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

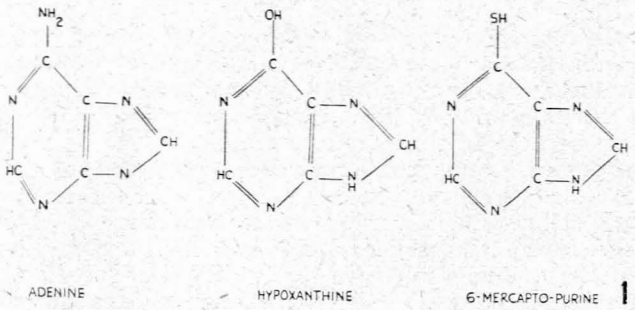

Fig. 1. Structural formula showing relation of 6-mercapto-purine (Purinethol) to adenine and hypoxanthine.

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

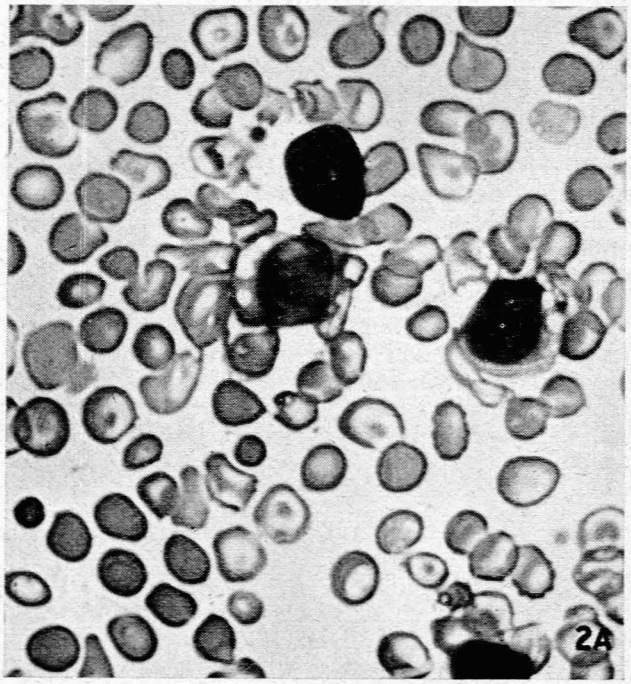

Fig. 2. (*a*) Blood Film: Wrights stain (× 620). This shows the marked anisocytosis with macrocytosis of the red cells in a patient after treatment with Purinethol in full doses for 3 months. There is also conspicious target cell formation.

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others prolonged therapy was necessary to effect any alteration in the blood picture.

Toxicity. Leucopenia is usually induced and is, indeed, a prerequisite of successful therapy in most cases. A curious feature noted early in our series was the appearance under treatment of very unusual leucocytes in the peripheral blood, which often defied accurate morphological description. Usually they appeared to be 'monocytoid myelocytes', less commonly 'monocytoid lymphocytes', and their morphology did not seem to depend on the original cytological type of leukaemia. These cells are depicted in Fig. 2.

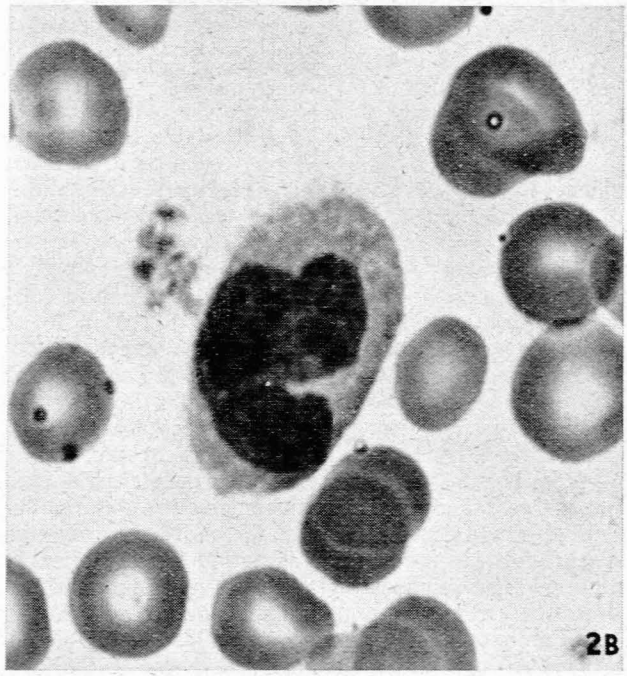


Fig. 2. (*b*) Blood Film: Wrights stain (×1600). Showing an example of the atypical leucocytes which we have regarded as 'monocytoid lymphocytes' which commonly appear in the peripheral blood of patients treated with Purinethol. In staining reactions they closely resemble 'glandular fever' cells.

Thrombocytopenia is rarely seen as a result of therapy; on the contrary, a pre-existing thrombocytopenia often disappears and bleeding phenomena are cured. Irreversible bone-marrow depression attributable to the Purinethol has not been seen. Anaemia has usually not been benefited by the drug, and the appearance of a macrocytic red-cell picture with marked anisopoikilocytosis is common in cases maintained for any period of time on maximum dosage. The bone-marrow in these cases shows partial megaloblastic change of erythropoiesis. In one case, where anaemia was severe and the marrow showed partial megaloblastic changes, folic acid orally was tried without benefit to the anaemia (or detriment to the leukaemia).

Oral lesions and gastro-intestinal symptoms referable to the therapy have not been observed. Marked loss of hair was noted in one patient, but this had commenced prior to the treatment, and so was probably to be attributed to the leukaemia.

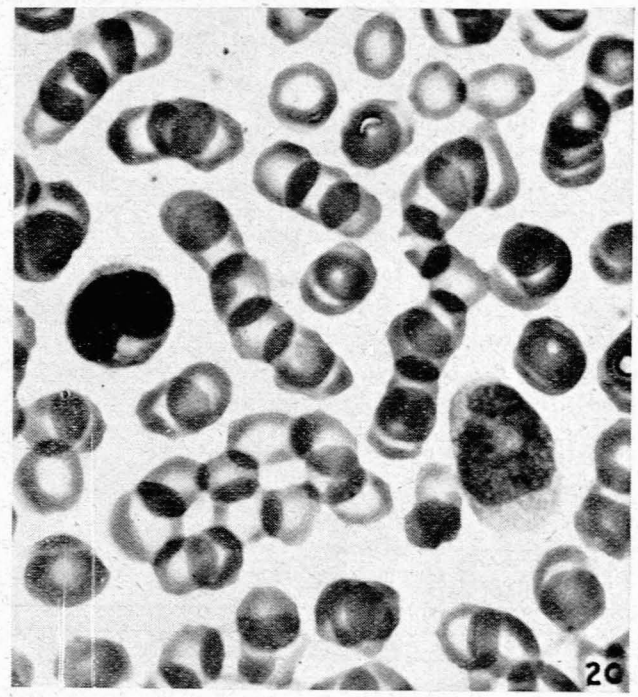


Fig 2. (*c*) Blood Film: Wrights stain (×1200). Further examples of 'monocytoid lymphocytes'.

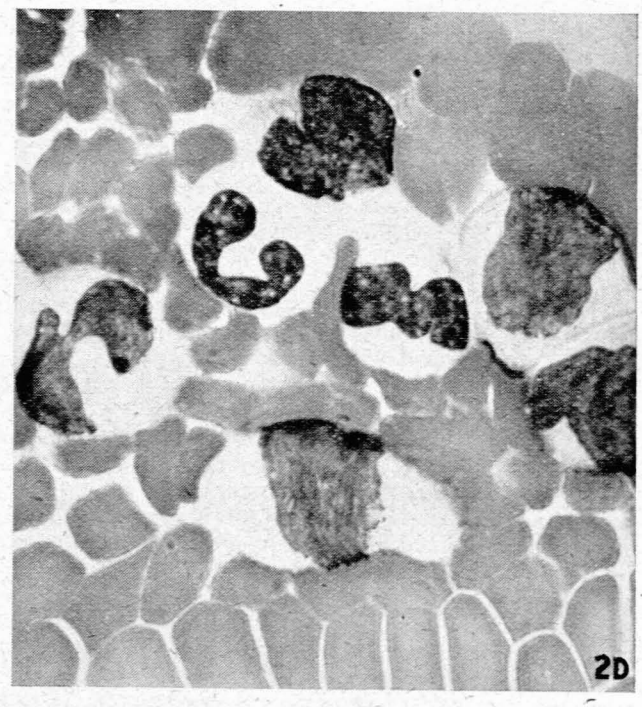


Fig. 2. (*d*) Blood Film: Wrights stain (×1200). Examples of the other type of atypical leucocyte frequently observed which we have reagrded as 'monocytoid myelocytes'.

MATERIAL AND RESULTS

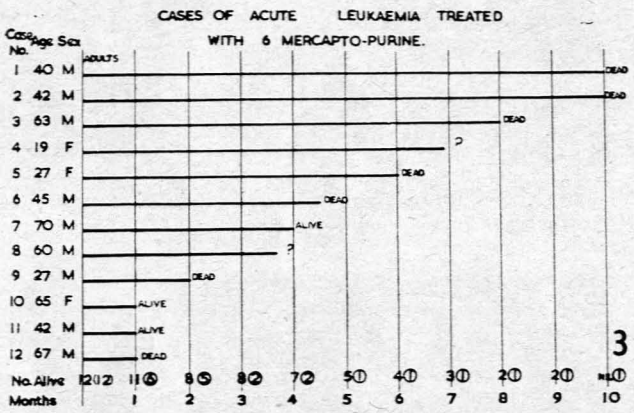
We have had experience of the drug now in a total of 35 cases, and the various cases treated are shown in Table 1.

TABLE I. CASES TREATED WITH PURINETHOL

Disease	*No. of Cases*
Acute Leukaemia in Adults	17
Acute Leukaemia in Children	5
Acute 'Blastic' terminal phase of Chronic Myelogenous Leukaemia	7
Chronic Myelogenous Leukaemia ..	1
Reticuloses	4
Chronic Lymphocytic Leukaemia ..	1
	35

Acute Leukaemia in Adults

This is the condition where we have had the most experience in the use of Purinethol and the condition where we believe it has its principal use. It is undoubtedly superior to any other threapeutic agent we possess at present. Purinethol has been used in 17 cases of acute leukaemia in adults. Fig. 3 summarizes our findings in



This figure shows graphically the survival of 12 cases of acute leukaemia in adults treated with Purinethol. The figures show the number alive each month after diagnosis and the figures in parenthesis show the number alive of a control series not treated Purinethol (see text).

12 cases. In order to see if any significant increase in expectation of life had resulted from Purinethol treatment, a comparison was made of the duration of life after diagnosis of the 12 cases of acute leukaemia which had been encountered immediately before the introduction of Purinethol. All these cases occurred between 1951 and 1954, and all except 2 received antibiotics. Data relative to these 'control' cases is shown in Table II and in Fig. 3. It will be seen that by this assessment there is significant prolongation of life coincident with the use of Purinethol. The effect does not seem attributable to the use of antibiotics or blood transfusions, since these were used in the majority of the control cases. On the whole, considerable clinical benefit ensued in 6 of the 12 cases; cessation of bleeding phenomena, clearing up of mouth and throat ulceration in a remarkable fashion, and general improvement in well-being. Objective benefit, such as diminution of lymphadenopathy and

TABLE II. DATA RELATING TO 'CONTROL' CASES

Case	*Age*	*Sex*	*Survival* (months)	*Treatment*
1.	57	F	1½	Antibiotics. Blood transfusions.
2.	17	M	2½	Aminopterin. Blood transsions.
3.	29	F	5	Aminopterin. Antibiotics. Blood transfusions.
4.	36	M	1	Blood transfusions. Antibiotics.
5.	42	M	2 wks.	Blood transfusions. Antibiotics.
6.	74	F	1 wk.	Radiotherapy.
7.	58	F	14	Blood transfusions. Antibiotics.
8.	35	M	2	Blood transfusions. Cortisone. Antibiotics.
9.	53	F	1	Blood transfusions. Cortisone. Antibiotics.
10.	30	M	1	Blood transfusions. Cortisone. Antibiotics.
11.	46	M	3	Blood transfusions. Cortisone. Antibiotics.
12.	49	F	1	Blood transfusions. Cortisone. Antibiotics.

splenomegaly was very much less constant. Improvement in the blood picture was also very irregular in its occurence. In most cases leucopenia with apparent diminution of primitive cells occured, but was not consistently matched by clinical improvement; *per contra*, in some (a fewer number) clinical improvement occurred without any appreciable change in the leucocyte picture. The reappearance of platelets was found to be more unequivocal evidence of benefit than any changes in the leucocyte picture. As indicated above, the anaemia was but rarely benefited, even in cases which otherwise had a good clinical and, so far as the leucocyte and platelet pictures were concerned, haematological response to the therapy. It did not appear that corticosteroid therapy had any real synergistic effect when given with Purinethol.

Five of these cases were of the monocytic variety—4 acute and 1 of the 'chronic' variety, having survived for 10 years after diagnosis. This type of leukaemia has been notoriously resistant to all forms of therapy, but 3 of the 4 acute cases had good clinical and haematological remissions, the fourth showing a response in the blood picture without any benefit to the clinical state. The chronic case, an elderly man of 73, had as his main complaint persistent painful ulceration of the tongue, gums, and throat. Treatment with Purinethol proved efficacious in clearing up these lesions and permitted the patient to eat normally once more.

Acute Leukaemia in Childhood

Five cases of acute leukaemia in childhood treated with Purinethol have been observed. Remissions occurred of 6, 5, 3, 3, and 2 months respectively, and in all cases it was possible for the child to return home and be treated as out-patient. The remarks above relative to the adult cases are applicable to the childhood cases.

Myeloblastic Terminal Phase of Chronic Myelogenous Leukaemia

We have treated 7 cases in this phase. In all there was a measure of clinical improvement, but in most it was short lived, resistance to Purinethol appearing in 2-6 months. Purinethol, however, is the only agent so far available which has been found to have any effect on this condition.

Miscellaneous Conditions

Purinethol has been used with considerable benefit in a case of chronic myeloid leukaemia which had become resistant to radiation therapy and Myleran. A satisfactory remission lasting 6 months was induced.

In 4 cases of malignant reticulosis, 2 of which were histiocytic medullary reticulosis, 1 a 'myeloid reticulosis' (Israels) and 1 an atypical lymphosarcoma with leukaemic blood changes, no benefit of any kind ensured from the use of Purinethol. Purinethol was similarly without effect on one terminal case of chronic lymphocytic leukaemia.

DISCUSSIONS

The use of Purinethol in the treatment of leukaemia and allied conditions has been reported by Burchenal *et al.*,[3] Burchenal,[4] Fountain,[5] Hayhoe and Whitby,[6] Hayhoe,[7] and Hall *et al.*[8]

Evaluation of the place of Purinethol in the chemotherapy of leukaemia and allied conditions is difficult; in its favour is the fact that it is the only agent we have capable of producing remissions in the acute terminal phase of chronic myelogenous leukaemia and in monoblastic leukaemia; it also produces remission in adults with myeloblastic leukaemia more often than any other agent.

On the other hand, it has clearly no place in the reticuloses generally and, as all the published reports show, it is very inconstant in its action, causing considerable amelioration in one patient and none in the next. Yet it is our impression that in those cases where clinical benefit has occurred the very distressing symptoms of acute leukaemia have been mitigated for the patient and the end, when it came, has been sudden—very sudden and quite unexpected in some cases—and even this we regard as a blessing in this disease. As Thomas Fuller said of the good physician, 'When he can keep life no longer in, he makes a fair and easy passage for it to go out'.

We wish to express our thanks to the many physicians and practitioners who have cooperated in the study of these patients. Thanks are also due to Mr. M. Ulrich of the photographic department of the S.A.I.M.R. for the photomicrographs.

REFERENCES

1. Rhoads, C. P. (1954): Science **119,** 77.
2. Hitchings, G. H., Elion, G. B., Falco, E. A., Russell, P. B. and van der Werff, H. (1950): Ann. N.Y. Acad. Sci., **52,** 1318.
3. Burchenal, J. H., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leone, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W. and Rhoads, C. P. (1953): Blood, **8,** 965.
4. Burchenal, J. H. (1954): Cancer Res., **14,** 615.
5. Fountain, J. R. (1955): Brit. Med. J., **1,** 1119.
6. Hayhoe, F. G. J. and Whitby, L. E. H., (1955): Brit. J. Haemat, **1,** 1.
7. Hayhoe, F. G. J. (1955): Lancet, **2,** 903.
8. Hall, B. H., Richards, M. D., Willet, F. M. and Feitchtmeir, T. V. (1954): Ann. N. Y. Acad. Sci., **60,** 374.