreed

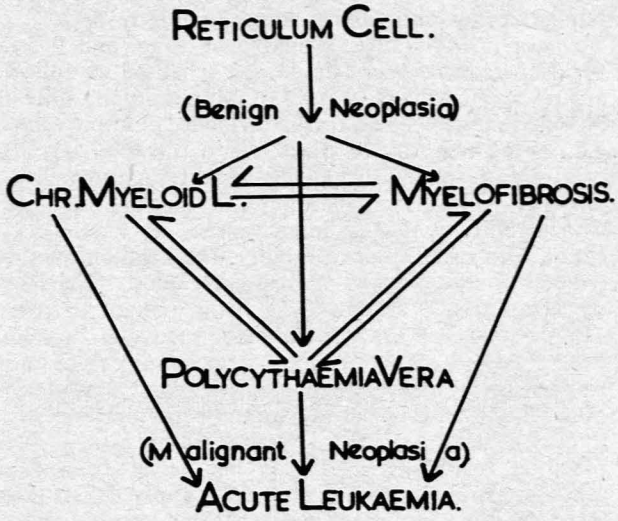

Fig. 1. A schema showing the myelo-proliferative diseases and their interrelations. Chronic myeloid leukaemia, myelofibrosis and polycythaemia vera are regarded as benign neoplasms and acute leukaemia as a malignant neoplasm.

multipotentiality of the primitive reticulum cell, enabling benign neoplasia to occur along the various developmental lines and often along more than one simultaneously, leading to known associations of these conditions. Thus polycythaemia has an association with chronic myeloid leukaemia, and with myelofibrosis. Myelofibrosis may be the end-result of a chronic myeloid leukaemia or of a polycythaemia. Any may terminate as the malignant form, to wit, acute myeloblastic leukaemia. This has been known for some years now to occur more commonly after treatment of polycythaemia with ^{32}P than in untreated cases.

CONCLUSION

To conclude then, the following suggestions are made:

1. Leukaemia is a true neoplasm.
2. The chronic myelogenous and chronic lymphatic forms are benign neoplasms which, on account of the ubiquity of the tissue affected, have far reaching and ultimately fatal effects. (In this sense they are not benign.)
3. Acute myeloblastic leukaemia is the malignant neoplasm corresponding to chronic myelogenous leukaemia, and a lymphoid reticulum cell neoplasm is the malignant neoplasm corresponding to chronic lymphatic leukaemia.
4. This view of the leukaemias is in keeping with the concept of the myeloproliferative diseases.
5. The change from benign to malignant neoplasms is being seen more frequently now as a result of the use of carcinogenic therapeutic agents.

REFERENCES

Bennet, J. H. (1845): Edinb. Med. J., **64**, 413.
Boycott, A. E. (1929): Proc. Roy. Soc. Med., **22**, 15.
Ciba Symposium on Leukaemia Research: ed. Wolstenholme, G. E. W., and Cameron, M. P. (1954): London, J. & A. Churchill, Ltd.
Craigie, D. (1845): Edinb. Med. J., **64**, 400.
Ewing, J. (1940): *Neoplastic Diseases.* Philadelphia, Saunders.
Furth, J. (1951): Blood, **6**, 964.
Gross, L. (1954): *Ibid.*, **9**, 557.
Haddow, A. (1953): In *The Physio-pathology of Cancer*, ed. Homburger, F. and Fishman, W. H. London, Cassel.
Shimkin, M.B., Mettier, S. R. and Bierman, H. R. (1951): Ann. Intern. Med., **35**, 194.
Shimkin, M. B., Lucia, E. L., Opperman, K. C. and Mettier, S. R. (1953): *Ibid.*, **39**, 1254.
Virchow, R. Quoted by Wintrobe, M. M. (1951): *Clinical Haematology*, 3rd ed. London, Kimpton.
Whitby, L. E. H. (1951): J. Clin. Path., **4**, 129.

CHEMOTHERAPY OF LEUKAEMIA*

1. MYLERAN IN THE TREATMENT OF CHRONIC MYELOID LEUKAEMIA

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Rational cancer chemotherapy, according to C. P. Rhoads of the Sloan Kettering Institute for cancer research, has passed through two phases and has entered upon a third.[1]

The first phase was the discovery of agents or procedures causing atrophy of specific tissues and, by virtue of this property, able to influence tumours of that tissue. Examples of this phase are the use of oestrogens in the treatment of cancer of the prostate and radio-active iodine for the treatment of carcinoma of the thyroid. The substance 'Myleran' also belongs to this first category.

The second phase according to Rhoads is the use of compounds injurious to cells in direct ratio to their rate of growth. Examples of these, he suggests, are the antimetabolites of folic acid, aminopterin, etc. The third phase is the use of substances which selectively injure by virtue of the biochemical specificities of the target cells, characteristics which distinguish the neoplastic cell from its normal analogue growing at the same rate. Such a substance he believed was 6-mercapto-purine.

Now while Rhoads described these phases as chrono-

* A paper presented at the South African Medical Congress, Pretoria, October 1955.

logical, I do not think that he would imply that we have by any means exhausted the possibilities of the first two in having perhaps arrived at the third. Indeed, I feel that there is much potential still to be discovered in the first category although I am not very sanguine about the potentialities of the second.

MYLERAN IN THE TREATMENT OF CHRONIC MYELOID LEUKAEMIA

Myleran (1·4 dimethane-sulphonoxybutane) was the outcome of research by Haddow and his associates who found that members of a series with the following type formula shown

$$RN\begin{matrix}\nearrow CH_2CH_2OSO_2R \\ \searrow CH_2CH_2OSO_2R\end{matrix}$$

possessed cytostatic properties for various experimental animal tumours.[2] This finding led them to investigate other substances bearing sulphonic-acid ester groups, and in particular the methane-sulphonoxy-alkanes.[3, 4] The type formula of these substances is as follows:

$$CH_3SO_2O(CH)_nOSO_2CH_3$$

If the value of n lies between 2 to 10, cytostatic activity is found to be present, but maximum activity was found if $n=4$ or 5.

The substance 1·4 dimethane-sulphonoxybutane was found to have a marked inhibitory effect on the Walker rat-carcinoma 265 and a selective depressant effect on myeloid cells both in the rat and man. This effect on the myeloid series is selective, in that doses depressant for that series have no effect on the lymphocyte or erythroid series.[4]

The precise mechanism of the cytostatic action of these compounds is still uncertain,[5] but the substances are bifunctional alkylating agents and may act through formation of carbonium ion ($R.CH_2$) according to the following formula:

$$R.CH_2OSO_2R^1 = R.CH_2^{+}{}_{+}{}^{-}OSO_2R^1$$

or alternatively, as suggested by Timmis, by the capacity of these compounds to form ring compounds with amino or sulphydryl groups. These substances, in keeping with Haddow's general hypothesis,[5] are carcinogenic, the substance Myleran (1·4 dimethane-sulphonoxybutane) being particularly active in this respect.

Dosage. Myleran is available in 2-mg. and 0·5-mg. sugar-coated tablets. The dosage schedule we followed at first was 2 tablets (4 mg.) of Myleran daily until the blood count showed no further evidence of improvement; i.e., in the majority of cases, when the total leucocyte count had reached normal levels and immature cells had virtually disappeared from the peripheral blood. Concurrently with the improvement in the leucocyte count, and usually more rapidly, the haemoglobin and red-cell count returned to normal values. The length of time a course lasted varied from patient to patient and in some, as the improvement seemed to continue over a period of many months up to a year or more, we were led to try maintenance treatment, when instead of ceasing therapy when maximum benefit has occurred, it is continued at a dose varying from $\frac{1}{4}$ to $\frac{1}{2}$ of the previous treatment level. It has never been found necessary to use a dosage above 4 mg. per day although in some cases doubtless a more rapid response would have been obtained in this way. Continuous therapy at 1-2 mg. per day has been continued throughout the period of observation in some patients.

Results. A total of 34 cases of chronic myeloid leukaemia have been treated with this drug, 22 of whom were Europeans (12 men and 10 women) and 12 Bantu (8 men and 4 women). Of the Europeans 13 are still alive, 8 have died, and information is not available regarding 1. On account of the difficulties of following up the Bantu cases, no general assessment of the results of therapy in them can be made. In all except 3 of the European cases immediate benefit ensued, but it was short-lived (less than 3 months) in 2. The longest remission has been 24 months. Two courses of therapy have been given to 13 Europeans and the response to the second course

TABLE 1. EUROPEAN CASES

Case No.	Age (*a*)	Sex	Previous Treatment	Resistant To DXT	Type of Myleran Treatment	No. of Courses	Response to Courses				Length of Remission (Months)				Alive / Dead
							1	2	3	4	1	2	3	4	
1.	35	F	DXT, many courses	Yes	Courses	2	Good	None	—	—	3	none	—	—	D
2.	30	F	DXT, 2 courses	No	Courses M	2	Good	Good	—	—	7	1 yr. (*b*)	—	—	A
3.	45	M	DXT ^{32}P	Yes	Maintenance	—	Good	—	—	—	2 yr. (*b*)	—	—	—	A
4.	45	M	DXT, many courses	Yes	Course	1	Poor	—	—	—	1	—	—	—	D
5.	37	F	DXT, 2 courses	Yes	Maintenance	—	Good	—	—	—	2 yr. (*b*)	—	—	—	D
6.	52	M	DXT, 2 courses	No	Courses M	4	Good	Good	Good	Good	1	8	10	2 (*c*)	A
7.	64	F	None	—	Courses M	4	Good	Good	Good	Good	8	6	4	6 (*b*)	A
8.	34	M	DXT, 2 courses	No	Course	1	Good	—	—	—	2 (*c*)	—	—	—	A
9.	72	M	TEM. DXT, many courses	Yes	Courses	2	Poor	None	—	—	1	none	—	—	A
10.	24	M	DXT, 2 courses	No	Courses	3	Good	Good	None	—	8	2	none	—	D
11.	40	F	None	—	Courses M	2	Good	Good	—	—	10	14 (*b*)	—	—	A
12.	48	M	None	—	Courses M	2	Good	Good	—	—	8	1 yr. (*b*)	—	—	A
13.	49	F	None	—	Courses M	2	Good	Fair	—	—	1 yr.	6 (*b*)	—	—	D
14.	34	M	DXT, 2 courses	No	Courses	2	Good	None	—	—	8	none	—	—	D
15.	53	F	None	—	Courses	2	Good	Good	—	—	8	4 (*c*)	—	—	A
16.	60	F	DXT, 4 courses	Yes	Courses	2	Good	None	—	—	3	none	—	—	D
17.	73	M	None	—	Courses	2	Good	Good	—	—	6	4 (*c*)	—	—	A
18.	55	M	None	—	Maintenance	—	Good	—	—	—	15 (*b*)	—	—	—	A
19.	49	M	None	—	Course	1	Poor	—	—	—	none	—	—	—	D
20.	67	M	None	—	Course	1	Poor	—	—	—	none	—	—	—	? (*d*)
21.	38	F	None	—	Maintenance	—	Good	—	—	—	1 (*c*)	—	—	—	A
22.	43	F	None	—	Maintenance	—	Good	—	—	—	2 (*c*)	—	—	—	A

DXT = Deep X-ray therapy.
(*a*) = Age at diagnosis.
(*b*) = Length of remission on maintenance therapy.
(*c*) = Remission continuing.
(*d*) = Patient refused hospital treatment: presumed dead.
Courses M = Initial treatment by courses of Myleran with subsequent assumption of maintenance treatment.

was poor or absent in 5 and good in 8. Seven of the 8 are still alive and a third course has been given with benefit to 2 of them, and without benefit to 1; a fourth course has been given to the same 2 cases. Seven are on continuous dosage and have remained well for periods of 24, 24, 15, 14, 12, 12 and 6 months respectively. Eleven cases had previously received deep X-ray therapy or other source of ionizing radiation, e.g. ^{32}P. Of these only 2 failed to respond to Myleran. Longer remissions as a result of Myleran therapy than were obtained with deep X-ray therapy have been observed in 8 of the 11 cases (Tables I and II).

TABLE II. BANTU CASES

Case No.	*Age*	*Sex*	*Previous Treatment*	*Initial Response to Myleran*	*Notes*
1	30	F	None	Good	In remission from 1 course of 10 mths. Relapse resistant to Myleran. DXT tried without benefit. Became acute and died.
2	26	F	None	Good but short	After 1 mth's. remission became acute in type and died 3 wks. later.
3	45	M	DXT	Fair. Splenomegaly and some anaemia persisted.	No follow-up.
4	23	M	None	None. Given DXT with benefit.	Subsequently required 2 more courses of DXT, became acute and died.
5	?	M	None	Fair. Splenomegaly persisted.	No follow-up.
6	28	M	None	Good.	No follow-up beyond 6 mths., during which time he remained well.
7	40	M	None	Good. Splenomegaly persisted.	No follow-up.
8	42	M	DXT	Good.	Remained well for 10 mths. No further follow-up
9	?	F	None	Poor, after 8 wks. treatment given DXT.	Relapsed after DXT in 2 mths. No further follow-up
10	35	M	None	Good. Splenomegaly persisted.	No follow-up.
11	29	M	None	Good.	Remained well for 4 mths. No further follow-up.
12	30	F	None	Fair. Splenomegaly persisted.	No follow-up. Took own discharge from hospital before treatment was complete.

Toxicity. We have found Myleran to be singularly free from side-effects for a potent cytostatic agent. Bone-marrow depression has been observed once only. Thrombocytopenia has not been observed as a result of therapy, but in two cases thrombocytopenia was present at the start, and in both these cases, the platelet deficiency and haemorrhagic phenomena were aggravated to such extent that therapy had to be discontinued. Minor disturbances due to Myleran have been few; the increase in skin pigmentation noted by Galton[6] and by Petrakis *et al.*,[11] has been observed in 2 cases. Bollag[13] notes amenorrhoea as a complication of Myleran therapy, and menopausal symptoms with amenorrhoea have been observed in 3 female patients in this series.

Termination as acute myeloblastic leukaemia has been observed in 9 cases, 7 of whom received deep X-ray therapy in addition to Myleran and 2 received Myleran only.

DISCUSSION

Galton,[6, 7] Galton and Till,[8] Ledlie[9] and Wilkinson,[10] in Britain, Petrakis *et al.*,[11] and Wintrobe[12] in the USA, Bollag[13] in Switzerland, Hansen[14] in Denmark, Gigante, Teodori and Zoppini[15] in Italy, and Kurrle[16] in Australia, have reported on the use of this drug in cases of chronic myeloid leukaemia.

This literature is uniform regarding the beneficial effects of Myleran therapy in chronic myeloid leukaemia, a situation unusual in the literature relating to a chemotherapeutic agent. All stress the haematological benefit matched by clinical improvement and the remarkable absence of toxic or undesirable side-effects.

In general the results described in this paper are similar to those obtained by the other authors quoted, but several points merit further discussion. It has become apparent that patients kept on maintenance dosage of a low order ($\frac{1}{2}$-1 mg. *per diem*) are maintained more able than those treated with interrupted courses. An important point, however, not to be lost sight of in discussing the relative merits of various forms of treatment, is that all treatment available to date against chronic myeloid leukaemia is palliative only. The best treatment is not necessarily the one which will prolong life longest but the one which will maintain the patient at his fittest in the least disturbing fashion for the remainder of his life. And here Myleran therapy has undoubted advantage over external radiation therapy. All patients who have previously had deep X-ray therapy are unaminous in their preference for Myleran.

We have confirmed the value of myleran therapy in patients in whom radiation therapy is ceasing to have effect. We have also proved its value in cases where deep X-ray therapy could not be carried out on account of the patient's condition.

CONCLUSION

Myleran is an effective, and satisfactory palliative therapy for chronic myeloid leukaemia. Side-effects are very few, and dangerous toxic effects, provided adequate haematological control is exercised, very rare indeed.

I wish to express my thanks to the many physicians and practitioners who have cooperated in the study of these patients; also to Prof. A. Haddow of the Chester Beatty Institute, for generous supply of Myleran.

REFERENCES

1. Rhoads, C. P. (1954): Science, **119**, 77.
2. Haddow, A. and Timmis, G. M. (1951): Acta Un. int. Cancr., **7**, 469.
3. Timmis, G. M. (1951): Abstracts of Papers, XII Internat. Congr. Pure and Applied Chemistry, p. 334.

4. Haddow, A. and Timmis, G. M. (1953): Lancet, **1**, 207.
5. Haddow, A, in Homberger, F. and Fishman, W. H., eds. (1953): *Physiopathology of Cancer*, p. 495. London: Cassel, Ltd.
6. Galton, D. A. G. (1953): Lancet, **1**, 208.
7. *Idem* (1953): Brit. J. Radiol., **26**, 285.
8. Galton, D. A. G. and Till, M. (1955): Lancet, **1**, 425.
9. Ledlie, E. M. (1953): Brit. J. Radiol., **26**, 290.
10. Wilkinson, J. F. (1953): Proc. Roy. Soc. Med., **46**, 685.
11. Petrakis, N. L., Bierman, H. R., Kelly, K. H., White, L. P. and Skunkin, M. B. (1954): Cancer, **7**, 381.
12. Wintrobe, M. M., Cartwright, G. E., Fessas, P., Hault, A. and Altman, S. J. (1954): Ann. Intern. Med., **41**, 447.
13. Bollag, W. (1953): Schweitz. med. Wschr., **83**, 872.
14. Hansen, P. B. (1954): In *Ciba Foundation Symposium on Leukaemia Research*, p. 205. London: J. and A. Churchill, Ltd.
15. Gigante, D., Teodori, S. and Zoppini, A. (1955): Minerva Med., **1**, 221.
16. Kurrle, G. R. (1955): Med. J. Austral., **1**, 636.

CHEMOTHERAPY OF LEUKAEMIA*

II. 6-MERCAPTO-PURINE ('PURINETHOL') IN THE TREATMENT OF ACUTE LEUKAEMIA AND SOME OTHER NEOPLASTIC DISEASES OF THE RETICULOENDOTHELIAL SYSTEM

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6-Mercapto-purine ('Purinethol†) is an example of a chemotherapeutic agent of the third phase of Rhoads.[1] It is an analogue of the nucleic-acid constituent adenine and the physiological purine-base hypoxanthine (Fig. 1) and was one of a very large series of analogues prepared and studied by Hitchings and his colleagues[2] at the Wellcome Research Laboratories. This work was a consideration of the possibility that cells of different characteristics and so having different genes might have desoxyribose-nucleic acid (DNA) of differing

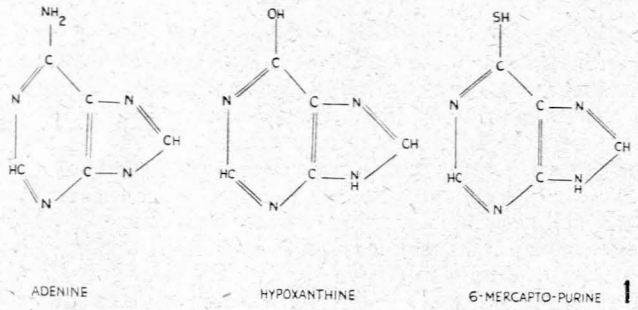

Fig. 1. Structural formula showing relation of 6-mercapto-purine (Purinethol) to adenine and hypoxanthine.

composition in these genes. It was shown conclusively that specificity of DNA does exist and this in turn established a firm foundation for the possibility of developing selectively toxic compounds. 6-Mercapto-purine has been shown to be a purine antagonist for lactobacillus casei, but studies in animals have shown that neither the toxic nor the anti-leukaemic effects can be reversed by simple purines. Indeed, no antidote to its cytotoxic effects in animals has so far been discovered.

Dosage. In patients the drug is generally given at a dosage level of 1 mg. per lb. body-weight, in a single dose daily by mouth. At least 3 weeks of therapy and often up to 6 or 8 weeks are needed before remissions are achieved, and then maintenance therapy at the same or a reduced dose-level is applied. In some cases steroid therapy (cortisone or ACTH) was employed concurrently with Purinethol therapy. Careful haematological control was exercised on the patients, especially during the initial phase of therapy, as the response of any given patient we found to be highly unpredictable. In some, precipitous drops in the leucocyte count occurred; in

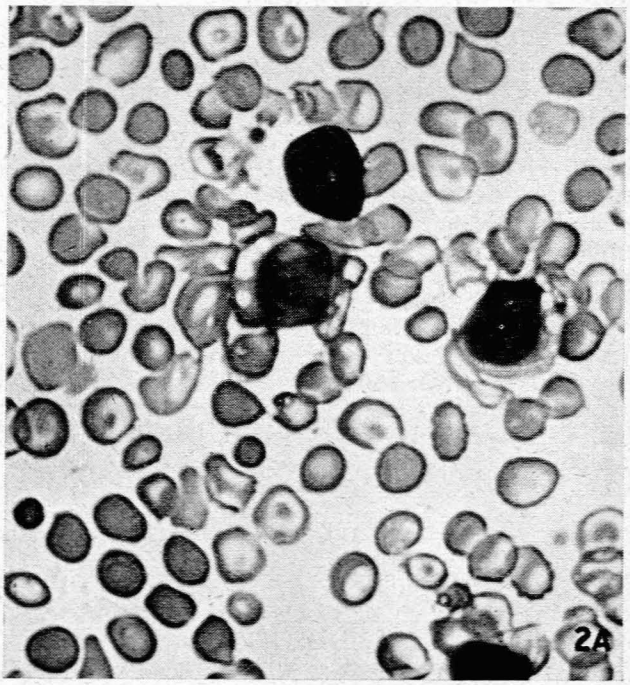

Fig. 2. (*a*) Blood Film: Wrights stain (×620). This shows the marked anisocytosis with macrocytosis of the red cells in a patient after treatment with Purinethol in full doses for 3 months. There is also conspicious target cell formation.

* A paper presented at the South African Medical Congress, Pretoria, October 1955.

† Trade name Burroughs Wellcome Ltd.