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outcome of one year's maintenance treatment with cimetidine seems to be no different (taking into account the rate of recurrence during treatment and relapse after treatment) than the outcome with no treatment at all after the initial healing course. Whether the tendency to relapse decreases after more prolonged treatment with cimetidine is not yet known, but at present it seems that, for about three-quarters of the patients with duodenal ulcer, we have only deferred further therapeutic decision by a year or two.

Long-term treatment with cimetidine cannot be justified unless adverse reactions are very infrequent. We know that short-term treatment is remarkably safe, but long-term safety is still being studied. Might repeated episodes of drug-induced healing result in an increased incidence of pyloric stenosis? Recurrences of ulceration (whether presenting as pain, as hæmorrhage, or as perforation) may show themselves within hours or days after the end of treatment:[8] is the rapidity of the relapses fortuitous, or might it be causally connected with the treatment. Some of the laboratory findings during long-term treatment with cimetidine may prove clinically important. For example, warfarin and cimetidine interact to raise the prothrombin time by about 20%.[9] Changes in the blood-levels of gonadotrophins and testosterone, suggestive of an anti-androgenic effect, have been reported in long-treated patients,[6] findings compatible with the anti-androgenic effects observed in animals.[10] Cimetidine has also been shown to inhibit the absorption of protein-bound vitamin B_{12},[11] so that patients on long-term maintenance treatment with cimetidine require monitoring for clinical B_{12} deficiency. Suppresion of T-lymphocyte function (as a result of H_2-receptor blockade) may alter the production of immune factors[12–14] and, conceivably, may alter immune responses for the worse. While none of these effects has yet proved clinically important, patients on long-term cimetidine (like those on long-term beta-blockers[15]) must be monitored closely.

How, then, should cimetidine be used in symptomatic duodenal ulceration? If the symptoms of uncomplicated duodenal ulcer can be controlled with regular tablets or sips of antacid, and an occasional day or two in bed, then the answer is probably "not at all". If symptoms prove more troublesome—intractable used to be the term—then a short healing course of cimetidine will put about one patient in four into prolonged remission. The remainder, who relapse again, should have maintenance treatment with 400 mg at night indefinitely, if they are to be treated with cimetidine at all. One can always try stopping the maintenance treatment after a year or two, but the patients must then be closely monitored (preferably endoscopically) for recurrence. No patient must be submitted to a prolonged course of treatment with a powerful and expensive drug like cimetidine without unequivocal confirmation of the diagnosis. That means confirmation by endoscopy, if possible, since standard barium meals do not display all duodenal ulcers and sometimes give falsely positive information. Since serial clinical pathological investigations are needed during maintenance treatment, hospital outpatient follow-up is desirable.

Even with the best medical treatment, duodenal ulcers are still liable to relapse. So why bother with medical treatment at all? Why not treat the ulcers surgically as soon as the clinical condition warrants or, alternatively, operate on those 70% or so of patients who do not remit after the initial course of cimetidine? For uncomplicated duodenal ulcers operation should generally be avoided because it poses some of the same problems as treatment with cimetidine. Like cimetidine, operation relieves the immediate symptoms of the duodenal ulceration in most patients; but unlike cimetidine, ulcer operations of all types can cause symptoms much more difficult to control than those of the original duodenal ulcer. In addition, some of the patients—and probably more than we realise—have postoperative ulcer recurrence. Surgeons have only lately started routine endoscopic follow-up of their patients, and the proportion of symptomless recurrences seems to be at least as high as after medical treatment. Furthermore, we must not forget that surgical treatment irreversibly alters the structure and functions of the upper alimentary tract, and since the pharmacological treatment of duodenal ulceration, as exemplified by cimetidine, is making such rapid strides, probably the most satisfactory treatment for duodenal ulceration is to put the surgeon off for as long as possible.

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What Proportion of Cancers are Related to Occupation?

SUGGESTIONS that most cancers are attributable to environmental factors[1–3] are based largely on variations in cancer mortality by site from one country to another. The lowest rate in any country, so the assumption goes, indicates the genetic component, with any mortality above this reflecting

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environment. An extension of this approach has been to look at the reported attempts to quantify the relative risk of various cancers in workers exposed to particular agents. Hitherto there has been a fair consensus that the occupational component of the total cancer toll is about 1–5%,[4–6] though last year COLE[7] reckoned it at 10–15%.

Now FRAUMENI, HOOVER, and their colleagues from the National Institutes of Health[8] maintain that such estimates are often badly awry, because they take no account of the multiple causation of many cancers and of the fact that many industrial studies, because the men were not followed throughout retirement, have detected only a small fraction of the cancers. The paper then deals at some length with the relationship of exposure to asbestos and the generation of lung cancer, cancer of the larynx, and mesothelioma. On the basis of data stemming predominantly from one follow-up study, the N.I.H. workers suggest that, over the next three decades, roughly 13–18% of the total cancer mortality will be due to work-exposure to asbestos. Publications which have dealt with a range of other established occupational carcinogens are reviewed and the report comments that for five of them taken together (arsenic, benzene, chromium, nickel, and petroleum fractions) the effect may be comparable with that suggested for asbestos. Combination of these two estimates indicates that between 23 and 38% of the total cancer mortality in forthcoming decades might be occupationally related —even excluding the effects of radiation and of several known chemical carcinogens. The report points out that, though exposure to several important occupational carcinogens has been reduced in recent years, there are still many unregulated carcinogens in U.S. workplaces and there is no sound reason to assume that the consequences of present-day exposure to carcinogens will be less grave in the future than they have been in the past; it suggests that the conclusions are consistent with the trends in incidence and mortality from malignant disease in the U.S., and not incompatible with a substantial fraction of cancers being associated with cigarette smoking, diet, and other such factors.

This report immediately received wide publicity; it was quoted by the Secretary for Health, Education and Welfare,[9] and obtained coverage in the world news. Yet its framework is insubstantial—remarkably so, in view of the fierce criticism of other people's work. The asbestos extrapolation is based predominantly on follow-up of American shipyard workers;[10] there is no review of the full range of epidemiological studies that have been published on this subject (in which, as usual in cancer epidemiology, there is not complete agreement). More important is the fact that, often, occupational studies have been carried out in particular subgroups of workers who have been exposed more heavily than the generality of workers in the same industries. Though cancer mortality is estimated for the very large workforce potentially exposed to asbestos since the 1940s, no data are presented on the *degree* of exposure in these workers, and hence on their risk of lung and other cancers; it seems very rash to suppose that these risks may be estimated from one specific study, by the use of a crude division of workers into heavily and less heavily exposed. (Exactly the same point can be raised about the five other specific agents identified as the main occupational carcinogens.)

Another source of data is the British Registrar General's Decennial Supplement on Occupational Mortality.[11] This tabulates the mortality from malignant disease by social class. There is a gradient, with skilled manual, semiskilled, and unskilled manual workers having a progressively higher mortality from all malignant neoplasms; for example, skilled manual workers have an S.M.R. of 113, whilst office workers &c. (skilled non-manual workers) have an S.M.R. of 91. However, the gradient in risk is not as steep as one would anticipate from the American paper—particularly in view of the fact that occupation is only one of the factors that can determine social-class mortality gradients (smoking and way of life in general play an important part). From data on smoking by social class[12] and risk of lung cancer for various levels of smoking,[13] a crude calculation suggests that manual labourers might have a lung-cancer risk 22% higher than that of the administrative and clerical workers. Because lung cancer in men is responsible for just under two-fifths of deaths from all cancers, by its impact on lung cancer alone smoking would increase the risk, in manual workers, of all cancers by about 9%. (This approach is susceptible to the argument of the multiplicative ætiology in malignant disease; the American report[8] suggests that a considerable proportion of the deaths in smokers are as much due to other agents as to the fact of smoking.) These pointers from the crude national data from England and Wales suggest that occupation is associated with in-

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creased risk of malignant disease, but other known variations external to the work environment also play an important part. These data do seem compatible with the very high proportion of malignancies that BRIDPORT and others[8] seek to attribute to previous occupational factors. Though the problems of assessing the proportion of cancers related to occupation are acknowledged in the report, these difficulties seem to have been forgotten when the conclusions were drafted. The N.I.H. report ends by stressing that occupational cancer is preventable; this is certainly a view accepted in Britain by research-workers, central Government, industry, trades-unions, and individuals at work. Quantification of the hazards of occupations is a complex matter. BRIDPORT and his colleagues were well placed to set matters in proper perspective. It is sad to see such a fragile report under such distinguished names.

PREVENTING GROUP-B INFECTIONS IN BABIES

DEATH from uncontrolled infection within the first 24 hours of life, sometimes despite antibiotics,[1] is ample reason for the emphasis on group-B streptococci at the recent International Symposium on Streptococci and Streptococcal Diseases held at Oxford[2] and at last year's National Institutes of Health Workshop.[3] In addition to meningitic infections of early and late onset, discussed in a previous editorial,[4] a group from Houston now reports that, in the past twelve years, group-B streptococci caused more bone infections than did staphylococci.[5]

The streptococcal cells have been analysed for epidemiological markers and for mediators of pathogenicity. Human strains, unlike bovine, do not ferment lactose. Serotyping reveals a complex association of protein and polysaccharide antigens. Polysaccharides define three main types (I, II, and III), while three shared proteins divide type I into three subtypes, and two other proteins R and X) define other serotypes. Stringer and Maxted[6] described an alternative system, based on patterns produced by mitomycin-induced bacteriophages, which enabled them to type three-quarters of the strains with 98% reproducibility. The types defined were in fact more stable than the R and X serotypes, and used together with serotyping their method provided excellent discrimination and should allow more detailed longitudinal surveys of carriage during pregnancy and of hospital nursery infections.

Serotype III causes many cases of neonatal meningitis, and the chemistry of the type-specific polysaccharide has been studied in detail. Kasper et al.[7] found important differences in the reactivity of polysaccharides prepared by the classic "acid extract" and by a gentler "neutral buffered E.D.T.A." method. The acid extract produced a smaller molecule termed a core antigen, which resembles the type XIV pneumococcal polysaccharide, but does not excite a human antibody response. Human antibodies to the larger E.D.T.A.-extracted "native" antigen can be detected by a radioactive binding assay. Interestingly enough, the extra material in the native antigen is sialic acid, also found as a homopolymer on the surface of strains of *Escherichia coli* type K1, the other main cause of neonatal meningitis.

Why should type-III strains be pathogenic for babies (and neonatal rats) when large numbers can be injected without effect into the mouse peritoneum? Hill and Shigeoka[8] measured phagocytosis of group-B streptococci by chemiluminescence—an attractive technique based on the observation that when a polymorph attacks a microbe it emits a flash of light. They found that opsonisation needed type-specific antibody and complement. Strain specificity was also important. Neonatal polymorphs, however, were inhibited by opsonised streptococci, suggesting that both humoral and cellular factors were involved. 20% of adult sera contain antibodies to native type-III antigen, and a plausible hypothesis is that risks of infection are greatest for the baby whose mother carries streptococci in the vagina but lacks transmissible antibodies.

Studies of maternal carriage reveal a changeable pattern. Using selective media, workers in Sydney[9] found that 19% of non-pregnant women were vaginal carriers, while in California[10] the carriage-rate in pregnancy was 28%, although only a third of these mothers carried the same serotype throughout. Streptococci have been isolated from the throat, perianal skin, and urethra of mothers—and their consorts too. Like gonococci the bacteria can adhere to urethral cells, and urethral carriage may be commoner than vaginal. The exact modes of spread remain uncertain; and promiscuity as measured by attendance at a V.D. clinic does not result in a higher carriage-rate. With so many possibilities for reinfection it is not surprising that benzylpenicillin, given to mothers in the hope of eradicating streptococci, did not prevent colonisation of the neonate.

Two different methods of prophylaxis have been advocated—vaccines for mother, antibiotics for baby. Vaccine supporters say that we now know enough about the group-B immunochemistry to make a vaccine similar to those against pneumococci and meningococci. On the other hand, an Aberdeen group (see p. 1254) treat all low-birthweight babies with benzylpenicillin at birth, a policy supported by the Sydney workers[9] who also regard prolonged rupture of the membranes as a risk factor. 8% of babies get this treatment. Some see this as an invitation to ecological trouble—an entrée for hospital-acquired antibiotic-resistant microbes to a fertile seedbed.

The arguments will doubtless continue, but for the moment the last word is with the late A. J. Steigman[11] who noted that 130 000 babies had been delivered in the Mount Sinai Hospital, New York, since 1952 without a single group-B infection, although current incidence in neighbouring hospitals was 1 per 1000 births. The

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