Allopurinol for Gout

In few diseases have more therapeutic advances been made than in that most ancient of disorders, gout. Apart from the use of colchicine for acute attacks and dietetic restrictions between them, almost all other therapy has changed since 1952, when probenecid and phenylbutazone appeared. As often happens today, pharmacological advances helped to throw light on physiological and pathological processes. Therapeutic advances and an understanding of what happens during and between attacks of gout have gone hand in hand. The latest therapeutic advance has been the introduction of allopurinol.[1-3] This week in the *B.M.J.* an article by Drs. J. T. Scott, A. P. Hall, and R. Grahame at page 321 gives a clear account of its uses and indications in primary gout. As they point out in their first paragraph, this new treatment is itself a by-product of treatment; the drug was first used to suppress the oxidation of 6-mercaptopurine to the therapeutically inert metabolite 6-thiouric acid.

Opinions still differ on what the metabolic defect is in gout. Good evidence points to overproduction of urates, but opinion is divided on the part played by renal clearance of them. The opposing views of those who find no evidence of primary defect in the function of the renal tubules, and of those who do, is well reviewed by S. L. Wallace and D. Bernstein.[4] Recently workers in the Mayo Clinic[5] reported that one of two normal persons and one of five gouty patients with normal renal function, as judged by the usual tests, were unable to increase their uric-acid clearance ratios more than 40% when given uric-acid loading; such patients excreted less uric acid than usual in response to probenecid. Urates are partly eliminated in the faeces, but in gouty subjects the kidneys deal with most of the excess load, and in both primary and secondary gout tophaceous material may be deposited in the renal substance, some of the heaviest deposits occurring in lymphosarcomatous and leukaemic conditions while under treatment. The question whether uricosuric drugs eventually help or harm renal function after prolonged administration is still open, but though there are theoretical objections to their use the passing of fourteen years since the introduction of probenecid has not shown them to be a great or frequent danger. While renal function in certain cases may deteriorate on uricosuric therapy, in others it appears to improve. The genitourinary surgeon is no stranger to the gouty kidney, which may mislead him by presenting with renal colic and haematuria and giving rise to bizarre pyelograms. In the past, gouty kidneys have occasionally been removed, having been misdiagnosed as carcinomatous ones. While gouty patients commonly live to ripe old age, renal function has always to be watched, and biopsy material from the gouty kidney frequently shows pathological changes. Any therapeutic agent, therefore, which is likely to spare the kidney damage is very welcome. Probenecid, ethebenezid, and sulphinpyrazone, though effective uricosuric agents, do not always hold the uric-acid levels in the plasma within the normal range or prevent acute attacks, even though renal function is apparently normal. In patients with renal disease the function of the kidneys may deteriorate during therapy. In this respect allopurinol was a particularly useful addition to the drugs for the long-term control of gout.

Allopurinol acts by inhibiting the enzyme xanthine oxidase from oxidizing the oxypurines, xanthine and hypoxanthine, to uric acid. The solubility and renal clearance of these two substances are greater than those of uric acid, and they are the more easily excreted. Levels of uric acid in the plasma fall, and likewise the output of urates falls in the urine, though not all workers find an equivalent rise in the output of oxypurine.[6]

Introduced in 1963,[7] the drug has been under trial now for over three years. Though generally released in the United Kingdom some three months ago, it is still restricted to research centres in the country of its birth, the United States. While under trial it has proved remarkably free from toxic effects. Diarrhoea, fever, and rashes have all occurred, but more serious complications have not been reported. The high incidence of abnormalities in the bromsulphalein test reported by Dr. Scott and his colleagues occurred both in allopurinol-treated and probenecid-treated patients. Further study of this is needed in untreated gouty subjects. Acute attacks of gout may occur soon after the introduction of the drug. Although sometimes they are due to discontinuance of the uricosuric drug previously given, they are not always, and Scott and his colleagues suggest a possible explanation. Further use of the drug will probably lead to a wider range of toxic effects being reported. The risk of them will have to be weighed against the benefits.

In what conditions may allopurinol be recommended? A dogmatic answer cannot be given yet, but a provisional list would be as follows. First, when other forms of treatment, by breaking down malignant or leukaemic or polycythaemic tissues, are flooding the system with urates, causing increased levels in the blood and urine, with the risk not only of acute gout but of renal damage (group 7 of Scott and his colleagues). Secondly, for patients with gout who also have damaged renal function or who have had uratic calculus or gravel. Thirdly, when existing uricosuric therapy has proved inadequate or unsatisfactory. And, fourthly, when gross overproduction of uric acid occurs in primary or secondary gout (group 4 of Scott and his colleagues). But in many cases allopurinol may prove to be more effective than the present uricosuric drugs and come to replace them in long-term routine therapy if extended use shows that toxic effects are relatively rare. It would seem that here is a drug which has opened up new fields in the therapy of metabolic disease.

Dehydration in Acute Gastro-enteritis

Gastro-enteritis and its associated dehydration has become far less common in economically and medically advanced communities, even though the incidence of breast-feeding declined sharply. Application of the principles of hygiene and of correct feeding and the prevention of cross-infection in hospitals contributed more to this decline than the use of drugs, which still have only a limited value in the management of acute gastro-intestinal disorders. This is not to say that gastro-enteritis is rare even in Great Britain, and every paediatric unit must be well prepared to deal with its therapeutic problems. But in underdeveloped countries gastro-

[1] Hall, A. P., Holloway, V. P., and Scott, J. T., *Ann. rheum. Dis.*, 1964, **23**, 439.
[2] *Brit. med. J.*, 1965, **1**, 810.
[3] Proceedings of Conference on Gout and Purine Metabolism, ed. A. B. Gutman, *Arthr. and Rheum.*, 1965, **8**, 883.
[4] Wallace, S. L., and Bernstein, D., *Metabolism*, 1963, **12**, 440.
[5] Colton, R. S., Maher, F. T., Ward, L. M., and Fergusson, R. H., *Proc. Mayo Clin.*, 1966, **41**, 326.
[6] Seventeenth Rheumatism Review, *Arthr. and Rheum.*, 1966, **9**, 169.
[7] Rundles, R. W., Wyngaarden, J. B., Hitchings, G. H., Elion, G. B., and Silberman, H. R., *Trans. Ass. Amer. Phycns*, 1963, **76**, 126.

enteritis with severe dehydration is still common, as it is also among the poorer communities of some better-off countries. A recent report from South Africa by H. de V. Heese and colleagues[1] gave some pertinent information.

In their hospital in Capetown, as well as in many other places in Africa and Asia, gastro-enteritis is so common that infants have to be treated either in large special wards or in the "drip-room" in large tents in the open air, often by their hundreds each day. The parents bring their infants for treatment in the morning and help to look after the babies during the day. At night the drip is taken down and the babies are taken home till next morning, when they return for the next intravenous infusion, if this is still indicated. In such conditions it is obvious that the simplest, most effective treatment must be given which is applicable to the large majority of babies, for individual and repeated electrolyte studies cannot be performed as a routine. It is fortunate that such therapy is possible after simple clinical assessment and with a few standard intravenous solutions.

Not all infants with diarrhoea and vomiting require intravenous therapy. In early and mild cases replacement of milk by glucose-saline feeds until the vomiting has ceased is usually sufficient. This is followed by the gradual building up of milk feeds according to the infant's tolerance over a period of three or four days, by which time the diarrhoea usually ceases, either on its own or through the use of one of the many antibacterial agents now available.

In more severe cases intravenous therapy is essential. Such babies are usually clinically dehydrated and suffer from metabolic acidosis. Clinically the acidosis shows itself by the increased rate and depth of the respiration. Dehydration is shown by a decrease in skin turgor. The baby's colour is grey, its eyes are sunken and soft, and its anterior fontanelle is depressed. The baby usually, but not always, feels cold. In isotonic dehydration it is lethargic, and in hypotonic dehydration it may even go into coma, while in hypertonic dehydration irritability is notable. The degree of dehydration may be estimated by the severity of these symptoms and by the loss of weight as judged by records (if available) or by the difference between the expected and actual weight of the baby. In profound dehydration signs of shock appear with rapid, thready pulse and very low blood-pressure. The volume of urine passed is very low, but owing to the young kidneys' relative inability to concentrate the specific gravity is not high.

In acute dehydration with metabolic acidosis the carbon-dioxide content of the serum is usually very low and the bicarbonate level may be as little as 5 mEq/litre. The level of sodium may be low or high, while that of potassium is more often low than high, though the true deficit of potassium from the cells is not necessarily reflected in the serum levels. The blood urea is often raised. More accurate assessment of the acidosis can be obtained by estimating the *p*H of arterial blood, but this is rarely done except for the purpose of specific investigations.

The main problem is to replace the lost fluids and electrolytes and provide for the baby's nutritional needs while allowing for the continued excessive losses until the diarrhoea has been brought under control. Although the normal electrolyte balance in the body is maintained by many complicated hormonal and biochemical mechanisms, not all of which are yet fully understood, the principles and practice of treatment are relatively simple, as has been shown by many authors, including Dr. Heese and his colleagues. So long as an adequate volume of an isotonic solution is offered, the kidneys are remarkably competent to conserve or excrete electrolytes according to need. In most instances it is not necessary to give alkalis, such as 4% sodium bicarbonate or 1/6M sodium lactate solutions. In the controlled trial in Capetown the infants treated with half-strength Darrow's-2.5% dextrose solution improved satisfactorily, as did those who were given sodium bicarbonate in addition. A normal acid-base balance was achieved quicker in the latter group, but by 24 hours there was no difference biochemically between the two. Nevertheless, in very severe cases, with profound dehydration and acidosis, the addition of sodium bicarbonate or of 1/6M sodium lactate is a life-saving emergency measure. Naturally, under good laboratory control more precise treatment is possible, particularly with regard to potassium replacement. But as the intravenous administration of potassium can be dangerous it is best to give it by mouth unless the physician has great experience in this field of therapy.

[1] Heese, H. de V., Tonin, C., Bowie, M.D., and Evans, A., *Brit. med. J.*, 1966, 2, 144.

Selection and Pecking Order

The traditional role of the doctor is to identify and treat his patient's ills, and his patients have selected themselves by consulting him in the first place. A doctor is not usually required to select people having certain qualities which fit them for a particular task, though there are occasions when he may be asked to do that. This is exceedingly difficult because he can never be sure that those he rejected might not have performed better than those he selected, whereas a disease he misses may often become obvious enough later.

The difficulties of selecting for certain positive qualities arise in many fields, and a familiar case is the selection of medical students. Most persons concerned in this have a fairly clear idea of the sort of men they want as future doctors, but they are to a certain extent crystal-gazing in trying to predict what a man will be like five or six years hence. Never far from the interviewer's mind is the thought that his selection procedure may have eliminated a potentially good doctor, and very much to the forefront is the knowledge, based on bitter experience, that he is selecting a certain number who will fail at one stage or another.

The public and armed services have a wealth of experience in the problems of sorting out men for particular tasks. One example is the selection of aircrew. Here special attention is paid because training is expensive and highly technical and failure can be disastrous in terms of national effort and life. The criteria used to select aircrew are not restricted to that procedure alone.[1] To fly an aeroplane requires intelligence, mechanical and scientific aptitude, a high degree of proficiency in motor skills of various kinds, and the temperament to deal with complicated and unexpected situations. These are the qualities in fact needed to hold many responsible positions in our society. Though it is clear in the abstract that certain qualities are desirable and others are not, when it comes to detecting and measuring these qualities in selection procedures every interviewer has his own yardstick. A battery of tests for various skills and aptitudes combined with interview has been found to work in practice—up to a point. In the selection of aircrew the aptitude scores are well correlated with subsequent success at training, but