*A Reprint from*

# THE PREVENTION OF CANCER

*EDITORS*

*Clinical Aspects*

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*Experimental Aspects*

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*Published by*

BUTTERWORTHS

CHAPTER 5

# PHARMACEUTICAL PREPARATIONS

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## INTRODUCTION

Many constituents of pharmaceutical preparations have been found to exert carcinogenic or co-carcinogenic effects in the course of experiments on laboratory animals. Only in a few cases, however, has such an effect been observed in man. This discrepancy cannot, for the most part, be explained on the grounds that man is relatively insensitive to chemical carcinogens, there is no evidence that this is the case. It is more probable that several factors contribute to the discrepancy: first, that substances showing positive results in animal tests have only recently been introduced into clinical medicine, so that the minimum induction period for cancer in man has not been exhausted; secondly, that the clinical doses, based on body weight, are lower than those which induce cancer in animals; and thirdly, that a weak carcinogenic effect in man may have been missed because no adequate epidemiological study has been undertaken.

The slightest suspicion of carcinogenicity in the case of, say, a colouring agent added to food, should lead to the abandonment of its use. The situation is quite different in the case of pharmaceutical preparations. The possibility of inducing cancer is but one of many factors to be considered. Indeed, it is only one of many equally serious and unwanted side-effects (for example, marrow aplasia, anaphylaxis) which need to be considered by the responsible physician when he is prescribing. Clearly his decision whether or not to prescribe a potentially toxic drug depends upon the seriousness and prognosis of the condition for which it is to be prescribed, upon the chances that the treatment will be effective, upon the extent of the cancer hazard, and upon the existence of safer therapeutic alternatives. When all these factors are taken into account, it may still be justifiable to prescribe a drug even when its use carries a theoretical or real risk of carcinogenesis.

Because adequate data from epidemiological studies are so scanty, it is impossible to calculate how much human cancer is attributable, in whole or in part, to drug treatment. On the other hand, it is likely that the effective treatment by drugs of many benign conditions acts indirectly to reduce the incidence of cancer, or at least to delay its appearance.

It is not our purpose here to suggest that potentially carcinogenic drugs are prescribed irresponsibly, but only to point out that practising doctors should not be unaware of the possible or actual carcinogenic hazard inherent in the use of certain agents. Clearly, no doctor can balance the likelihood that a drug will benefit a particular patient with the risk of unwanted side-effects (including the induction of cancer) unless he has full knowledge of those side-effects.

## ANTIMICROBIAL CHEMOTHERAPY

### Sulphonamides

Hansen and Bichel (1952) observed renal adenocarcinomas, lymphosarcomas or spindle-cell sarcomas in rats treated with a mixture of three sulphonamides by injection, or the implantation of pellets, subcutaneously. None of the tumours arose at the injection site as had been reported earlier by Haerem (1948). More recently, 4-ethylsulphonylnaphthalene-1-sulphonamide was shown to cause marked hyperplasia and cancer of the urinary tract epithelium (Sen Gupta, 1962a; 1962b; Bonser and Clayson, 1964). Fortunately the latter compound did not come into clinical use. Felistovich (1960) attributed the development of myeloid leukaemia in a woman aged 63 years to treatment with sulphonamides.

### Penicillins

Dickens and Jones (1961; 1963) observed sarcomas at the site of subcutaneous injections of penicillic acid, penicillin G, or other lactones in rats.

### Chloramphenicol

Mukherji (1957) reported a case of acute myeloblastic leukaemia following marrow aplasia which he attributed to treatment with chloramphenicol. Felistovich (1960) described leukaemoid reactions in some 25 per cent of a group of 50 mice given chloramphenicol by stomach tube repeatedly throughout a 12-month period. German and Tran-ba-Loc (1962) saw a sarcoma at the site of injection of chloramphenicol in a rat.

### Streptomycin

Felistovich (1960) saw leukaemoid reactions in mice given streptomycin by stomach tube repeatedly.

### Actinomycins

Injection-site tumours have been seen in mice in response to various actinomycins (Kawamata and colleagues, 1958; 1959) and Dipaolo (1960) reported 3 squamous-cell carcinomas in 31 mice injected, subcutaneously, with actinomycin D.

### Griseofulvin

Arrest of mitosis in metaphase in response to griseofulvin was reported by Paget and Walpole (1958), but no tumours were seen at the site of subcutaneous injection in rats or mice (Paget and Walpole, 1960). Barich and colleagues (1960) reported that the oral administration of griseofulvin in large doses enhanced the induction of skin tumours by methylcholanthrene in mice. Enlargement, but no neoplasms, of the liver due to griseofulvin was also observed.

### Isonicotinic Acid Hydrazide (INH)

Of all antimicrobial chemotherapeutic agents in large scale use, INH causes the most worry with regard to cancer hazard. Numerous workers have reported the induction of lung tumours in mice with INH (Juhász,

Baló and Kendrey, 1957; Mori and Yasuno, 1959; Biancifiori and Ribacchi, 1962; Weinstein and Kinosita, 1962). The first of these groups of workers also recorded a higher incidence of leukaemia and various reticuloses in their animals, and confirmed this finding in a later experiment (Juhász, Baló and Szende, 1963). So far no one has reported the experimental induction of cancer in any other species, including the rat (Pansa, Picco and Gnavi, 1962; Peacock and Peacock, 1963), but there have been few attempts to do so.

Hein and Stefani (1952) reported adenomatous hyperplasia in two patients treated with INH. Pompe (1956) calculated that treatment of lupus vulgaris with INH increased the risk of skin cancer nine-fold.

INH is a drug of almost incalculable value in relation to the treatment and control of tuberculosis. For patients with active tuberculosis it would at present be unthinkable to withdraw the drug because of a theoretical risk of cancer. Is it justifiable, therefore, to administer INH prophylactically to tuberculosis contacts? INH has been in widespread clinical use for only 13 years. This may well be shorter than the minimal induction time for cancer in man. It has been argued elsewhere (Roe, Boyland and Haddow, 1965) that a full epidemiological evaluation of the cancer risk for man should be begun without delay. A major difficulty is that there are virtually no tuberculosis patients who have not had INH, so that there can be no satisfactory control group.

## ANTI-CANCER CHEMOTHERAPY

### Biological Alkylating Agents

It is a well-known paradox that many of the chemical agents currently used in the treatment of cancer are themselves carcinogenic. Virtually, all the commonly used alkylating agents, including the simple nitrogen mustards, HN2 and HN3, tretamine (TEM), chlorambucil, sarcolysin and melphalan, and busulphan (Myleran) can induce cancer fairly readily in experimental animals (Roe, 1966). It is difficult to estimate the extent to which the use of these substances has been responsible for inducing cancer in man because of the difficulty in distinguishing induced from spontaneous disease. There is good evidence, however, that bladder cancer has resulted from the use of 2-chlornaphazin in the treatment of polycythaemia vera and Hodgkin's disease (Videbaek, 1964; Thiede, Chievitz and Christensen, 1964). In the light of this evidence there can be no justification for the continued use of this agent since there exist equally effective agents for treating these disorders.

Another alkylating agent, $\beta$-propiolactone, is used, not in the treatment of cancer, but in the sterilization of plasma and arterial grafts. It has been shown to be carcinogenic in itself (Walpole and colleagues, 1954; Roe and Glendenning, 1956), but in aqueous solution it is rapidly hydrolysed and there appears to be no carcinogenic hazard from materials sterilized with it (Laws and Zinnemann, 1963).

### Urethane

This substance has been shown to be carcinogenic for a wide variety of tissues and species (Haddow, 1963). Despite this its continued use in the

treatment of multiple myelomatosis might, on occasions, be justified. On the other hand, it would not be justifiable to incorporate it (as once was done) in sclerosing solutions for the treatment of varicose veins, haemorrhoids and naevi.

### Anti-metabolites

In general, carcinostatic agents which act by blocking metabolic pathways are not carcinogenic. The only report of any relevance which we could find was that of Barich, Schwarz and Barich (1962), who demonstrated that orally administered methotrexate enhanced skin carcinogenesis by methylcholanthrene in mice.

## METALS USED IN THERAPY

### Arsenic

There is abundant evidence that the medicinal use of arsenic may cause both skin and lung cancer in man (Neubauer, 1947; Currie, 1947; Roth, 1958; Robson and Jelliffe, 1963). Curiously, attempts to induce cancer in animals with arsenic have all given equivocal or negative results.

### Iron

Several iron preparations intended for parenteral administration, including iron dextran, iron dextrin, formulations of saccharated iron oxide, ferrous glutamate, and ferric sodium gluconate complex (Haddow, Dukes and Mitchley, 1961; Haddow and colleagues, 1962) have been shown to induce cancer when injected subcutaneously or intramuscularly into various species of laboratory animal. Iron dextran is especially active in this respect and tumour incidences of close to 100 per cent have been seen in some experiments. In all except one experiment, the cancers induced have arisen at the site of injection and there is no evidence that the incidence of cancers at other sites is increased (Roe and colleagues, 1964). Excess of iron may lead to cirrhosis, but there is no clear association between iron-induced cirrhosis (haemochromatosis) and liver cancer (Sheldon, 1935; Willis, 1953). The exceptional case was an experiment reported by Langvad (1964), where mice injected with iron dextran had a significantly higher incidence of tumours of various sites than did untreated controls. It has been suggested that the high incidence of injection-site tumours has only been seen in iron-overloaded animals in which absorption from the injection site is slow (Golberg, Martin and Smith, 1960). However, Haddow and Roe (1964) reported tumours in rats given relatively small total doses of iron dextran.

As yet there is no evidence that cancer is induced at the site of injection of any of these preparations in man. However, the period during which the preparations in question have been in clinical use may be shorter than the minimum cancer-induction period in man. Moreover, the first cases may easily be missed as no specific epidemiological follow-up survey of treated persons has been undertaken.

Clearly, much benefit may sometimes accrue from the parenteral administration of iron, but in our opinion the evidence from the laboratory is serious enough to suggest that iron should not be given parenterally unless it cannot be given satisfactorily by mouth. Nor should it be given routinely to young

pregnant women on the off-chance that it may do them some good. Above all, it is quite unjustifiable to use the parenteral route simply for the convenience of the doctor or patient.

**Silver and Gold**

Occasional injection-site tumours have been seen in rats injected, subcutaneously, with a colloidal silver preparation (Schmähl and Steinhoff, 1960). Gray, Liebelt and Liebelt (1960) thought that the hepatomas which arose in mice injected with gold thioglucose were secondary to damage to the hypothalamus.

## PHENYLBUTAZONE

Several authors have reported leukaemoid reactions and deaths from acute leukaemia following treatment with phenylbutazone (Bean, 1960; Lawrence, 1960; Garrett, 1961; Scheuer-Karpin, 1961; Cast, 1961; Cadman and Limont, 1962; Chalmers and McCarthy, 1964; Chatterjea, 1964; Thorpe, 1964; Golding, Hamilton and Moody, 1965). Woodliff and Dougan (1964) found that 9 per cent of patients with acute leukaemia had a history of having taken phenylbutazone, compared with 1·2 per cent of patients with chronic leukaemia, lymphoma and allied disorders.

## TAR AND CREOSOTE

Despite abundant evidence from the laboratory that they contain carcinogenic constituents, coal tar and creosote preparations are still often prescribed in the treatment of a wide variety of respiratory and skin disorders. Undoubtedly, some who prescribe such preparations think that the materials as refined for pharmaceutical use are free from carcinogenic activity. This is, however, not true: Sternberg (1923) and Berghoff (1928) induced skin tumours in mice by applying three different clinically used tar preparations, and Berenblum (1948) did so with *Liquor Picis Carbonis* (B.P.). Rook, Gresham and Davis (1956) suggested that the application of tar in aqueous or alcoholic solution, or in water miscible bases, might involve greater risk than its application in paste or ointment form.

## MEDICINAL PARAFFIN

Boyd and Doll (1954) found a higher incidence of the use of medicinal paraffin in patients with gastro-intestinal cancers than in controls. The use of other purgatives was similar in the two groups. Experimentally, numerous mineral oils have been shown to be carcinogenic or co-carcinogenic. According to Druckrey, Schmähl and Preussmann (1959), purification methods used in the case of medicinal paraffins do not exclude the presence of known carcinogens in them.

## THYROID-SUPPRESSANT THERAPY

Doniach (1958) pointed to the dangers of combined treatment with $^{131}I$ and goitrogenic agents such as thiouracil. There is an undoubted risk that treatment with $^{131}I$ only will induce cancer of the thyroid gland. In rats,

this risk is magnified if thyroid suppressants are also given. Another carcinogenic hazard may be entailed in the use of thiouracil: Casas (1963) reported the induction of liver tumours in mice fed this substance for a prolonged period.

## HORMONES

### Oestrogens

In experimental animals cancer has been induced in a wide variety of endocrine glands and accessary sex glands by the administration of oestrogens. In addition, malignant lymphoma and cancer of kidney, bone and muscle have been attributed to oestrogen administration (Marois, 1964). In man there is no real evidence that oestrogens, in the doses normally given in the clinic, have induced cancer (Bishop, 1960; Brain, Parkes and Bishop, 1964). Zondek (1947) recommended that when oestrogens were given to post-menopausal women, the dose should be kept low, and that cystic mastitis, erosion of the uterine cervix, or a family history of genital cancer should be regarded as contra-indications to oestrogen therapy.

### Progestational Agents, Including Oral Contraceptives

Ovarian tumours in mice were attributed to treatment with 19-nor-progesterone by Lipschutz, Iglesias and Salinas (1963), whilst Cantarow, Stasney and Paschkis (1948), Jull (1954), Huggins, Briziarelli and Sutton (1959) and Poel (1965) have found that progesterone enhances mammary tumour induction by carcinogenic polycyclic hydrocarbons. The widespread clinical use of oral contraceptive progesterone preparations is too recent to judge whether a cancer hazard is involved.

### Cortisone and Corticosteroids

There is no evidence that cortisone or corticosteriods induce cancer directly. *A priori*, since such treatment suppresses the immune response one would expect that tumours would invade and give rise to metastases more easily. There is good experimental, and some clinical, evidence that this is the case (Green and Whiteley, 1952; Agosin and colleagues, 1952; Cortes, Morris and Hutter, 1962).

## MISCELLANEOUS AGENTS

Limitations of space prevent the full consideration of all cases where there is laboratory evidence of carcinogenicity. Fuller consideration is given elsewhere (Roe, 1966). Here only the more important examples are mentioned.

Acute liver damage in man and injection-site and hepatic cancer in rats in response to treatment with various tannins, both condensed and hydrolysable, have been reported (Korpássy, 1949; Korpássy and Kovács, 1949; Kirby, 1960).

Evidence for the carcinogenicity of 8-*hydroxyquinoline*, a constituent of some spermicidal contraceptive preparations, and of skin ointments, was recorded by Hoch-Ligeti (1957), Boyland and Watson (1956) and Hueper

(1965). This, and other constituents of spermicidal contraceptives were re-investigated recently by Boyland and Roe (1964). Occasional positive results were recorded.

The dangers of implanting foreign materials in the course of plastic surgery were underlined by the finding (Dukes and Mitchley, 1962) of a high incidence of sarcomas at the site of implantation of polyvinyl sponge in rats. Roe, Dukes and Mitchley (1964) have since shown that the thicker the piece of sponge implanted, the higher is the risk of cancer.

In the laboratory, phenols, cresols, anthralin (used in the treatment of psoriasis), various essential oils (including turpentine oil, eucalyptus oil, orange oil) and lipophilic-hydrophilic surface active agents of the Tween and Span types, enhance the induction of tumours in response to known carcinogens (Salaman, 1958; Salaman and Roe, 1964). The clinical significance of these findings is unknown at present.

Over 30 different viruses have been isolated from monkey kidneys from which Salk anti-poliomyelitis vaccine is prepared. One of them, Simian virus 40 (SV40) is capable of inducing various neoplasms in several strains of rodent. This virus was at one time certainly present in the living state in many batches of polio vaccine. No case of human cancer directly attributable to its presence has so far been reported. However, unless a deliberate attempt is made to investigate this possibility by epidemiological means, a weak effect may be overlooked.

## CONCLUSION

It would be easy to assume, on the basis of present evidence, that current prescribing habits entail little risk of carcinogenesis. However, one should bear in mind that the new cases of cancer we see today might be attributable to medical treatment given more than 20 years ago, and that the dangers of what we prescribe today may not be manifest for a similar period. In any case, a weak effect is likely to be missed unless special epidemiological surveys are undertaken. At present, retrospective epidemiology is hampered by the poor standard of medical records and by the fact that such records tend to be discarded after 10 years. In general, people have become aware of the possibility that food additives or contaminants may cause cancer. Adequate animal tests are demanded and positive results in these lead to the abandonment of such agents. It is surprising, therefore, that little heed is given to strongly positive results in the case of some pharmaceutic preparations. The thalidomide tragedy helped to stir people from their apathy in this respect, but a great deal more experimental and epidemiological work is needed before the situation can be regarded as satisfactory.

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