SESSION III
SECONDARY HYPERURICAEMIA
(Chairman: Dr. W. S. C. Copeman)

ALLOPURINOL IN THE PREVENTION OF HYPERURICAEMIA
SECONDARY TO THE TREATMENT OF NEOPLASTIC DISEASES
WITH ALKYLATED 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 authors (Koniger, 1966; Merrill, 1940; Kravitz, Diamond, 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 sur
vived 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.
cautious initiation of chemotherapy or radiotherapy. These measures, however, are not always effective, and treatment by alkalization of the urine, extracorporeal 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 urine 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 amount of 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>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Allopurinol</th>
<th>Urinary Excretion (mg./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With</td>
<td>Hypoxanthine</td>
</tr>
<tr>
<td>1</td>
<td>Chronic granulocytic leukaemia</td>
<td>Without</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>Chronic granulocytic leukaemia</td>
<td>With</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>Primary gout</td>
<td>With</td>
<td>4.0</td>
</tr>
<tr>
<td>4</td>
<td>Lymphosarcoma</td>
<td>With</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Studies were done in which hypoxanthine-8-C'4 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
incorporation of C\(^{14}\)-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 C\(^{14}\) 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-C\(^{14}\) 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.

Although not entirely relevant to the theme of this conference, it is appropriate to consider briefly the marked enhancement of uric acid production \textit{de novo} produced by the 2-substituted thiadiazoles, a group of compounds with which we have been concerned (Krakoff and Balis, 1959). These substances have been shown to enhance markedly the \textit{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, thiadiazole (EA-TDA), these two compounds were given together to a 48-year-old man with
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.

As in previous studies, EA-TDA caused a marked increase in SUA and UUA along with the characteristic leiomysarcoma (Fig. 5).

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.