THE LANCET

Immunocompromised Homosexuals

IN early June of this year GOTTLIEB and co-workers[1] recorded the cases of 5 young homosexual men, previously in good health, who were treated for *Pneumocystis carinii* pneumonia in three Los Angeles hospitals. Soon afterwards came reports[2,3] of 26 young male homosexuals with an unusually severe form of Kaposi's sarcoma (KS) involving both skin and lymphoid organs. 5 of these 26 patients also had opportunist infections such as pneumocystis pneumonia, cryptococcosis, or severe candidiasis which are usually seen only in the setting of a severely immunocompromised host. By August, 70 further cases of KS and/or pneumocystis pneumonia had been confirmed.[4] Currently the C.D.C. (Centers for Disease Control) in Atlanta is aware of nearly 180 cases, and the numbers are increasing at 7–10 a week. The epidemic seems to be largely confined to urban areas of New York State and California. Most of the patients are young white males (95% aged less than 50) and 94% of them are homosexual or bisexual. The case fatality rate, due to the effects of the tumour or overwhelming infection, has been an alarming 40%.

What makes these events so extraordinary is the occurrence of both KS and opportunist infections in a population of previously healthy young men. Kaposi's sarcoma is a rare vascular neoplasm which, in the United States at least, typically produces cutaneous lesions in elderly males, runs an indolent course of 8–13 years, and is rarely fatal.[5] *Pneumocystis carinii* is a protozoon-like organism which causes a severe interstitial pneumonia. Although it was originally recognised in malnourished children, nowadays pneumocystis pneumonia most frequently arises in immunocompromised hosts.[6] What is the cause of this outbreak of bizarre infections and a rare tumour in these young homosexuals?

As well as their sexual preference, almost all of the patients have had in common cultural or serological evidence of infection with cytomegalovirus (CMV). Viral infections such as measles, influenza, or rubella may produce an immunosuppressive effect in man, but this has been particularly well recognised with CMV.[7,8] Mice exposed to a sublethal dose of CMV have shown an increased mortality from bacterial and fungal infections.[9] As with other herpesviruses, primary CMV infection results in a latent state which may be activated by, for example, an allogeneic stimulus.[10] Lymphocytes from patients with acute CMV mononucleosis showed a diminished responsiveness to certain mitogens—possibly due to an effect on cells of the monocyte-macrophage system.[11] Furthermore, analysis of lymphocyte subpopulations during human CMV infection has shown a reversal in the normal ratio of T helper to T suppressor cells.[12] That these in-vitro observations may have clinical relevance in man has been suggested by studies in renal allograft recipients:[13] most patients with opportunist bacterial or fungal infection had evidence of concurrent active CMV disease.

The suggestion that CMV is involved in the pathogenesis of KS and the infections seen in these young men receives further support from evidence that KS may be a virus-induced tumour. The epidemiology of this disease is of interest. In certain parts of equatorial Africa it accounts for nearly 10% of all malignant neoplasms. In those areas it affects predominantly young men, involves lymphoid organs rather than the skin, and is rapidly fatal. Familial clustering is rare, even in endemic areas, and serological studies in Americans with KS have shown an extremely high rate of CMV seropositivity (13–16 times greater than in healthy men).[14,15] These findings are reminiscent of those which implicated Epstein-Barr virus in Burkitt's lymphoma. The case against CMV has received further support by the description of herpesvirus-like particles in cell lines derived from KS tumours,[16] and, more recently, the use of DNA-DNA reassociation kinetics which suggested the presence of CMV DNA and early antigens with KS tumour cells.[17] Reports of an increased incidence of the

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758a

tumour in immunosuppressed patients strengthen the possibility that the development of KS may be associated with reactivation of latent CMV infection.[18-20]

A further link in the chain is the recognition that CMV is extremely prevalent amongst homosexuals in America. In one study, 94% of 190 homosexuals had serological evidence of exposure to CMV—as against 54% of heterosexuals and 43% of male blood-donors.[21] However, the very fact that CMV is so widespread among this population will be an obstacle to determining whether it has a causal role. Even if CMV is involved, it is unlikely to be solely responsible for the profound defect in immune surveillance which apparently develops in these patients. Some other factors, acting alone or together with CMV, must be responsible for the depression of cell-mediated immunity,[22] and perhaps also for reactivation of latent CMV infection. Such factors may include the many recreational drugs used by homosexuals (as suggested by Dr BRENNAN and Dr DURACK on p. 1338), new or unrecognised environmental pollutants, or even another infective agent; the parallels with the legionnaires' disease episode are clear. Another report this week (p. 1339) shows that the immunocompromise syndrome is not confined to the United States, though the patient, from Bournemouth, had been to Miami nine months before becoming ill.

Obviously, clinicians must be on the alert for this syndrome, with its high mortality. In addition, there is a good chance that these bizarre events will further our understanding of questions such as the site of CMV latency in man, the cell of origin of KS, and the nature of acquired immunosuppression. Since they arise in a well-defined population they provide the setting for a classic epidemiological investigation, and such work is under way at the C.D.C. in Atlanta.

Diphosphonates: Aimed in a Chemical Sense

PAUL EHRLICH saw chemotherapy, in terms of targeting: "We must learn to aim, and aim in a chemical sense".[1] In the case of metabolic bone disease the targets are excessive bone resorption and inappropriate calcification and ossification. Since their introduction over a decade ago, the diphosphonates have been aimed at these targets.

Diphosphonates were introduced as analogues of pyrophosphate, which had been investigated by FLEISCH as an inhibitor of calcium phosphate crystallisation.[2] The observations became particularly interesting when pyrophosphate was found in biological fluids at concentrations which were chemically active. It was a short step to suggest that pyrophosphate was involved in calcification in vivo. Investigation was hampered, however, by the inability to deliver pyrophosphate in adequate doses to the appropriate tissues. This obstacle was circumvented by the use of diphosphonates, since, unlike pyrophosphate, they were insensitive to ubiquitous phosphatases, and could be administered by mouth. The experimental profile of ethane-1-hydroxy-1, 1-diphosphonate (EHDP) in crystallisation was similar to that of pyrophosphate. The crystallisation of calcium phosphate from supersaturated solutions was retarded by EHDP, as was the dissolution of preformed crystal. These findings were shown to be relevant to calcification in biological systems when EHDP inhibited bone resorption in vitro and in vivo, and prevented ectopic soft tissue calcification in laboratory animals.[3,4]

EHDP has since been investigated in several disorders of man. Most attention has been given to Paget's disease of bone. The drug can abolish or improve the bone pain sometimes associated with the disease, and returns bone turnover towards normal values. However, at the doses necessary to diminish bone resorption, EHDP produces a defect in bone mineralisation. At high doses the bone is left covered with a thick layer of osteoid tissue, bare of cells. Clinically, the drawbacks to high-dose treatment have been recurrence of bone pain and a tendency to fractures. There has therefore been some juggling of dose regimens, and a consensus is emerging that 20 μmol/kg/day, given in six-month courses, represents a satisfactory compromise between clinical and biochemical improvement and the mineralisation disorder. The effects of EHDP on bone turnover, however, are dose-dependent, and this compromise is bought at the cost of a reduction in efficacy. Response to EHDP at this level is not far from that to calcitonins, and patients with the most active disease do not respond.[5] An attempt to improve results by combination of EHDP with calcitonin has been reported, but there has been little subsequent enthusiasm for this approach—perhaps partly because other centres are engaged in studies of combination

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7586