

Reports on Individual Drugs

Oral contraceptives and cancer

When oral contraceptives first became widely available in the early 1960s the possibility that their extended use might carry a risk of cancer was a distant hypothetical concept. Estrogens and progestogens, including those of synthetic origin, were regarded as essentially physiological, non-toxic substances. This complacency was short-lived. Within a decade it had become apparent that estrogens administered alone to older women have an undoubted carcinogenic potential. Over 15 000 cases of endometrial cancer diagnosed among post-menopausal women in the USA in the five years from 1971 to 1975 were attributed, on the basis of epidemiological evidence, to estrogen replacement therapy (1). Sequential contraceptives, which provided estrogen alone during the proliferative phase of the menstrual cycle, were hurriedly withdrawn from use in 1975 by the United States Food and Drug Administration as soon as case reports and cancer registry data suggested they might also invoke this risk (2-4). Shortly afterwards, diethylstilbestrol, a synthetic estrogenic substance once widely used in high-risk pregnancies because it was claimed to reduce the risk of spontaneous abortion, was similarly withdrawn in the USA when it was discovered that a high proportion of women exposed *in utero* had developed vaginal adenosis during adolescence and early adulthood (5, 6). More recently, a small but significant increase in the incidence of breast cancer has been reported among the treated mothers (7, 8). This trend only became apparent 20 years or more after exposure and, as yet, no such risk has been associated with post-menopausal use of estrogens (9).

Such findings leave no doubt about the need to remain alert to possible long-term effects of combined steroidal contraceptive preparations. There is now much evidence, however, that concomitant administration of progestogens negates the potential carcinogenic effect of estrogens on the female reproductive system. No less than five retrospective studies undertaken in the USA suggest that combined oral contraceptives reduce the risk of endometrial cancer (10-14). In

each case, the incidence of this cancer was halved among oral contraceptive users, at least during the period of exposure. Moreover, three case-control studies reported from the USA (15-17), and an interim analysis of an ongoing prospective study in the United Kingdom (18), suggest that prolonged use has an even greater and more persistent protective effect against ovarian cancer.

As yet, less certainty exists regarding the influence of oral contraception on cancers of the cervix and the breast. Studies in both industrialized and developing countries on invasive and non-invasive cancerous lesions of the cervix have, in several instances, demonstrated a positive association with long-term use (19-23). Most investigators agree that this association is unlikely to be causal, and they point to confounding bias arising from differences in sexual behaviour, the incidence of sexually transmitted disease, and even enhanced detection rates of carcinoma *in situ* among users of oral contraceptives.

An even more intensive effort has been directed to the influence of these preparations on breast cancer which, overall, remains the most highly prevalent cancerous lesion among women in industrialized countries. At least ten substantial case-control studies have been undertaken since 1980 (24-33). In several of these, no evidence of an association has been found (30-33), but in others a moderately increased risk was reported among women who started to use the pill at an early age before their first pregnancy (24-29). Interpretation of the association is complicated because postponement of child-bearing is known, of itself, to raise the risk of breast cancer (34). Moreover, because the nature and amounts of the estrogens and progestogens contained in marketed combined contraceptive preparations have changed over the years, the relevance of the results to current contraceptive use is uncertain.

It is important to recognize that no substantiated risk of cancer has been attributed to the use of oral contraceptives within a family setting for birth spacing following a pregnancy. Concern is directed only to their prolonged use early in reproductive life. This relates not only to the possible association with breast cancer, but to the increased risk of cervical

cancer resulting from multiple sexual partners. With the advent of AIDS oral contraceptive use seems destined to decrease in this population of women. A recent statement by the Committee on Safety of Medicines in the United Kingdom (35) reflects a widely-held view that there is no call to recommend any change in contraceptive practice in the light of the epidemiological findings, except to emphasize the need to prescribe a product with the lowest content of estrogen and progestogen that is suited to each woman's needs.

Despite difficulties inherent in the interpretation of the data, it is vital to continue to monitor cancer incidence in the first generation of women to use steroidal contraceptives. There is now no doubt that these substances exert an important influence on the development of the endocrine-sensitive neoplasms of the reproductive system. However, the estimated reduction in ovarian and endometrial cancer seems destined to outweigh any adverse effect on the breast (36). This conclusion is tentative and needs to be verified in the light of further investigation. Ultimately, the aim must be to advise women with reasonable confidence on how contraceptive use can best be planned to minimize the known risks.

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36. European Organisation for Cooperation in Cancer Prevention Studies. Workshop on "Optimization of influence of ovarian steroid consumption on cancer risk". *European Journal for Obstetrics, Gynecology and Reproductive Biology*, **26**: 1-6 (1987).

Auranofin licensed in the UK

United Kingdom — Until 1982 gold salts could only be administered to patients with rheumatoid arthritis by intramuscular injection. In that year a lipid-soluble, orally-active gold preparation, auranofin (Ridaura®: SK&F), was introduced which has now been registered in most countries with highly-evolved drug regulatory authorities.

About 20 to 30 per cent of the administered gold is absorbed and, like gold injections, auranofin tablets are intended as a "second line" drug for patients with active, progressive rheumatoid arthritis in whom the response to nonsteroidal anti-inflammatory drugs is inadequate. Although the manufacturer claims that auranofin efficacy is comparable to that of injectable gold, some rheumatologists consider that it is somewhat less active. All are agreed that close monitoring of therapy is required, particularly for serious haematological adverse reactions.

Reference: *Pharmaceutical Journal*, **239**, 29 August 1987.

Efficacy of *Salmonella typhi* (Vi) capsular polysaccharide vaccine in Nepal

A preliminary report has recently been published of the performance of the Vi capsular polysaccharide *S. typhi* vaccine in a double-blind community trial undertaken in some 7000 residents of five Nepalese villages. The vaccine, manufactured by the Institute Merieux, was administered intramuscularly in single-dose syringes containing 25 µg in 0.5 ml. Controls received pneumococcus capsular polysaccharide vaccine. Seventeen months after vaccination, the codes were broken for 71 patients who had developed either culture-positive or clinically-suspected typhoid. The attack rate of typhoid was 16.2 per 1000 among the controls and 4.1 per 1000

among those immunized ($P < 0.00001$). The efficacy of Vi vaccine was estimated as 72 per cent in the culture-positive cases and 80 per cent in the clinically-suspected cases. Surveillance is being maintained to determine the duration of effective immunity.

Although the efficacy of the vaccine was lower than had been hoped, it holds several advantages over the cellular attenuated strain Ty-21 vaccine. One dose gave the same level of protection as two oral doses of the cellular vaccine. Adverse reactions were rare and similar to those elicited by other capsular polysaccharide vaccines. Vi vaccine may be reliably standardized using physicochemical methods and is stable at ambient temperatures, which greatly simplifies its use in the field.

Reference: Acharya, I.L. et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide vaccine of *Salmonella typhi*. *New England Journal of Medicine*, 317: 1001-1004 (1987).

Efficacy of thrombolysis with streptokinase after myocardial infarction

United States of America — A double-blind trial on the use of streptokinase in acute myocardial infarction recently reported from the United States indicates that this form of treatment is effective in improving left ventricular function and in reducing early mortality. A total of 219 patients presenting consecutively with a first myocardial infarction within four hours of the onset of chest pain were randomly assigned to treatment with intravenous streptokinase (1.5 million units given over 30 minutes). Mortality within the first 30 days was reduced from 12.9 per cent to 2.5 per cent. On average, the left ventricular ejection fraction was six per cent higher and the end-systolic volume smaller. These benefits occurred in both anterior and inferior infarctions whether or not intravenous propranolol was given concomitantly. Adverse effects were uncommon and reinfarction was infrequent, despite a conservative approach to the need for angioplasty or surgery.

Reference: White, H.D. et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *New England Journal of Medicine*, 317: 850-855 (1987).

Ciclosporin

United Kingdom — A group of doctors in a London teaching hospital have reported the case of a woman with polycystic renal disease who developed insulin-dependent diabetes twenty-five days after first receiving ciclosporin to prevent rejection of a renal allograft. The patient had no family history of diabetes; preoperative plasma glucose concentrations had been within normal limits on six separate occasions; and at no time were islet-cell antibodies detectable.

The authors note that post-transplantation diabetes has occurred in other renal allograft recipients in whom ciclosporin was not apparently implicated. Nonetheless, having regard to the apparent correlation between the intensity of the metabolic disturbances and the dose of ciclosporin in this case, they suggest that the effect may be due to a recently postulated toxic effect of the drug on pancreatic beta-cells.

Reference: Bending, J. J. et al. Diabetogenic effect of ciclosporin. *British Medical Journal*, 294: 401-402 (1987).

United States of America — Ciclosporin is frequently used to prolong graft survival, particularly in renal transplantation. Its use in children concurrently treated with prednisone has been associated in the USA with changes in facial appearance, including thickening of the nose and ears, puffiness of the cheeks, prominent orbital ridges and prognathism. Since such changes have not been seen in patients treated with azathioprine and prednisone, ciclosporin is clearly implicated in their etiology. The authors draw attention to the consequences that such striking and detrimental changes might have on compliance with therapy.

Reference: Reznik, V. M. et al. Changes in facial appearance during ciclosporin treatment. *Lancet*, 1: 1405 (1987).

Glibenclamide

Norway — The case is reported of a mildly diabetic patient who was given glibenclamide after having previously been treated with zuclopenthixol. He subsequently became jaundiced and increasingly fatigued, and was found to have developed haemolytic anaemia. After withdrawal of gliben-

clamide, recovery was rapid and complete. The authors suggest that an immune haemolytic response was triggered by non-specific binding of serum proteins, including IgG and complement, to a damaged or altered erythrocyte surface. However, sulfonyleureas have seldom been implicated in haemolytic reactions and this is the first report of a possible association with glibenclamide. This patient was found to have selective IgA deficiency which, for unknown reasons, is often associated with immunological disorders and which, on this occasion, may have caused the drug-induced haemolytic anaemia.

Reference: Nataas, O. & Nesthus, I. Immune haemolytic anaemia induced by glibenclamide in selective IgA deficiency. *British Medical Journal*, 295: 366-367 (1987).

Human insulin

Switzerland — Human insulin is often claimed to be equivalent in its effect to animal insulin and less likely to induce adverse effects. Transfer from porcine or bovine to human preparations was not anticipated to give rise to difficulty. However, reports that three patients experienced serious hypoglycaemia after changing from animal to human insulin have inspired a follow-up study involving 176 patients who switched from animal to human insulin. Over one third reported changes in symptoms. Most strikingly, the prodrome of hypoglycaemia — the classical warning signs of sweating and tremor — was much shorter than usual and sympatho-adrenal symptoms were not prominent. The patients were therefore much less aware of imminent hypoglycaemia. The authors conclude that human insulin is of benefit to patients with insulin allergy and the very rare condition of insulin resistance, but that the classical products of animal origin may hold advantage in other patients.

Reference: Teuscher, A. & Berger, W. G. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet*, 2: 382 (1987).

Federal Republic of Germany — The Federal Health Office has received 12 reports of hypoglycaemia in diabetic patients who have switched from animal insulin to human insulin. The hypoglycaemia was atypical in that it was not heralded by the warning symptoms of restlessness, tremor, perspiration and hunger and the patients lost consciousness without warning.

The Federal Health Office and the Insulin Committee of the German Diabetes Society are seeking further information to establish if the absence of warning symptoms is specific to human insulin. Meanwhile, doctors are advised to exercise particular caution when transferring patients from animal to human insulin.

Reference: *Bundesgesundheitsblatt*, 30: 257-8 (1987).

Loperamide

United Kingdom — A case is reported in the *British Medical Journal* of a 15-month-old girl who developed acute diarrhoea after accidental scalding involving 35 per cent of the body area. The diarrhoea, which was diagnosed as a stress-response to injury, was treated on the ninth day with a single 1 mg oral dose of loperamide. Within 50 minutes she was collapsed, pale and unresponsive to pain. Pulse rate was 120/min and the respiratory rate 14/min. She was resuscitated with oxygen by Ambu bag and intravenous naloxone 0.3 mg. Within two minutes consciousness had improved and the respiratory rate had risen to 30/min, although she remained drowsy throughout the following day.

Loperamide is known to produce respiratory depression and coma after overdosage and prolonged therapeutic use. No other case of opioid toxicity after a single therapeutic dose is known to the authors. Serious toxicity is a rare occurrence but, particularly since loperamide is available over-the-counter in the United Kingdom, doctors are advised to be alert to the possibility of accidental overdosage.

Reference: Minton, N. A. & Smith, P. G. D. Loperamide toxicity in a child after a single dose. *British Medical Journal*, 294: 1383 (1987).

Nitrate tolerance reversed by acetylcysteine?

Acetylcysteine has been available for many years in an oral formulation as a mucolytic agent. More recently, its action as a donor of sulfhydryl groups has resulted in its use in the treatment and prevention of paracetamol poisoning. Its efficacy in this situation has now led to speculation that it may be of value for the treatment of nitrate tolerance. This is

based on the suggestion that nitrates produce their therapeutic vasodilator effect by reacting with sulphhydryl-containing molecules on receptors in vascular smooth muscle and that tolerance may occur when the sulphhydryl groups become flooded. Some preliminary trials with an intravenous formulation have recently been reported to have produced positive results. This is regarded as particularly encouraging, having regard to the increasing trend towards use of sustained long-term nitrate therapy in the management of stable angina and the frequency with which nitrate tolerance develops in these patients, particularly those in whom constant blood concentrations are maintained by using transdermal nitrate patches as a sustained-release delivery system.

Reference: *Pharmaceutical Journal*, 239, 14 November 1987.

Nonsteroidal anti-inflammatory drugs

United States of America — In a large-scale study undertaken in the USA that provided information on 584 million person days at risk, no evidence was generated to relate use of non-salicylate nonsteroidal anti-inflammatory drugs with gastro-duodenal perforation. Only 54 patients with perforated ulcers had presented a prescription for an NSAID within 90 days of admission. This provides a crude estimate of 0.26 per million person-days at risk. The crude admission rate among non-users was 0.09 per million person-days at risk. Adjusted for age and sex, the rate ratio for NSAID-users compared with non-users was 1.6 (95 per cent confidence interval 0.68-3.7). The case-control analysis yielded a similar result. The authors comment that, although few analogous data are available on long-term use, there is no suggestion that long-term users of NSAIDs are at greater risk than non-users. (see also, however, p. 46).

Reference: Jick, S. S. et al. Non-steroidal anti-inflammatory drugs and hospital admission for perforated peptic ulcer. *Lancet*, 2: 380-382 (1987).

Oral rehydration salts

Global production of oral rehydration salts for use in acute diarrhoeal diseases has increased rapidly in the last few years. According to WHO's estimates,

the total stood at some 270 million litre equivalents in 1986. The substitution of sodium bicarbonate by trisodium citrate dihydrate in the recommended WHO formula, as revised in 1984, has considerably improved the stability of the preparation. A number of manufacturers are additionally adding flavouring and colouring materials. This is a practice that is not recommended by WHO, since assurances need to be provided that these additives affect neither the safety nor the stability of the formulation.

Reference: *Update No. 2*, November 1987. Programme for Control of Diarrhoeal Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

Phenytoin

United Kingdom — Five male patients are reported to have developed gynaecomastia after being treated with phenytoin for several years. The condition resolved in two cases when phenytoin was replaced by other anticonvulsants. The data are consistent, it is suggested, with the hypothesis that phenytoin both decreases free testosterone concentrations by stimulating the production of sex-hormone-binding globulin and also promotes the conversion of testosterone to 17-beta estradiol.

Reference: Monson, J. P. & Scott, D. F. Gynaecomastia induced by phenytoin in men with epilepsy. *British Medical Journal*, 294: 612 (1987).

Retinoids — Oral therapy

Retinoids are naturally-occurring compounds with vitamin A activity. A number of compounds with analogous activity have recently been synthesized and two, *isotretinoin* and *etretinate*, have already been registered in many countries for use in specific disorders of keratinization. Their general advantage is that they are less likely than vitamin A to induce signs of hypervitaminosis at therapeutic dosage. However, extended administration can result in bone lesions and raised serum lipid concentrations. Most importantly, particularly since these products are commonly prescribed for younger women of child-bearing age, it is of paramount importance to exclude pregnancy before treatment is started, and that the patient understands and accepts the need to maintain effective

body. Use of these products has already resulted in several cases of serious congenital deformity. The search for further analogues with more potent antipsoriatic and anti-inflammatory effects and with substantially shorter elimination half-lives is ongoing. At least three compounds (acitretin and two arotinoid analogues) are already under clinical trial. As yet, however, isotretinoin and etretinate remain the only two synthetic retinoids in widespread routine use. Isotretinoin is used primarily in the treatment of severe acne, and also in severe Gram-negative folliculitis and rosacea unresponsive to other therapy. Etretinate, in contrast, is used in severe forms of psoriasis, generalized lichen planus, Darier's disease and severe congenital ichthyosis. Both drugs are used in dosages ranging from 0.2 to 1.0 mg/kg/day for several months, following which a potential teratogenic risk persists for one month in the case of isotretinoin and for up to 12 months in the case of etretinate.

Reference: Orfanos, C.E. et al. The retinoids. A review of their clinical pharmacology and therapeutic use. *Drugs*, **34**: 459:503 (1987)

Warfarin: interaction with imidazoles

United Kingdom — The antimycotic substances *ketoconazole* and *miconazole* are known to potentiate the anticoagulant effect of warfarin, probably by inhibiting its metabolism in the liver. A case report has recently been published of marked loss of anticoagulant control in a patient who received miconazole as an oral gel whilst under treatment with warfarin. The authors conclude that, even with this dosage form, sufficient buccal absorption may occur to exert a systemic effect and they recommend that patients receiving these drugs in combination be carefully monitored.

Reference: Colquhoun, M. C. et al. Interaction between warfarin and miconazole oral gel. *Lancet*, **1**: 695-696 (1987).