Papers and Originals

Cancer Hazards of the Pharmacy*

GEORGIANA M. BONSER, M.D., F.R.C.P.

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New therapeutic agents are constantly being synthesized and then scrutinized from the viewpoint both of their value in the treatment of disease and of their possible undesirable effects. One such effect is the induction of cancer, and I shall recount the steps which are being taken at the present time to ensure that cancer-producing chemicals are not used in the treatment of human beings. This is far more difficult than appears at first sight, for the following six reasons.

(1) The chemical structure of a compound rarely allows prediction of its carcinogenic properties. Though ideas have been suggested for a connexion between structure and activity, important exceptions to all such correlations have been found. Minor variations in molecular structure can lead to enhancement or abolition of carcinogenic activity. None the less, as new carcinogens are discovered the field of relation of chemical structure to carcinogenesis will be widened so that at least some compounds may be detected by structure alone. This argument provides a strong justification for the pursuit of studies which elicit carcinogenic activity from compounds hitherto untested.

(2) As little help can be got from chemical structure, theoretically it becomes necessary to test every proposed synthetic drug by well-planned and prolonged animal experiments. This is quite impracticable, and therefore a selection of compounds has to be made. Great efforts are in train to devise shorter screening tests for carcinogenicity, such as the use of newborn rodents or the detection of reliable precancerous changes.

(3) The time between the first administration of a carcinogen and the appearance of the tumour is a long one. In the human being it ranges from about 5 to 40 years (longer in exceptional cases); in the rat from nine months to two years. This is known as the latent or induction period.

(4) There is no need for the carcinogen to be present during the whole of the latent period. For example, Case, Hosker, McDonald, and Pearson (1954) recorded that 6 out of 281 men exposed to carcinogens in industry for six months to one year developed tumours of the bladder 10 to 25 years after leaving the industry. There are numerous examples in animals where a single dose of a carcinogen may be followed months later by the development of a tumour. Limited doses are, however, unlikely to be effective unless a subsequent latent period is allowed to elapse.

(5) Species differences in response to the administration of chemicals are very great, and therefore tumours induced in animals may not reflect what is likely to happen in man. But it is a fact that with one important exception all the *known* chemicals causing tumours in man cause tumours also in the experimental animal. The importance of species variations in response to drug administration is emphasized by Roe (1966).

(6) Little is known about the relation between the dose of chemicals and tumour induction in various species. Therapeutic doses may never attain to those required to induce tumours in animals; but we do know that small doses can induce tumours in human beings. For example, there was 0.2% of 2-naphthylamine in rubber, which could be the cause of bladder cancer in an exposed tire-maker.

In January 1964 the Ministry of Health set up a Committee on Safety of Drugs. The scheme is voluntary and the terms of reference are wide. The two which concern us are: (1) to invite from the manufacturer or other person developing or proposing to market a drug in the U.K. any reports they may think fit on the toxicity tests carried out on it; to consider whether any further test should be made, and whether the drug should be submitted to clinical trial; and (2) taking into account the safety and efficiency of each drug, and the purpose for which it is to be used, to consider whether it will be released for marketing, with or without precautions or restrictions on its use.

It is thus clear that the manufacturer is guided by the committee in the selection of drugs for carcinogenic testing. The sole means of judging carcinogenic potentiality, apart from unfortunate unwitting occurrences in man, is by tests in animals. The difficulty which arises is in the interpretation of the results of animal tests in relation to man. This is recognized as needing an expert Panel on Carcinogenesis to advise the Minister of Health.

I propose now to consider carcinogenic therapeutic agents under two headings (Table I). (1) Those of which the cancer-inducing properties were first demonstrated in man; some of these were later confirmed in animals and some not. (2) Those of which the cancer-inducing properties were first demonstrated in animals; some of these later induced tumours in man and some have not done so until the present time. Added to these are the drugs which aroused suspicion on toxicity testing and were therefore not administered to man.

TABLE I.—Classification of Carcinogenic Therapeutic Agents

1. Carcinogenic activity first seen in man
Arsenic
Chlornaphazin
X-radiation (confirmed in animals)
Carcinogenic activity first seen in animal:
Thorotrast (confirmed in man)
Iron-dextran
Isoniazid
Trypan blue
Griseofulvin
Urethane
Goitrogens
Oestrogens
HPA* (not given to man)
SADA† (not given to man)

* 4-Ethylsulphonylnaphthalene-1-sulphonamide (anticonvulsant and diuretic).
† 2-p-Methoxybenzenesulphonamido-5-isobutyl-1,3,4-thiadiazole (hypoglycaemic agent).

Group 1

Arsenic

Neubauer (1947) collected from the literature 143 cases of skin cancer attributed to the medicinal use of arsenic, and Hueper (1957) recorded a further 37 cases. In Neubauer's

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series the disease for which the arsenic was given was known in 125 cases. In 89 (71%) there was an underlying skin condition, psoriasis being the commonest (54%), so that in the subsequent development of the skin tumours another factor, apart from the arsenic, might have been operating as well. In only 2 of the 125 cases had arsenical treatment been given for syphilis. This is surprising, as it was the usual treatment for that disease before the advent of antibiotics. No attempt has been made to relate arsenical skin cancer in man to the size of population from which the cases were drawn. For these reasons a valid statistical evaluation of the carcinogenic properties of arsenic in man is still awaited. Many attempts have been made over the past 40 years to induce tumours experimentally in animals with arsenic and none has been successful (Baroni, van Esch, and Saffiotti, 1963). This may be due to the toxic nature of arsenic and its derivatives, which effectively precludes the administration of sufficiently large doses to animals and also shortens the life of the animals.

Chlornaphazin

Chlornaphazin (*N,N*-bis(2-chloroethyl)-2-naphthylamine) has been used, especially in Scandinavia (Thiede, Chievitz, and Christensen, 1964) for the treatment of polycythaemia vera. This compound is a mustard derivative of 2-naphthylamine, which is an important industrial bladder carcinogen, and it might be expected to yield 2-naphthylamine or its metabolites when introduced into the human body. Or the compound might act in virtue of the mustard moiety, or in both ways. The effect of the drug was favourable to the original disease in 75% of patients. Of the 61 treated patients, seven developed tumours of the bladder (five carcinomas and two papillomas), all of these having received a dose greater than 100 g. and having been treated for 2 to 11 years. Some of these patients also received treatment with ^{32}P , but it seems clear that the chlornaphazin was responsible for the induction of the bladder tumours. No more recent report has been published, but it seems probable that further cases will have emerged in the time intervening since 1964.

This drug has also been used in the treatment of Hodgkin's disease, where survival is likely to be much shorter than in polycythaemia, and at least two cases of bladder cancer have been recorded after five and six years of treatment respectively (Videbæk, 1964). Thus chlornaphazin is carcinogenic to man when given in adequate dosage for an adequate period of time. No animal experiments have been reported, but when tested this drug is certain to be carcinogenic.

X-radiation

X-radiation was first used for diagnostic purposes and occasionally for therapy at the end of the last century (Schuster, 1962). Such use caused squamous carcinomas of the skin of the exposed areas in those who worked with the rays unless rigid precautions were taken. During the years 1935–54, of 14,554 patients treated in Great Britain for ankylosing spondylitis by means of ionizing radiations (Court-Brown and Doll, 1965), a highly significant increase in mortality from leukaemia and aplastic anaemia was observed—52 actual deaths from

TABLE II.—Two Examples of Post-irradiation Tumours in Man

Disease Treated	Irradiated Patients		Non-irradiated Patients	Tumour Deaths		Latent Period (Years)
	Years	No.		Treated	Control	
Ankylosing spondylitis	1935–54	14,554		52 leukaemias	5.48 (expected)	5–25
Thymic enlargement	1925–51	1,722	1,795	6 thyroid carcinomas 9 thyroid adenomas	0 1	5–15

leukaemia (0.36%) against 5.48 deaths expected (Table II). The proportion of the myeloid over the lymphatic type was also increased.

In 1955 Simpson, Hempelmann, and Fuller showed that children who had received local irradiation for "thymic enlargement" were more likely to develop thyroid tumours than non-irradiated children. Among 1,722 irradiated children there were six thyroid cancers and nine thyroid adenomas compared with none and one respectively in 1,795 related non-irradiated children. The mechanism of this occurrence is presumably radiation damage to the thyroid gland causing the blocking of thyroxine secretion followed by excess thyroid-stimulating hormone secretion by the pituitary gland. The latter causes the remaining thyroid cells to undergo excessive growth and finally neoplasia.

Both these findings, but especially the first, demonstrate that the association between administration of a carcinogen and the subsequent development of a neoplastic condition need not be an obvious one and may need patient research in order to uncover it and advanced statistical methods to elucidate it. The chances that any single practitioner will encounter a case are remote indeed.

Group 2

Thorotrast

Thorotrast (colloidal thorium dioxide) is not strictly a drug but has been widely used in man as a contrast medium for diagnostic purposes. It was shown to induce subcutaneous sarcomas in rats and mice (Selbie, 1938) and in guinea-pigs (Foulds, 1939) following injection, the tumours being attributable to its radioactivity. Much later it was realized that tumours were occurring in man, and in 1961 Dahlgren (Table III) collected some 60 cases from the literature of which I have selected the following examples. In all, 24 tumours occurred where thorotrast had been placed in hollow organs, seven being situated in the maxillary sinus. Twenty-seven were due to the compound injected systemically, taken up in the reticulo-endothelial system and deposited chiefly in the liver, spleen, and bone marrow. Though the compound was administered at sites distant to those of the tumours, the latter must be regarded as due to the local presence of the radioactive material in the affected organs. The variety of induced tumour was very great, the commonest being in the liver—hepatomas, bile-duct carcinomas, or haemangioendotheliomas. The induction period was 6 to 35 years. In many cases this could be calculated exactly, as only one dose was given. No tumours were recorded in bone. An unusual tumour was a carcinoma of the kidney occurring after cerebral angiography. No estimate can be made of the total number of thorotrast-treated patients from whom these cases were drawn, and to establish cause and effect with certainty this information is necessary. However, it was possible to demonstrate radioactive material in the vicinity of the tumours in many cases.

TABLE III.—Examples of Tumours in Man Induced by Thorotrast (Dahlgren, 1961)

Mode of Origin	Procedure	Nature and Site of Tumours	Range of Latent Period (Years)
At site of injection	Cerebral angiography (1)	Sarcoma	6
After deposition in pre-formed cavities	Pyelography (7)	Sarcoma } Kidney	16–25
	Maxillary visualization (7)	Carcinoma sinus	10–21
	Dacryocystography (1)	Carcinoma eyelid	35
	Hepatolienography (9)	Sarcoma } Liver	12–24
After systemic injection	Arteriography (13)	Carcinoma } Liver	12–24
	Cerebral angiography (1)	Carcinoma kidney	20

Iron-dextran

Iron-dextran (Imferon) has wide use in man as a means of supplying parenteral iron. It is a complex of colloidal ferric chloride and a dextran of low molecular weight. It has been found to induce sarcomas on intramuscular and subcutaneous injection into rats, mice, and hamsters (Richmond, 1960; Haddow and Horning, 1960) and rabbits (Haddow, Roe, and Mitchley, 1964). The latent period was 12 months or more in rodents and three to four years in rabbits.

The experimental doses were large in relation to the size of the animals, but Roe, Haddow, Dukes, and Mitchley (1964) argued that "since the size of body cells is similar in man and laboratory animals, the actual dose, and not the body weight, may be the critical factor in determining the induction of tumours . . . a particular volume of material will come into contact with approximately the same number of body cells in the rat as it does in man." They then conducted an experiment directed to finding out "whether the incidence and time of appearance of tumours in rats given a fixed number of injections of iron-dextran would be affected by distributing the injections between 2, 4, or 6 sites, instead of giving them, as in previous experiments, all into the same site." This is important from the viewpoint of clinical use.

Twenty-four subcutaneous injections of 0.5 ml. were given to each rat, all in the same site in group 1 and distributed among six sites in group 4 (Table IV). It is seen that increasing the number of injection sites does reduce, but does not abolish, the chance of tumour development at any one site and does delay the date of their appearance. It also decreases their malignancy. However, it is to be noted that as little as 2 ml. of iron-dextran induced 12% of tumours at 75 weeks.

TABLE IV.—*Iron-dextran Tumour Incidence After Subcutaneous Injection at One or More Sites (Rat)*

Group:	1	2	3	4	5
No. of rats	24	24	24	24	24
No. of injection sites per rat	1	2	4	6	0
Total amount injected at each site (ml.)	12	6	3	2	0
Time of appearance of first malignant tumour (weeks)	47	66	64	75	—
Injection sites with tumours	14/22 64%	11/46 24%	29/96 30%	17/138 12%	0

It is suggested that in order to exert a carcinogenic effect an excess of heavy metal must be present, and this could lead to oxidation of sulphhydryl groups and in turn to gross disturbance of enzyme systems in adjacent cells. Whatever the mechanism, the local excess of iron seems to be important. The role of dextran may be to aid penetration of iron into the cell.

No tumours have yet been reported in man, but patients will need to be followed for 15 to 40 years before they can be regarded as safe. The accumulation of iron in human tissues has been suggested as carrying a carcinogenic risk—for example, the hepatomas found in haemochromatosis and the carcinomas of the bronchus in iron-ore miners (Faulds and Stewart, 1956). Stewart (1931) could not satisfy himself that the former was the case, though other authors have been more positive, but he accepted the association between iron-ore mining and lung carcinoma.

Isoniazid

As a most useful therapeutic adjunct to streptomycin in the treatment of tuberculosis isoniazid has proved its worth. Since 1957 it has become increasingly clear that this drug is carcinogenic in the experimental animal (Biancifiore and Severi, 1966). Pulmonary adenomas and carcinomas have been induced by oral and other administration to mice (Table V). Furthermore, hydrazine (a hydrolysis product of isoniazid) caused pulmonary tumours and hepatomas in mice, but isonicotinic acid was

much less effective. A derivative of hydrazine (Natulan) caused mammary tumours in male and female rats; hydrazine sulphate caused lung tumours in rats (Biancifiore, Giornelli-Santilli, Milia, and Severi, 1966). It is suggested that isoniazid acts by virtue of its hydrazine component.

TABLE V.—*Induction of Tumours by Isoniazid and Derivatives in Mouse and Rat*

Compound	Species	Sites of Tumours
Isoniazid	Mouse	Lung. Lymph nodes
Hydrazine sulphate		Lung. Liver
Isonicotinic acid		Lung (a few)
Natulan	Rat	Breast (male and female)
Hydrazine sulphate		Lung

No tumours have been reported in man following the prophylactic or therapeutic use of isoniazid, and it will be unusually difficult to demonstrate such an association because virtually all tuberculous patients receive the drug and so there is no comparable untreated population to evaluate. Hammond, Selikoff, and Robitzek (1967) have attempted an evaluation of the effects of isoniazid in the 16 years since the introduction of therapy with this drug in 1951. In a series of several thousands of tuberculous males and females, some of whom may have been given isoniazid, there was a slight excess of lung cancer compared with the general population in males but not of a magnitude to be regarded as significant. Of a much smaller series of tuberculous patients treated with isoniazid there was no excess of lung cancer in the few who have died, nor was there any suggestion of a dose-response relationship. Of a series of pregnant women treated prophylactically, together with a scrutiny of their offspring (some of whom had attained an age of 13 years) there was again no evidence of an increase in lung cancer. This investigation is still in progress, and though the results are reassuring so far they cannot be expected to give the complete answer regarding the carcinogenic effects of isoniazid in the human being.

Ferebee (1965) has been undertaking since 1955 an investigation of the carcinogenic effects of isoniazid used prophylactically in 70,000 persons ranging in age from 2 months to 100 years. This author argues that a comparison of lung cancer incidence in treated tuberculous patients with that of the general population would not be valid because (1) tuberculosis may predispose to lung cancer; (2) tuberculous patients receive extra radiation for diagnostic and therapeutic purposes; and (3) tuberculous patients may smoke more and they usually belong to selected poorer social groups. Therefore the control population for this investigation is derived from a group of subjects given a placebo in place of isoniazid. The results are not yet available.

An additional difficulty in assessing the effects of the drug is that only a small number of patients treated with isoniazid, with or without tuberculosis, come to necropsy, and in those that do the past history is often not known. None the less, the starting-point of all the work which has been done on these compounds was the observation of Berencsi, Entz, and Vajkoczy (1952) that in a patient being treated with isoniazid presumptively for tuberculosis, but actually suffering from carcinoma of the lung, the clinical course was extremely rapid owing to precocious, numerous, and voluminous metastases due, it is suggested, to the enhancing effect of the isoniazid.

Trypan Blue

Trypan blue has been used in man, by intravenous injection, for the estimation of blood volume and also to demonstrate the lymphatic pathways in block dissection of lymph nodes. Gillman, Gillman, and Gilbert (1949) gave intravenous injections of 10 mg. of trypan blue in water to pregnant rats and induced malformations in the offspring resembling those caused by rubella in the human being. They then continued the experiments in the same mothers, and in new females and males,

giving a total of 100–200 mg. of the chemical to each animal. They obtained a high yield of reticulum-cell sarcomas in the liver, smaller numbers of spindle-cell sarcomas, and many lymphomas and proliferations resembling Hodgkin's sarcomas in nodes. The latent period was less than a year. They found that the dye was bound to plasma albumin and then taken up by reticuloendothelial cells throughout the body, but especially in the liver. They were able to demonstrate spindle-cell sarcomas in the liver after a single injection in as short a period as 19 weeks. They found also that Evans blue had a similar action in causing liver tumours. They made the very interesting observation that although trypan red and Congo red do not cause proliferation of the reticuloendothelial cells in treated mothers, Congo red causes malformations in the offspring. Thus trypan blue is carcinogenic and teratogenic, and Congo red is teratogenic but not carcinogenic, and trypan red has neither action. Obviously much more information about the effects of these compounds is needed.

Griseofulvin

Griseofulvin is an antibiotic derived from three types of *Penicillium* (*P. patulum*, *P. griseofulvum*, and *P. janczewski*) and is extensively used in the systemic treatment of superficial fungal infections in man and animals. When it is administered orally and continuously to mice (Weston Hurst and Paget, 1963) this drug causes derangement of the porphyrin mechanism so that protoporphyrin is deposited in large quantities in the liver. Consequent on this, liver-cell necrosis, bile-duct proliferation, and cirrhosis occur, followed by the induction of multiple hepatomas. If the conditions of the experiment are such that the protoporphyrin can be eliminated from the liver—for example, if the dose is small or discontinuous—the liver damage and tumours do not occur. It could be postulated that continuous absorption could take place in treated patients, but the amount absorbed would be unlikely to reach a sufficient dimension to cause the damage seen under experimental conditions. No tumours have been reported in man or in the veterinary field. It is of significance that other mould products, such as aflatoxin derived from *Aspergillus flavus*, are potent liver carcinogens.

Urethane

Urethane, which induces lung tumours in rodents, has the property of initiating tumour formation in mouse skin even when administered orally, but requires the topical administration of a co-carcinogen to render the tumours manifest. It has been virtually abandoned for therapeutic use as more efficient tumour chemotherapeutic agents have been found.

Goitrogens

Goitrogens act by a feedback mechanism similar to that described in thymic irradiation. When given orally they cause carcinomas of the thyroid gland in rodents. The incidence can be increased and the malignancy enhanced by combining the short-term administration of a known chemical carcinogen with subsequent administration of the goitrogen (Bielschowsky, 1945).

Oestrogens

Oestrogens, by whatever route administered, cause mammary carcinomas in mice, but only if other factors such as a virus or progesterone are also present.

The work of Court-Brown and Doll (1965) has emphasized how advantageous is a large population in demonstrating a

carcinogenic risk in treated patients. This would apply also to those treated with goitrogens and oestrogens, but so far no large series has been analysed from the point of view of cancer induction. The small amount of evidence available does not suggest that these compounds have induced tumours in man. Another factor is present, however, in the use of synthetic and semisynthetic hormones. Apart from their cancer-inducing potentialities due to their hormonal action they may induce tumours, especially of the liver, by virtue of their chemical structure. A large-scale trial of the long-term effects of synthetic oestrogens and progestins has been initiated in the introduction of the contraceptive pill, and information will certainly eventually become available in regard to the presence or absence of tumour-inducing properties in these compounds in man. Meanwhile straws are blowing in the wind. Poel (1966) found an enhanced incidence, earlier onset, and more rapid development of pituitary tumours in female mice treated with progestins than in virgin controls (Table VI). But old breeding mice of this strain in another laboratory developed many pituitary tumours, so that the meaning of this experiment is far from clear. He also found 10 hepatomas in 96 treated mice and none in the controls, but unfortunately gave no further details.

TABLE VI.—Pituitary Tumours in Mice Treated with Progestins (after Poel, 1966)

Compound	Daily Dose	Tumours in Survivors to 85 Weeks or More	Approximate Size (mm.)
50 parts norethynodrel and 1 part mestranol	70 µg.	7/7	2-7
	7 "	6/11	1-5
50 parts norethindrone and 1 part ethinylloestradiol	70 "	5/8	2-4
	7 "	7/15	2-6
Control	None	2/15*	< 1-1

* Killed at 90 weeks.

Cahal (1966) referred to experiments by manufacturers of oral contraceptives and concluded that "mestranol, when administered in high doses and for prolonged periods to rats, causes liver damage which is sometimes severe, including on occasion the development of hepatomas. Adequate experiments have not been carried out on other species of animals."

Stoll (1967) used Lyndiol (a contraceptive pill containing ethinylloestrenol as progestin and mestranol as oestrogen) in the treatment of breast cancer in postmenopausal women. He found disordered liver function, jaundice, or hepatic necrosis on biopsy in 15 of 38 patients, apparent at the contraceptive dose of one tablet a day but more marked when the dose was increased to six tablets.

It would be very reassuring to learn of negative results in well-conducted long-term experiments in animals before the human experiment has assumed too great a dimension.

HPA

Brimelow and Vasey (1958), in a British patent, described the chemical synthesis of a new class of sulphonamides which held promise as anticonvulsants and diuretics. Walpole (personal communication) and Paget (1958) observed hyperplasia of urinary tract epithelium in rats fed relatively large amounts

of one of these compounds, 4-ethylsulphonylnaphthalene-1-sulphonamide, or HPA (see Formula). The incorporation of as little as 0.01% in the diet of rats—that is, one part in 10,000—induced focal hyperplasia of urinary tract epithelium. For this reason the drug was not introduced for human therapy. This is an excellent example of the piercing scrutiny which is applied during toxicity-testing of new drugs.

My colleagues and I decided that this was an unusual compound, worthy of further investigation, because we knew of no other chemical which had been demonstrated to cause hyperplasia of renal tract epithelium on short-term testing. We therefore gave this compound to mice in the diet at a level of 0.01% for up to 65 weeks (Clayson and Bonser, 1965) and obtained five transitional-cell papillomas and 23 carcinomas of the bladder in 73 effective mice, but no tumours in any other organ. This was also unusual as all the other members of the small group of mouse-bladder carcinogens had induced tumours in other organs as well (Table VII).

TABLE VII.—Bladder Tumours Induced by Oral HPA (Mouse)

Dose	Sex	No. Surviving 30–69 Weeks	Papillomas	Carcinomas	
				No.	%
0.01% in diet {	M	34	2	5	15
	F	39	3	18	46

Paget and Walpole's observation was thus very astute, as the hyperplastic action of the drug proved to be the first stage in the carcinogenic action. Clayson, Lawson, Santana, and Bonser (1965) have extended this observation in an attempt to devise a short-term test which could be used to pick out compounds carcinogenic to the bladder by means of their hyperplastic action and thus reduce the testing time to six weeks or less.

SADA

This compound was being investigated for use as a hypoglycaemic agent when it was discovered that it caused bladder tumours when given in the diet to rats, and it was therefore discarded. The chemical structure bore no resemblance to that of any other known carcinogen, which emphasizes how impossible it is, at present, to foretell carcinogenic activity from chemical structure (see Formula).

In Table VIII the results of tests in rats by the oral route are shown. This was a large experiment, adequately controlled. No tumours were obtained until one year of experiment had elapsed, and then only when the drug was given at a concentration of 0.6% or over in the diet, which is much more than is needed relatively in the mouse treated with HPA. Again no tumours were observed in organs other than the bladder.

TABLE VIII.—Induction of Bladder Papillomas and Carcinomas by SADA (Rat)

Dose (% in Diet)	No. of Rats at Start		Bladder Tumours				3 Years	
			1 Year		1½ Years			
	M	F	M	F	M	F	M	F
Control 1 ..	20	20					0	0
0.05-0.4 ..	80	80					0	0
Control 2 ..	10	10		0/4		0/5		
0.6	10	10		1/5		1/5		
0.8	10	10		2/4		1/4		
Control 3 ..	20	20			0/15	0/15		
0.8	30	30			9/22	4/22		

Although we have no information about the way in which HPA and SADA would act in the human being, no one would dream of permitting their clinical use, because of the extreme potency in man of several other known experimental bladder carcinogens.

Discussion

I have brought to your attention some known or suspected carcinogenic properties of certain therapeutic agents in use or discarded before use in the human being. A more complete list may be found in Roe's (1966) paper.

We are now in a position to discuss the more philosophical problems raised by the facts that I have described to you.

We would all agree that therapeutic compounds which have been proved to induce tumours in man should not be administered for any but the most exceptional clinical purposes—for example, where the expectation of life is short and no other suitable drug is available. It might be suggested also that if a drug is still in the trial stage and is found to be carcinogenic to animals it should be withheld from human use. If we adopt this policy we shall have to realize that we may be withholding a drug which would be of inestimable value in the treatment of a disease or a group of diseases. But what attitude are we to take in regard to a drug which has already proved its worth in the treatment of human disease and has subsequently been shown to cause tumours in animals? The examples I would quote are iron-dextran and isoniazid. In the former case we know that one factor in the development of the experimental tumours is the local accumulation of iron at the site of injection. Therefore I should reserve the use of iron-dextran for patients in the older age groups who do not require large doses continuously or for the acute emergency. I consider that its routine use in pregnant women is unjustified. To vary the injection site might be useful. In regard to isoniazid I should use it as required in the treatment of tuberculosis, though there seems to be recent evidence of bacillary resistance to this compound, but I should not give it prophylactically to young contacts of tuberculous patients, as is the practice in some boroughs in the United Kingdom and elsewhere. It has to be remembered that the duration of the latent period is the most important factor in the quantitative assessment of the causes of cancer and that the longest latent period occurs when exposure starts in childhood.

We now come to the problem of whether all new drugs should be tested for carcinogenic activity before they are marketed. If it were possible to predict this property from chemical structure then such tedious biological work would be avoided. Only occasionally can carcinogenicity be predicted from chemical structure (as I think could now be done in the case of chlor-naphazin). No one could have predicted that HPA and SADA would have this property. I suggest that a commonsense view must be taken of this matter. If a drug is to be used only to treat degenerative disease in old age there is less need for testing than if it is to be used for chronic disease in the young. Any new compound should be tested if a related compound (whether near or distant) is known to be carcinogenic. The strongest argument against testing all new compounds is that it is an expensive task which consumes much skilled scientific labour that could be put to more constructive use, such as the synthesis and preliminary trials of new compounds.

As carcinogenesis is dependent upon the interaction between chemicals and enzyme systems, it is not surprising that species and even strains within a species react in different ways. For example, when the industrial carcinogen 2-naphthylamine is administered to man and the dog, tumours occur in the bladder (and nowhere else), but when administered to the mouse the tumours are in the liver, and in the rat no tumours occur at all. Thus if, on testing a compound in the experimental animal, tumours are induced in the liver, it may be necessary to look for them in the exposed human being in the intestine or bladder. If it happens that the site of election is an organ, such as the intestine, where so-called spontaneous tumours are frequent, any association between the drug and subsequent cancer will not be evident and will require diligent search to uncover it. Linked to this aspect is the gap between the discoveries of the experimentalist and the appreciation by the

clinician of the significance to him and his patient of what has been discovered in the laboratory. Means must be found to bridge this gap.

Summary

The synthesis and exploitation of new therapeutic agents bring hazards as well as benefits to the patient. One hazard is actual or potential carcinogenic action. It is often not realized that the chemical structure of a compound rarely allows prediction of its carcinogenic properties, though it is to be hoped that such a relation will eventually be discovered. At present the only method of demonstrating carcinogenic activity is by laborious tests in animals, and even then the relevance of the results to man is uncertain.

The latent period of tumour induction is long, ranging in the human being from 5 to 40 years. There is no need for the carcinogen to be present during the whole of the latent period, so that a limited exposure in childhood may declare itself later in adult life. Little is known about the relation between the dose and tumour induction.

Carcinogenic therapeutic agents are here discussed as: (1) those of which the cancer-inducing properties were first demonstrated in man; (2) those of which the carcinogenic activity was first seen in animals but the compound had already been given to man; and (3) those which were withheld from man because their tumour-producing potential was discovered by animal experiment.

It is emphasized that laborious statistical investigation may be needed to uncover a relation between therapy and subsequent tumour induction, the treatment of ankylosing spondylitis by x-irradiation being cited as an example.

I hold the view that compounds which have been proved to induce tumours in man should not be administered to patients for any but the most exceptional clinical needs—for example, where the expectation of life is short and no other suitable drug is available. Drugs shown in the trial stage to be carcinogenic in animals should normally be withheld from man, in the knowledge that thereby valuable therapeutic agents may be lost. Drugs which have already proved their worth in therapy and which have subsequently been shown to induce tumours in

animals should be regarded with much suspicion and should in general be withheld from the young and from use as prophylactics. Thus an assessment must be made of the risks and of the benefits in each individual patient. This will be greatly helped by improved communication between the laboratory worker and the clinician.

REFERENCES

- Baroni, C., van Esch, G. J., and Saffiotti, U. (1963). *Arch. environm. Hlth*, **7**, 668.
 Berencsi, G., Entz, A., and Vajkoczy, A. (1952). Quoted by Biancifiore and Severi (1966).
 Biancifiore, C., and Severi, L. (1966). *Brit. J. Cancer*, **20**, 528.
 — Giornelli-Santilli, F. E., Milia, U., and Severi, L. (1966). *Nature (Lond.)*, **212**, 414.
 Bielschowsky, F. (1945). *Brit. J. exp. Path.*, **26**, 270.
 Brimelow, H. C., and Vasey, C. H. (1958). U.K. Patent No. 791,529.
 Cahal, D. A. (1966). *Brit. med. J.*, **1**, 1540.
 Case, R. A. M., Hosker, M. E., McDonald, D. B., and Pearson, J. T. (1954). *Brit. J. industr. Med.*, **11**, 75.
 Clayton, D. B., and Bonser, G. (1965). *Brit. J. Cancer*, **19**, 311.
 — Lawson, T. A., Santana, S., and Bonser, G. M. (1965). *Ibid.*, **19**, 297.
 Court-Brown, W. M., and Doll, R. (1965). *Brit. med. J.*, **2**, 1327.
 Dahlgren, S. (1961). *Acta path. microbiol. scand.*, **53**, 147.
 Faulds, J. S., and Stewart, M. J. (1956). *J. Path. Bact.*, **72**, 353.
 Ferebee, S. H. (1965). *Brit. med. J.*, **2**, 1122.
 Foulds, L. (1939). *Amer. J. Cancer*, **35**, 363.
 Gillman, J., Gillman, T., and Gilbert, C. (1949). *S. Afr. J. med. Sci.*, **14**, 21.
 Haddow, A., and Horning, E. S. (1960). *J. nat. Cancer Inst.*, **24**, 109.
 — Roe, F. J. C., and Mitchley, B. C. V. (1964). *Brit. med. J.*, **1**, 1593.
 Hammond, E. C., Selikoff, I. J., and Robitzek, E. H. (1967). *Ibid.*, **2**, 792.
 Hueper, W. C. (1957). In *Cancer*, vol. 1, p. 404, edited by R. W. Raven. London.
 Neubauer, O. (1947). *Brit. J. Cancer*, **1**, 192.
 Paget, G. E. (1958). In *A Symposium on the Evaluation of Drug Toxicity*, edited by A. L. Walpole and A. Spinks. London.
 Poel, W. E. (1966). *Science*, **154**, 402.
 Richmond, H. G. (1960). In *Cancer Progress 1960*, edited by R. W. Raven, p. 24. London.
 Roe, F. J. C. (1966). *Clin. Pharmacol. Ther.*, **7**, 77.
 — Haddow, A., Dukes, C. E., and Mitchley, B. C. V. (1964). *Brit. J. Cancer*, **18**, 801.
 Schuster, N. H. (1962). *Brit. med. J.*, **2**, 1164.
 Selbie, F. R. (1938). *Brit. J. exp. Path.*, **19**, 100.
 Simpson, C. L., Hempelmann, L. H., and Fuller, L. M. (1955). *Radio-logy*, **64**, 840.
 Stewart, M. J. (1931). *Lancet*, **2**, 565.
 Stoll, B. A. (1967). *Brit. med. J.*, **1**, 150.
 Thiede, T., Chievitz, E., and Christensen, B. C. (1964). *Acta med. scand.*, **175**, 721.
 Videbæk, A. (1964). *Ibid.*, **176**, 45.
 Weston Hurst, E., and Paget, G. E. (1963). *Brit. J. Derm.*, **75**, 105.

Six Cases of Acrylamide Poisoning

T. O. GARLAND,* M.D., D.P.H.; M. W. H. PATTERSON,* M.B., CH.B., B.SC.

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Early in February 1967 a 19-year-old youth (Case 1) was admitted to the Central Middlesex Hospital with severe peripheral neuropathy and dermatitis of the hands. The occupational health unit was asked to report on any toxic material that he might have contacted at work.

A director of the small factory where he was employed said that they had carefully reviewed all the materials he had handled and none of them could have poisoned him. He was held to be a rather dull lad, who virtually did only labouring work. He lodged with a local farmer, was a poor time-keeper, and by way of recreation spent much time in a local dance hall, which was under suspicion as a place where drugs were peddled.

In appearance the patient bore out this story. His ataxic walk and tendency to fall over almost emphasized it. His

mother had died when he was a child, and life had not been easy for him. He agreed that he was a bad time-keeper, especially lately. However, he denied that he had ever taken drugs, though he had been offered them at the dance hall, and added that lately he had given up smoking and drinking. He knew that he had been working with acrylamide, some of which came from the Cyanamid Co. of New Jersey, and some from Japan, and he told us that the bags from the U.S.A. had a warning label on them.

A further call was made to the factory chemist. He thought that acrylamide could be toxic and remembered having read in a booklet, issued by Cyanamid International, that it poisoned small mammals. The London headquarters of the Cyanamid Co. produced a paper on the toxicology of acrylamide by D. D. McCollister, F. Oyen, and V. K. Rowe, but assured us emphatically that they had no knowledge of any humans having suffered from it. McCollister's description of poisoned

* Central Middlesex Hospital, London N.W.10.