being those referred to above) and three were from wards in which neomycin-resistant infections already existed or subsequently occurred.

Treatment of nasal carriers of these organisms presents a problem. Almost all are resistant also to penicillin, streptomycin, tetracycline, and erythromycin, there are obvious objections to the use of methicillin or chloramphenicol, fucidin is irritant as a nasal cream, and a small trial of vancomycin produced uncomfortable side-effects. White (1964) treated 20 nasal carriers with an ointment containing 1 or 3 mg. of gentamicin per gramme and found total suppression of staphylococci while treatment lasted, but a large proportion relapsed after it ceased. The use of gentamicin as a spray may well be more successful and fully justifies clinical trial.

Summary

The antibacterial activity of gentamicin has been examined and compared with that of related antibiotics.

It has two promising properties: (1) consistently high activity against *Ps. pyocyanea*, exceeding that of either streptomycin or kanamycin; and (2) unimpaired activity against staphylococci resistant to neomycin and kanamycin—the majority of these strains (recent clinical isolates) were also resistant to bacitracin.

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Allopurinol* and Acute Uric Acid Nephropathy

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Acute uric acid nephropathy is a rare complication of leukaemia, the reticuloses, and other malignant diseases. The renal tubules are blocked by precipitated uric acid formed by the nucleoprotein breakdown due to treatment with cytotoxic drugs. It has to be distinguished from post-renal obstruction caused by the deposition of uric acid crystals. The nephropathy usually responds to the induction of a vigorous water diuresis and alkalinization of the urine.

Allopurinol (4-hydroxypyrazolo (3,4-d)pyrimidine) is a structural isomer of the purine base hypoxanthine. It reduces uric acid production by inhibiting xanthine oxidase and has been used successfully in gout to control the hyperuricaemia and to promote the mobilization of tophi (Rundles, Wyngaarden, Hitchings, Elion, and Silberman, 1963; Klinenberg, Goldfinger, Miller, and Seegmiller, 1963; Yü and Gutman, 1964; Hall, Holloway, and Scott, 1964; Klinenberg, Goldfinger, and Seegmiller, 1965).

The present paper describes two cases of acute uric acid nephropathy, with observations on the therapeutic use of allopurinol in this condition.

Case 1

A man aged 66 with chronic myeloid leukaemia presented with excessive haemorrhage after the excision of nasal polypi in August 1963. At that time the spleen was enlarged and palpable 9 cm. below the costal margin, and the main haemotological findings were: haemoglobin 12.7 g./100 ml.; total leucocyte count 99,000/c.mm. (promyelocytes 5%, myelocytes 2%, metamyelocytes 45%, segmented neutrophil polymorphs 34%); platelets 292,000/c.mm. The spleen was irradiated and the leucocyte count fell to 37,600/c.mm. He relapsed in January 1964 and was given busulphan (2 mg. daily) with temporary improvement. In August the leucocyte count rose to 66,000/c.mm. ("blasts" 58%) and mercaptopurine 150 mg. daily was given with good response. The drug was stopped and he remained well until November, when the leucocyte count rose again to 190,000/c.mm (blasts 35%) and mercaptopurine was restarted.

Bilateral renal colic developed acutely on 25 December and was associated with dysuria, increased frequency of micturition, and nycturia. However, no calculi were passed and there was no overt haematuria. When admitted to hospital on 1 January 1965 (day 1 of this study, see Fig. 1) he was in considerable pain but not dehydrated, the spleen was enlarged and palpable 8 cm. below the left costal margin, and the blood-pressure was 115/60 mm. Hg. Uric acid crystals and red blood cells were present in the urinary centrifuged deposit, and the peripheral blood contained 102,000 leucocytes per c.mm. (blasts 60%). In spite of a positive fluid balance and the maintenance of a normal blood-pressure the volume of urine decreased from 1,300 ml. on day 2 to 85 ml. on day 10; during this period hyperuricaemia (51 mg./100 ml. on day 10) and azotaemia (blood urea 330 mg./100 ml. on day 10) progressively increased (see Fig. 1). No renal calculi were visible on a plain *x*-ray film of the abdomen. Retrograde ureteric catheterization was unsuccessful because of extensive inflammatory changes which obscured the ureteric orifices. A diuresis occurred after the administration of 20% mannitol intravenously (300 ml. given in one hour on days 11, 12, and 13). The urine volume reached its maximum (5,485 ml./24 hr.) on day 15. The urine was kept alkaline by intravenous injection of 100–150 mEq of sodium bicarbonate daily, the dose being regulated by measuring the *p*H of each specimen immediately it was passed. Hypokalaemia, hypo-

* Allopurinol is at present available for clinical trial purposes only.

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calcaemia, and hypomagnesaemia, which developed during the diuretic phase, were treated with potassium chloride, calcium gluconate, and magnesium sulphate as necessary. Allopurinol (200 mg. every eight hours) was given orally from day 14 to day 19 inclusive.

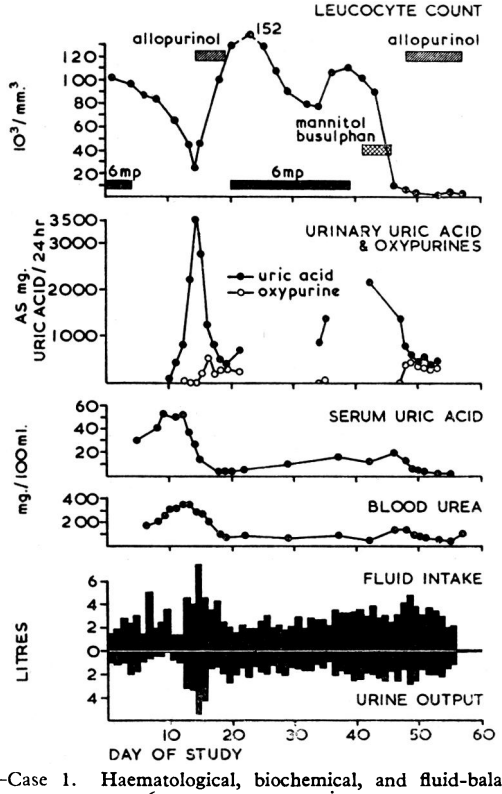

FIG. 1.—Case 1. Haematological, biochemical, and fluid-balance data. 6 mp=mercaptopurine.

The patient made a satisfactory recovery from the uraemic episode, but in spite of the renewed administration of mercaptopurine (50 mg. daily) the leucocyte count remained high (152,000/c.mm., blast 34%, on day 22), subsequently falling to 76,000/c.mm. on day 34. This fall was associated with an increase in the serum uric acid concentration to 14.7 mg./100 ml. on day 37 (Fig. 1) and uric acid crystals were present in the urinary centrifuged deposit at this time. The cytotoxic treatment was changed to intravenous mannitol busulphan on day 41. Two grammes of the drug given intravenously on days 41 to 46 inclusive caused a prompt fall in the leucocyte count from 110,000/c.mm. (blasts 75%) on day 39 to 1,000/c.mm. on day 53. The blood urea rose to 125 mg./100 ml. on day 46, the minimum urine volume over this period being 500 ml./24 hr. Allopurinol (200 mg. every six hours) was given from the 48th day onwards.

Pneumonia developed on the 55th day and he died from pneumococcal septicaemia on the 77th day.

Post-mortem examination showed the characteristic changes of uncontrolled acute myeloblastic leukaemia. Each kidney weighed 150 g. and appeared grossly normal. Histology revealed some active tubular regeneration and some of the tubules contained protein casts. No uric acid crystals (sections stained by the Schultz-Schmidt (Lillie, 1947) method) or xanthine crystals (sections studied in the polarizing microscope) were seen. No uric acid crystals were detected in the synovium of the right knee-joint.

Case 2

A boy aged 16 with acute lymphoblastic leukaemia presented in September 1964 with cervical lymphadenopathy, epistaxes, and petechial haemorrhages. The main haematological findings were: haemoglobin 11.2 g./100 ml. ; total leucocyte count 114,000 c.mm. (lymphoblasts 72%, lymphocytes 23%) ; platelets 24,000/c.mm. A complete clinical and haematological remission followed treatment with prednisolone 40 mg. and mercaptopurine 125 mg. daily. Lymphadenopathy and malaise recurred in late December, and he began to vomit the day before he was admitted to hospital (1 January 1965 ; day 1 of this study, see Fig. 2). He was ill with fever and vomiting, widespread lymphadenopathy, and hepatosplenomegaly. The leucocyte count was 45,000/c.mm. (blasts 64%). The treatment was changed to oral methotrexate 5 mg. daily, and the leucocyte count fell rapidly to a minimum of 400/c.mm. on the 14th day. He continued to vomit and developed uraemia with gross hyperuricaemia (blood urea 450 mg./100 ml. on day 7 ; serum uric acid 81 mg./100 ml. on day 9), and the urine contained many uric acid crystals. His state of hydration was satisfactory on admission and remained so. A fluid intake of 1–1.6 l./24 hr. was maintained with a urine output of approximately 1.5–2 l. except on one occasion (day 7) when it decreased to 650 ml./24 hr. (Fig. 2). A diuresis began on the 10th day and reached a maximum of 6,910 ml./24 hr. on day 12.

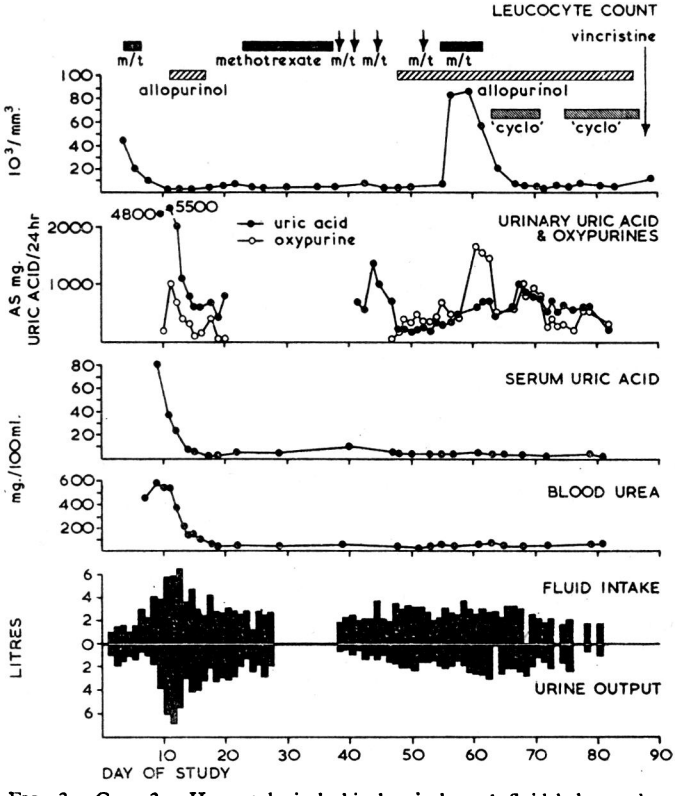

FIG. 2.—Case 2. Haematological, biochemical, and fluid-balance data. M/t=Methotrexate. Cyclo=Cyclophosphamide.

Allopurinol (200 mg. by mouth every eight hours) was given from the 11th to the 18th day inclusive. The serum potassium, which rose to 8 mEq/l., was controlled by Resonium-A retention enemata. Sufficient sodium bicarbonate was administered to render the urine *p*H alkaline, and hypokalaemia, hypocalcaemia, and hypomagnesaemia were corrected during the diuretic phase. He subsequently suffered several haematemeses and then made an excellent recovery. The administration of prednisolone (15 mg. daily) and methotrexate (5 mg. daily) was continued until lymphoblastic meningitis developed and required treatment with intrathecal methotrexate. The dose of prednisolone was increased to 40 mg. daily on day 58. Allopurinol administration (200 mg. every eight hours) was resumed on day 48 in order to study the pattern of uric acid and oxypurine (xanthine plus hypoxanthine) production should a relapse occur and be treated while xanthine oxidase activity was inhibited. He relapsed haematologically (leucocyte count 82,000/c.mm., blasts 35% on day 57), and cyclophosphamide (100 mg. daily) was given on days 63 to 71 and on days 75 to 87 inclusive. The leucocyte count decreased rapidly to 2,700/c.mm. The urinary oxypurine excretion increased in association with the rapid fall in the leucocyte count, but there was only a relatively small rise in the urinary uric acid excretion and no hyperuricaemia or azotaemia occurred (Fig. 2). The patient died suddenly from a cerebral haemorrhage on the 91st day.

Determination of Urinary Purines

Except for minor modifications the oxypurines were determined by the unpublished method of Klinenberg, Goldfinger,

Bradley, and Seegmiller (J. E. Seegmiller, personal communication, 1965). The urine was diluted as for the determination of uric acid (Liddle, Seegmiller, and Laster, 1959) and the extinction at 292 mμ. (E_{292}) measured. Bovine milk xanthine oxidase (approximately 0.02 unit, 25 μl. of a tenfold dilution of C. F. Boehringer and Sohne's xanthine oxidase) was added to oxidize the oxypurines to uric acid, and further spectrophotometer readings were taken until there was no further change in E_{292}. Uricase (7.5 units of Leo Pharmaceutical Products' uricase) was added and the change in E_{292} due to the oxidation of uric acid to allantoin was measured. Corrections were made for the change in E_{292} due to the added enzyme solutions and for the dilution factors. The total amount of uric acid oxidized by the uricase was calculated from its molecular extinction coefficient. This gives the sum of the uric acid initially present in the urine plus that formed from the oxypurines during the analysis. The initial uric acid content of the urine was determined separately as described by Liddle *et al.* (1959) and the oxypurine content (expressed as the equivalent amount of uric acid) was obtained by difference.

Allopurinol is excreted in the urine partly unchanged, and partly as its oxidation product (2,6-dihydroxypyrazolo(3,4-d)-pyrimidine). There is some evidence that xanthine oxidase catalyses this oxidation (Elion, Taylor, and Hitchings, 1964), so that further oxidation of allopurinol could theoretically occur during the enzymatic determination of the oxypurines. The present method of determining the oxypurines would be invalid if this oxidation of allopurinol were accompanied by a change in E_{292}.

The ultra-violet absorption spectrum of allopurinol was shown to have two absorption bands with maxima at 221 mμ and 252 mμ respectively, under the conditions used for the analyses. The molecular extinction coefficients (ε) being $\varepsilon_{221}=7921$ and $\varepsilon_{252}=7420$ under these conditions. There was negligible light absorption at 292 mμ and no significant change in E_{292}, after correction for the enzyme blanks, when allopurinol was treated with xanthine oxidase and uricase as in the analyses. It was also established that significant xanthine oxidase was being used in the analyses to overcome the possible inhibitory effects of allopurinol and its metabolites in the urine.

Discussion

Leukaemia, the reticuloses, and other malignant conditions are associated with an increased turnover of nucleoprotein ; and an increased excretion of uric acid, as well as minor degrees of hyperuricaemia are not uncommon. The complications of hyperuricaemia and hyperuric aciduria occur as a result of low solubility of monosodium urate in the interstitial fluids and of uric acid in the urine. Approximately 10% of cases of clinical gout are secondary to blood dyscrasias (Seegmiller, Laster, and Howell, 1963) and 5% of leukaemic patients have uric acid stones (McCrea, 1955).

Kritzler (1958) and Frei, Bentzel, Rieselbach, and Block (1963) found that acute uric acid nephropathy was an important cause of acute renal failure associated with the treatment of acute leukaemia. Rieselbach, Bentzel, Cotlove, Frei, and Freireich (1964) presented experimental evidence to support the view that the renal lesion in these cases is obstructive in nature and that the degree of functional impairment is directly related to the increased rate of uric acid production.

Sandberg, Cartwright, and Wintrobe (1956) found that the excretion of uric acid rose as the leucocyte count fell ; however, the incidence of acute uric acid nephropathy does not seem to be closely related to the pretreatment leucocyte count. Other factors such as dehydration, metabolic acidosis associated with the catabolism of tissue protein due to the dissolution of leukaemic deposits, and the use of drugs with uricosuric properties are obviously important. The complication may be more likely to occur in subjects such as those studied by Metcalfe-Gibson, McCallum, Morrison, and Wrong (1965), who are prone to form uric acid stones, because they maintain a strongly acid urine throughout the 24 hours.

Allopurinol inhibits the enzyme xanthine oxidase which catalyses the oxidation of hypoxanthine to xanthine and xanthine to uric acid. The drug has been used on a limited scale in the management of primary and secondary gout, and systemic side-effects have been reported in only one patient (Klinenberg *et al.*, 1965). It also retards the metabolism of the thiopurines (Elion, Callahan, Nathan, Bieber, Rundles, and Hitchings, 1963). The administration of allopurinol is followed by a prompt decline in the levels of uric acid in the plasma and urine, and a rise in the oxypurines, xanthine and hypoxanthine ; the oxypurines are cleared more rapidly from the plasma than is uric acid, so that their concentration rarely exceeds 1 mg./100 ml. (Goldfinger, Klinenberg, and Seegmiller, 1965). Klinenberg *et al.* (1965) found that xanthine and hypoxanthine were excreted in approximately equal proportions during allopurinol administration. Thus three end-products of purine metabolism are excreted, each with its own solubility limit, and, in particular, the amount of uric acid present in the urine is reduced. There is some theoretical risk that xanthine might precipitate in the urinary tract ; however, this has not been observed when the drug has been used in the treatment of gout (Rundles *et al.*, 1963 ; Klinenberg *et al.*, 1963, 1965 ; Yü and Gutman, 1964), and it is not a major problem in the management of patients with xanthinuria, who lack xanthine oxidase and excrete 70% of their total purine output as xanthine and 30% as hypoxanthine (Engelman, Watts, Klinenberg, Sjoerdsma, and Seegmiller, 1964).

We do not consider that allopurinol affected the outcome in Case 1, because the drug was not given until a diuresis was already established. The observations on this patient showed that the expected rise in oxypurine excretion occurred, though it was relatively small when compared with the excretion of uric acid. Most of the latter represented uric acid which had been formed before the drug was given and which had been deposited in the renal tubules prior to the period of oliguria.

The maintenance of an adequate output of urine was easier in Case 2, and allopurinol was administered when the leucocyte count was falling in the first relapse studied (Fig. 2), and though the urinary uric acid decreased rapidly only relatively small amounts of oxypurine appeared in the urine, indicating that most of the uric acid had been formed before xanthine-oxidase inhibition was achieved. The blood urea and serum uric acid concentrations decreased concomitantly with the urinary uric acid and the relief of the renal tubular obstruction.

The administration of allopurinol was resumed on day 48 of the study, while the patient was still in apparent haematological remission, in order to observe its effect on the course of a subsequent relapse. There was a striking decrease in the excretion of uric acid before the second relapse, and it is apparent (Fig. 2) that the purine load consequent upon the response to methotrexate was spread between the uric acid and the oxypurines, and no azotaemia or hyperuricaemia occurred. This contrasted with the findings in the first relapse, when the drug was not given until the leucocyte count was falling and therefore too late to be effective. An adequate urine output was maintained in both relapses in Case 2 ; in spite of this, acute uric acid nephropathy occurred in the first relapse. The present evidence strongly suggests that the allopurinol cover played a large part in preventing acute uric acid nephropathy during the second relapse.

It is concluded that if allopurinol is to be effective in preventing acute uric acid nephropathy in acute leukaemia it should be given before cytotoxic treatment is begun, in order to cover the period of maximum tissue breakdown. The aim of its administration is to arrest purine catabolism at the stage of hypoxanthine and xanthine, and thus avoid overloading the kidneys with uric acid.

Summary

Two cases of acute uric acid nephropathy complicating acute leukaemia are described.

Some observations have been made which bear on the use of the xanthine oxidase inhibitor allopurinol in the management of acute uric acid nephropathy.

Allopurinol restricts the formation of uric acid in acute leukaemia, but to be effective in reducing the risk of acute uric acid nephropathy it must be given before chemotherapy is begun.

The patients were under the care of Sir Ronald Bodley Scott, K.C.V.O., and we are pleased to acknowledge our indebtedness to him for allowing us to study them, and for his help and encouragement. Some of the work was undertaken in the Medical Professorial Unit (Dunn Laboratories), and we are indebted to Professor E. F. Scowen for his interest. We also wish to thank the Governors of St. Bartholomew's Hospital for their generous research grant, and Burroughs Wellcome and Co. for supplies of allopurinol.

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Incidence of Candida in Hospital In-patients and the Effects of Antibiotic Therapy

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Until recently a majority of clinicians probably thought of candida only in relation to stomatitis in infants and vaginitis in women. Few appreciated its widespread distribution or its potential pathogenicity, particularly in debilitated or diabetic patients or after antibiotic or steroid therapy. Thus it may well go unrecognized as an infecting agent.

The widespread distribution of candida and its increase after broad-spectrum antibiotics has been studied at various sites. In addition carriers may be of importance because of their ability to infect others (Lepper *et al.*, 1958–9). The place of the intestinal reservoir in relation to skin lesions has been discussed by Marten (1959), and the occurrence of *Candida albicans* in angular cheilitis by Cawson (1963), in intertrigo by Shelmire (1925), and in paronychia by Whittle *et al.* (1959).

In this study the incidence of oral and rectal candida and changes coincidental with antibiotic therapy in unselected patients admitted to hospital were investigated. Murdoch (1964) recommended a combination of the non-absorbed antifungal agent, nystatin, with tetracycline (Mysteclin), to overcome an increase of the intestinal reservoir of candida, and this hypothesis was also studied.

Materials and Methods

The study was undertaken in a small general hospital serving both urban and rural areas. All patients admitted to the medical wards during one year were included in the study, except diabetics and those who had had steroid or antibiotic therapy in the previous year. Treatment was decided on clinical grounds, but where tetracycline was prescribed patients were given tetracycline or Mysteclin in a random fashion and under double-blind conditions. Antibiotic dosage was judged according to the clinical requirements ; tetracycline was generally given at 250 mg. q.i.d., and patients allocated to the antifungal combination received 250,000 units of nystatin with each 250 mg. of tetracycline. Penicillin was administered at a level of from 2 to 3 million units of benzylpenicillin intramuscularly daily.

Irrespective of antibiotic therapy, throat and rectal swabs were obtained on admission and again after five days. Standard throat swabs were used ; rectal swabs were similar except for the addition of a short length of glass tubing, which protected the swab during its introduction through the anus, so as to prevent skin and anal margin contamination.

In the laboratory the swabs were inoculated on to Sabouraud's medium. Where bacterial contamination from the rectal swabs became evident reinoculation as described by J. Walker (personal communication, 1957) was performed to obtain pure cultures. Gram-stained films were examined for morphology and purity, and further techniques as described by Conant *et al.* (1954) were used to identify the organisms isolated. Chlamydospore production was assessed by the method of Dawson (1962), and further guidance on colonial forms and slide culture appearances was culled from Benham (1957).

An attempt was also made to assess any variations in symptoms by questioning patients on admission and again on the sixth and twelfth days for the presence and severity of

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