

Even where such pathologists are in post, many are already overextended in subspecialties of paediatric pathology that themselves require special skills—such as infant tumours, inborn errors of metabolism, cytogenetics, or fetal pathology. To cover the country would require many more paediatric pathologists interested in the cause of death. Nevertheless, the need for very critical necropsies remains.

There is a good argument for leaving cot deaths in the hands of the coroner with a close liaison with forensic departments, as not all unexpected deaths in childhood are natural. Nevertheless, the investigation of cot deaths can be taken at several levels. In clinically unexpected death a general necropsy will rapidly exclude gross abnormalities such as congenital heart deformities that have not been diagnosed in life or gross evidence of trauma or of gross infection. Such necropsies establish a diagnosis of overt cot deaths, and the death certificate needs to be given at this time, if only for the support of the parents and family. Their needs are similar in all unexpected deaths irrespective of the detailed pathological findings.

We need to investigate cot deaths at a research level without interfering with the clinical care of the families. Such investigations usually take several weeks to complete—much longer than the delay that is possible for issuing the normal death certificate. Nevertheless, we also need to exploit the opportunities given by the non-specialist necropsy. One of the studies sponsored by the Foundation for the Study of Infant Deaths is using a system that could be used nationally. The child who has died unexpectedly is examined and a naked eye necropsy carried out locally, when cultures and such tests are performed. In the absence of overt disease or evidence of unnatural death, the manner of death is certified as a cot death. All the viscera are fixed and these are sent to a paediatric research laboratory, where a complete assessment of the tissues is carried out at leisure. The findings are reported back to the original pathologist and any review of diagnosis is left to him.

Several of us working on this subject feel that there is now an urgent need for the development of a few reference research centres in Britain. These could not only maintain close contact with one another but could also cooperate with those doing research in other disciplines.

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## Food, drink, and gout

The associates of a high uric acid are the associates of plenty.<sup>1</sup>

Victims of gout have been depicted over the centuries as being characteristically overweight and rather gluttonous. Research confirms these beliefs: for example, Kahn showed that people with gout esteemed their food highly, with eating and drinking being two of their greatest pleasures in life.<sup>2</sup> To what extent is this commonly accepted clinical picture supported and explained by recent scientific findings?

The metabolic disorder in gout is hyperuricaemia, an excess of urate in blood and tissue fluids, which in some (but by no means all) cases leads to deposition of crystals of sodium urate in the joints and the subsequent inflammatory reaction of acute gouty arthritis. Though hyperuricaemia is occasionally due to a single identified disorder, either genetic (for example, the rare Lesch-Nyhan syndrome, with deficiency of the enzyme hypoxanthine guanine phosphoribosyl transferase) or environmental (for example, lead poisoning), the cause is now recognised as being usually multifactorial. To an underlying and usually ill defined genetic predisposition, in which selective impairment of renal clearance of urate is the predominant factor in most instances, are added external agents—particularly food, alcohol, and drugs (commonly diuretics, now widely prescribed for the elderly). The part played by food and alcohol has been the subject of several recent studies.

Firstly, the purine content of the diet has been shown to influence serum concentrations of urate, which is the end product of purine metabolism in man. A diet rich in purines will raise the concentration: as an extreme example, it is possible to double it by consuming 4 g of ribonucleic acid daily. Conversely, the blood urate concentration may be reduced by about 60-120  $\mu\text{mol/l}$  (1.0-2.0 mg/100 ml) by a diet free of purine.<sup>3-4</sup> Relatively little is known, however, about the precise identity and quantity of individual purines in most of the foods that we eat. Overall protein consumption is often invoked as a contributory cause of hyperuricaemia but it may have the opposite effect—high protein diets being associated with increased excretion of urate.<sup>5-6</sup>

Secondly, the energy content of the diet probably influences the development of hyperuricaemia, whose relation to body weight has been shown in numerous epidemiological studies in Britain,<sup>7</sup> the United States,<sup>8</sup> and elsewhere. Notwithstanding many individual exceptions, the sufferer from gout tends to be a "big, well developed, and portly individual"<sup>9</sup> and surveys of patients with gout have shown an increased incidence of obesity. For example, in a British study of 354 patients with gout 48% were more than 15% over their ideal body weights,<sup>10</sup> and comparable findings have been reported from other countries including Denmark,<sup>11</sup> the United States,<sup>12</sup> and

Australia.<sup>13</sup> The relation appears to be one of cause and effect, since loss of weight lowers the serum urate concentration.<sup>14 15</sup> Its exact nature is poorly understood but has recently been reviewed, together with the further difficult interrelation with hyperlipidaemia and impaired glucose tolerance.<sup>16</sup>

Finally, the part played by alcohol must be considered, in the light of A B Garrod's opinion over 100 years ago that "fermented liquors" are a powerful predisposing cause of gout. Is it due simply to the high energy content of alcohol, or to its role in "washing down huge platters of meat,"<sup>17</sup> or, at least in former times, to heavy contamination with lead?<sup>18</sup> Or is there a more specific association?

The last suggestion receives support from a number of studies. High concentrations of blood alcohol produce a rise in lactate, which competitively inhibits the renal tubular excretion of urate.<sup>19</sup> Faller and Fox, of Ann Arbor,<sup>20</sup> have recently examined the effects of long term oral and short term intravenous administration of alcohol in patients with gout. During the long term study serum and urinary urate concentrations rose, as did urinary oxypurines and the daily turnover of uric acid. Short term intravenous administration of alcohol produced no substantial changes in urate clearance but urinary oxypurines were increased and after administration of radioactive adenine, urinary radioactivity was also increased. The conclusion drawn was that alcohol increases urate synthesis by enhancing the turnover of adenine nucleotides. This suggestion is not necessarily at variance with the lactate hypothesis. Plasma alcohol concentrations achieved in the Ann Arbor studies were considerably lower than those in the earlier work, and a picture emerges of chronic consumption of alcohol producing an increased synthesis of urate with acute intoxication adding an additional element of renal shutdown.

In a further interesting recent study Gibson *et al*<sup>21</sup> gave a careful dietary questionnaire to patients with gout and controls. The average intake of most foodstuffs, including total purine nitrogen, was similar in the two groups, except that the patients with gout drank significantly more alcohol. Beer was the most popular alcoholic beverage, and it was suggested that the intake of purine nitrogen derived from beer was sufficient to have a clinical effect, augmenting the hyperuricaemic influence of alcohol itself.

These investigations have obvious implications for some patients in terms of correcting the causes of hyperuricaemia and the management of gout, well reviewed by Emmerson.<sup>22</sup> Every patient with gout must be carefully assessed to determine, from history, examination, and investigation, the various factors which are contributing to his hyperuricaemia.<sup>23</sup> When these are explained he may be prepared to cooperate in correcting some possible contributory factors. A number of patients who do this will become normouricaemic and remain so, and of course improvement of life style in terms of overeating and overdrinking is desirable in itself quite apart from any link with hyperuricaemia. Drug treatment for hyperuricaemia and gout is effective but all too often is prescribed unnecessarily. It should be reserved for patients with gout who remain hyperuricaemic despite modification in their eating and drinking habits—or who, as is unfortunately often the case, disregard such wise counsel.

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## Cytotoxic drugs for non-neoplastic disease

Cytotoxic drugs are now being prescribed for conditions other than cancer more often than they were, but it is important to bear some reservations in mind. The expectations for new drugs often exceed their ultimate achievement and initial optimism has now been tempered by experience: not only is the choice of a drug important but so also is that of the patient to be treated.

Applying such principles may result in great benefit, relieving symptoms, improving the quality of life, and prolonging survival. Unfortunately, since we still have no way of identifying the patient who will or will not benefit, some patients will suffer the toxic effects of these drugs without the advantages which treatment will certainly bring to others. Experience is one guideline, and the creation of the specialty of medical oncology has meant that for cancer at least chemotherapy can be combined appropriately with other clinical modalities to meet the needs of the individual patient. The clinician planning to treat the occasional patient would therefore be well advised to seek advice from such a colleague.

The medical oncologist's horizons have not, however, encompassed all the conditions in which cytotoxic drugs are used. It is indeed curious that, while the infrequent user is being discouraged from prescribing anticancer drugs for the