SESSION III

SECONDARY HYPERURICAEMIA

(Chairman: DR. W. S. C. COPEMAN)

ALLOPURINOL IN THE PREVENTION OF HYPERURICAEMIA SECONDARY TO THE TREATMENT OF NEOPLASTIC DISEASES WITH ALKYLATING AGENTS, ADRENAL STEROIDS, AND RADIATION THERAPY*†

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Previous speakers have testified to the effectiveness of allopurinol in blocking uric acid production and to its usefulness in the management of gout. Experience with this compound to date has indicated that it is equally useful in the prevention and treatment of the hyperuricaemia which often occurs as a result of the rapid lysis of leukaemic or lymphoma cells by x rays or chemotherapeutic agents (Krakoff and Meyer, 1965). Many authors² (Koniger, 1906; Merrill, 1940; Kravitz, Diamond³ and Craver, 1951; Weisberger and Persky, 1953; Krakoff, Magill, Nary, and Balis, 1961) have emphasized the frequency and seriousness of this problem. In a series of 203 consecutive leukaemic patients observed in the Chemotherapy Service of Memorial Hospital, approximately one quarter had a serum uric acid (SUA) level greater than 12 mg./100 ml. at some time during the course. Serious uric acid nephropathy occurred in many of these patients and was a direct or contributory cause of death in some.

Fig. 1 shows the history of a 9-year-old boy with acute leukaemia, a white blood count of 120,000, marked splenomegaly, and a mediastinal mass, who was treated with adrenocortical steroids. There was a marked rise in SUA simultaneously with an enormous outpouring of uric acid in the urine during the first 24 hours. This resulted in precipitation of uric acid in the urinary tract with serious uric acid nephropathy. Although he survived this episode, his life was endangered by uric acid nephropathy in spite of having achieved a prompt haematological remission of the acute leukaemia.

The increasingly widespread recognition of this phenomenon has led to attempts to prevent it by vigorous administration of fluids, both orally and parenterally, alkalinization of the urine, and the

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Fig. 1.—Clinical course of a 9-year-old boy with acute leukaemia. Reprinted from Krakoff and others (1961).

cautious initiation of chemotherapy or radiotherapy. These measures, however, are not always effective, and treatment by alkalization of the urine, extra-corporeal haemodialysis, or peritoneal dialysis is unsatisfactory.

The availability of allopurinol has made it possible to treat leukaemic and lymphomatous patients much more vigorously without the hazard of uric acid nephropathy.

Fig. 2 shows the history of a 20-year-old girl with acute leukaemia, marked elevation of the white blood count, splenomegaly, and a mediastinal mass. She, too, was treated with adrenocortical steroids, but allopurinol was given first. There was a prompt and marked fall in SUA and urinary uric acid (UUA) in spite of the rapid

and progressive fall in the white blood count and the rapid decrease of the splenomegaly and the mediastinal mass.

In spite of the marked decrease in UUA, there was only a slight increase in urinary oxypurines (hypoxanthine and xanthine). This deficit in total oxypurine excretion has been a consistent finding in our experience with patients treated in this way. Thus, although the solubility of hypoxanthine is similar to that of uric acid and that of xanthine is somewhat less, the total amount of oxypurine excreted is less, and the total oxypurine is divided among three different purines of differing solubilities and with different mechanisms of renal clearance (Goldfinger, Klinenberg, and Seegmiller, 1965), so that the net effect is an advantage in purine excretion. No hypoxanthine or xanthine crystalluria has been seen in any patient treated in this manner in our series. A decrease in uric acid production has been consistent in our experience to date with approximately 150 patients and toxicity has been almost negligible.

In order to investigate the mechanism of the deficit in oxypurine excretion encountered in these patients, we have measured chromatographically the hypoxanthine and xanthine individually in patients with myeloproliferative disorders and with primary gout (Krakoff, Nary, and Balis, 1966). The Table demonstrates the excretion of hypoxanthine, xanthine, and uric acid in four such patients. More xanthine than hypoxanthine is excreted and when allopurinol is given this ratio increases further.

TABLE
DISTRIBUTION OF URINARY OXYPURINES IN FOUR PATIENTS WITH AND WITHOUT ALLOPURINOL

Patient No.	Diagnosis	Allo-purinol	Urinary Excretion (mg./day)		
			Hypo-xanthine	Xan-thine	Uric Acid
1	Chronic granulo-cytic leukaemia	Without	3.2	17	900
		With	7.0	117	200
2	Chronic granulo-cytic leukaemia	Without	4.7	11.4	1250
		With	7.0	27	400
3	Primary gout	Without	4.0	14	300
		With	11.0	72	206
4	Lymphosarcoma	Without	2.5	4	401
		With	3.6	8	65

Studies were done in which hypoxanthine-8-C¹⁴ was given to such patients and its fate observed.

Fig. 3 (opposite) shows the findings in a 56-year-old woman with a myeloproliferative disorder in whom, as expected, allopurinol produced a marked decrease in SUA and UUA, with an increase in oxypurine excretion which, though marked, was of much smaller magnitude than the decrease in UUA excretion. Fig. 3B records the

Fig. 2.—Clinical course of a 20-year-old woman with acute leukaemia. Reprinted from Krakoff and Meyer (1965).

Fig. 3A.—Clinical course of a 56-year-old woman with a myeloproliferative disorder.

Fig. 3B.—Incorporation of Carbon¹⁴ into urinary hypoxanthine, xanthine, and uric acid after the administration of hypoxanthine-8-C¹⁴.

incorporation of C¹⁴-labelled hypoxanthine into UUA, hypoxanthine, and xanthine in the same patient. When labelled hypoxanthine was given, the major portion of radioactivity was found in the urinary uric acid. When a second dose of labelled hypoxanthine was given during the administration of allopurinol, there was, as could have been expected, a much smaller incorporation of C¹⁴ into UUA. The incorporation into urinary hypoxanthine was represented by an initial peak of radioactivity which rapidly fell to undetectable levels, and recurred only with the administration of the second dose. An interesting finding was the pattern of isotope enrichment of urinary xanthine. After initial peak labelling this fell to very low levels, but then rose to a broad period of secondary isotope enrichment with the administration of allopurinol. The second dose of hypoxanthine-C¹⁴, while allopurinol was being given, led to prompt and prolonged enrichment of urinary xanthine.

This was interpreted as indicating that blockage of the oxidation of hypoxanthine to xanthine to uric acid did not prevent the formation of xanthine, indicating therefore that xanthine can arise in man by a route other than the oxidation of hypoxanthine. This may be, as shown in Fig. 4, by the direct conversion of guanylic acid or guanine to xanthine or by the mobilization of xanthine from a pool of xanthine-containing metabolites. This precise route has not yet been established, but further studies are in progress.

Fig. 4.—Diagrammatic representation of possible derivation of xanthine from sources other than oxidation of hypoxanthine.

Although not entirely relevant to the theme of this conference, it is appropriate to consider briefly the marked enhancement of uric acid production *de novo* produced by the 2-substituted thiazidiazoles, a group of compounds with which we have been concerned (Krakoff and Balis, 1959). These substances have been shown to enhance markedly the *de novo* synthesis of uric acid from simple precursors. They produce a characteristic glossitis and the effect can be entirely prevented by the simultaneous administration of nicotinamide or nicotinic acid. In order to determine the effect of administering the potent xanthine oxidase inhibitor, allopurinol, along with the potent uricogenic agent, 2-ethylamino 1,3,4, thiazidiazole (EA-TDA), these two compounds were given together to a 48-year-old man with

Fig. 5.—Effect on uric acid and oxypurine production of the administration of allopurinol and 2-ethylamino-1,3,4-thiadiazole singly and in combination in a 48-year-old man.

leiomyosarcoma (Fig. 5).

As in previous studies, EA-TDA caused a marked increase in SUA and UUA along with the characteristic

oral toxicity. When treatment with allopurinol was begun before the administration of EA-TDA, there was complete inhibition of the uricogenic effect. Fig. 5 also shows the moderate increase in urinary oxypurines produced by the administration of allopurinol and the failure of EA-TDA to produce a further increase in oxypurine excretion.

This latter observation may be additional evidence that allopurinol produces some degree of feed-back inhibition of *de novo* purine biosynthesis, since the inhibition of xanthine oxidase alone along with the marked increase in *de novo* uric acid production caused by EA-TDA would have been expected otherwise to result in a much more marked increase in urinary oxypurine excretion. Further studies of the relation of allopurinol to this interesting group of compounds are currently in progress.

In conclusion, it is considered that allopurinol has provided an important therapeutic means of preventing the marked hyperuricaemia and frequent uric acid nephropathy that accompanies the vigorous treatment of leukaemias and lymphomas with chemotherapeutic agents or radiation therapy. This has resulted in the virtual disappearance of this serious complication of the treatment of these neoplastic diseases and the ability to utilize these effective therapeutic measures much more vigorously than is otherwise possible. This compound has also been shown to be a valuable aid in studies of the excretion of intermediate purines with the suggestion to date that alternative routes to the formation of xanthine may be important in man. Further studies of the influence of allopurinol on purine excretion are clearly indicated and are in progress.