The reversibility of cancer

To the Editor: The article by Dippenaar et al. is interesting but needs immediate comment.

Reversal of tumour growth is a new idea. It has been reported in plants and in vertebrates, and it is possible that some 'spontaneous remissions' fall into this category, although the definition of spontaneous remission (namely 'partial or total disappearance of tumour with apparently inadequate treatment') tells its own story.

A statement in the article that is probably not justified as it stands is: 'It is a matter of dispute as to how effective this approach (referring to radio- or chemotherapy) is in the enhancement of either the quantity or ... the quality of the residual lifespan of the victors'. This statement illustrates either bias or ignorance or both. Many a cured cancer patient will testify to this! I am thinking of such diseases as carcinoma of the cervix uteri, carcinoma of the prostate, testicular carcinomas, Wilms' and other childhood tumours, sarcoma, reticulum cell, Hodgkin's disease, and many others. There is no dispute about non-curable cancers — for these patients the treatment resulting in a non-cure is probably not worth the discomfort. This first statement was therefore made, I think, rather in haste and does not reflect a well-considered evaluation of the available facts.

Since I am not a biochemist, I cannot comment on this aspect of the work. What worries me, though, is that editorial comment is not necessarily those of the Medical Association of South Africa.—Editor

Mrs Dippenaar and Professor Booyens reply: We read the above criticisms with interest, but would like to point out that we are testing a normalization approach to cancer, a hypothesis pur forward testing a normalization approach to cancer, a hypothesis put forward by Horrobin, and that our paper simply reported the first observations. By Horrobin, and that our paper simply reported the first observations. We would like to explain that the phrase 'one experiment in vitro' actually embraces a total of over 400 cell cultures. We totally agree with Professor Smit that at this early stage we have only demonstrated a reduced growth rate in malignant cells and therefore only go as far as to state that this work appears to support the normalization hypothesis of Horrobin.

We have definitely not stated that we have shown these cells to have normalized.


Pulmonary fibrosis following long-term nitrofurantoin therapy

To the Editor: Willox et al. reported on 3 patients who developed pulmonary fibrosis after treatment with nitrofurantoin for 3-4 years for chronic urinary tract infections. These patients had respiratory symptoms, including shortness of breath and dry cough, for 2 and 3 years and 1 year respectively. The package inserts for our nitrofurantoin products point out that a chronic pulmonary reaction of insidious onset is associated with prolonged therapy and describe the common symptomatic manifestations.

In general, it seems as if the chronic reaction is characterized by dyspnoea on exertion, a mild cough, and slowly progressive changes on the chest radiograph. If the reaction is not recognized, the symptoms and lung damage can worsen with time. It seems that the severity of the reaction, recovery and the time to recovery are directly related to how long nitrofurantoin therapy is continued after the first clinical signs appear. If the reaction is recognized early and the drug is stopped, all signs and symptoms usually disappear within a few weeks.

The Swedish data referred to in Willox et al.'s article are peculiar and may be a function of the Swedish populace and/or the design of their drug reaction reporting system. They are not confirmed by our world-wide experience or by the following information from the UK and Holland (Table I) presented in a recent article in the BMJ by Penn and Griffin.

Mrs Dippenaar and Professor Booyens reply: We read the above criticisms with interest, but would like to point out that we are testing a normalization approach to cancer, a hypothesis put forward by Horrobin, and that our paper simply reported the first of many observations we and others have made on the effect of gamma-linolenic acid when added to malignant cells. So far all animal and 7 human malignant cell lines have responded to these low doses (some of these results appeared in the SAMJ of 30 October 1982). Preliminary in vitro studies in various animals are already in progress, and results at this stage look promising. We would like to explain that the phrase 'one experiment in vitro' actually embraces a total of over 400 cell cultures. We totally agree with Professor Smit that at this very early stage we have only demonstrated a reduced growth rate in malignant cells and therefore only go as far as to state that this work appears to support the normalization hypothesis of Horrobin.

We have definitely not stated that we have shown these cells to have normalized.


Pulmonary fibrosis following long-term nitrofurantoin therapy

To the Editor: Willox et al. reported on 3 patients who developed pulmonary fibrosis after treatment with nitrofurantoin for 3-4 years for chronic urinary tract infections. These patients had respiratory symptoms, including shortness of breath and dry cough, for 2 and 3 years and 1 year respectively. The package inserts for our nitrofurantoin products point out that a chronic pulmonary reaction of insidious onset is associated with prolonged therapy and describe the common symptomatic manifestations.

In general, it seems as if the chronic reaction is characterized by dyspnoea on exertion, a mild cough, and slowly progressive changes on the chest radiograph. If the reaction is not recognized, the symptoms and lung damage can worsen with time. It seems that the severity of the reaction, recovery and the time to recovery are directly related to how long nitrofurantoin therapy is continued after the first clinical signs appear. If the reaction is recognized early and the drug is stopped, all signs and symptoms usually disappear within a few weeks.

The Swedish data referred to in Willox et al.'s article are peculiar and may be a function of the Swedish populace and/or the design of their drug reaction reporting system. They are not confirmed by our world-wide experience or by the following information from the UK and Holland (Table I) presented in a recent article in the BMJ by Penn and Griffin.

Mrs Dippenaar and Professor Booyens reply: We read the above criticisms with interest, but would like to point out that we are testing a normalization approach to cancer, a hypothesis put forward by Horrobin, and that our paper simply reported the first of many observations we and others have made on the effect of gamma-linolenic acid when added to malignant cells. So far all animal and 7 human malignant cell lines have responded to these low doses (some of these results appeared in the SAMJ of 30 October 1982). Preliminary in vitro studies in various animals are already in progress, and results at this stage look promising. We would like to explain that the phrase 'one experiment in vitro' actually embraces a total of over 400 cell cultures. We totally agree with Professor Smit that at this very early stage we have only demonstrated a reduced growth rate in malignant cells and therefore only go as far as to state that this work appears to support the normalization hypothesis of Horrobin.

We have definitely not stated that we have shown these cells to have normalized.

Adverse reactions are probably underreported, but the number of reports does give an indication of the incidence, which is not increasing.

W. van Rensburg  
Medical Director  
Smith Kline & French Laboratories  
Isando, Tvl

Dr Willcox and Professor Benatar reply: Our report of 3 cases of pulmonary fibrosis following nitrofurantoin therapy was intended to draw attention to this condition, which is not clearly appreciated despite the package insert information provided by the manufacturers and referred to by Mr Van Rensburg.

Our article was published in the SAMJ on 8 May 1982, i.e. 1 week before the paper in the BMJ to which Mr Van Rensburg refers. The information in that paper could therefore not have been available to us prior to publication of our report. The lower rate of reports of reactions to nitrofurantoin in the UK compared with that in Sweden could be due to several factors, including the overall lower rate of reporting of adverse drug reactions in the UK. Mr Van Rensburg cautions against the extrapolation of data from Sweden to other countries and quotes the British experience to suggest that adverse reactions to nitrofurantoin may also be less common in other parts of the world. Our report of 3 cases seen in one hospital in South Africa (population ± 25 million) over a 5-year period would seem to reflect a much higher incidence than in the UK, where only 9 chronic lung reactions were reported over a 16-year period in a population of 57 million. Assuming that the only cases of chronic pulmonary fibrosis following nitrofurantoin therapy in South Africa during that period were those seen by us, this would represent a rate per million population per year three times higher than the rate for chronic lung reactions in the UK. As this assessment is based on patients seen in a single hospital in a large country it would seem that if any conclusions can be drawn it is that chronic lung reactions to nitrofurantoin are more common in South Africa than in the UK.

We wish to emphasize once again that caution should be exercised when this drug is used, particularly when it is given on a long-term basis.

**Administration of depolarizing muscle relaxants after non-depolarizer reversal**

**To the Editor:** The article by Dr De Roubax,1 which reached me rather belatedly, contains a significant error in that the author has confused the drug physostigmine with pyridostigmine. He cites Miller et al.2 as comparing times to peak effect and duration of intravenous neostigmine and physostigmine. In fact, this study compared neostigmine with pyridostigmine, a drug widely used in neuromuscular blockade.

Physostigmine, also a reversible inhibitor of acetylcholinesterase, is not used to reverse neuromuscular blockade. It is a tertiary acetylcholinesterase inhibitor which crosses the blood-brain barrier and is used as a specific antidote for the central anticholinergic syndrome resulting from muscarinic blockers such as atropine, scopolamine and a host of other drugs with central anticholinergic activity. Neostigmine and pyridostigmine are quaternary acetylcholinesterase inhibitors which do not cross the blood-brain barrier, and their major clinical use relates to the neuromuscular junction.

De Roubax’s error in the citation of Miller et al.’s paper is compounded by repeating the incorrect information regarding physostigmine/pyridostigmine in both the conclusions and the summary. Incidentally, readers seeking to read reference 4 (Morris et al.) will not find it on the non-existent page 5421 as printed. This should read page S (for supplement) 421.

**D. T. Glauber**  
Anesthesia Clinical Services  
University Hospital  
Seattle  
Washington  
USA

**Neonatalyte formula**

**To the Editor:** With reference to the study by Andronikou et al.,1 the following points should be noted. Neonatalyte (Sabay) was formulated by consensus of paediatricians at meetings of the Inter-Provincial Pharmaceutical Committee between 1977 and 1980. The directions for use enclosed with the solution clearly state that it should not be used within the first 24 hours of life. It has been in general use since registration was obtained in May 1981, and no adverse effects have been reported despite its widespread use since that time.

H. van Wyk  
Director  
Scientific and Technical Services Department  
Sabay (Pty) Ltd  
Johannesburg

**B. Kengel**  
Medical Director  
Adcock-Ingram Laboratories  
Johannesburg


**Tardive dyskinesia**

**To the Editor:** I would like to reply to Dr Sandyk’s communication on tardive dyskinesia as follows:

1. In a review of tardive dyskinesia, Simpson et al.2 reaffirmed Klawans’3 proposal that tardive dyskinesia was caused by dopamine withdrawal leading to basal ganglia dopaminergic supersensitivity and to a relative dopaminergic overactivity compared with the cholinergic system. Theoretically treatment consists of dopamine receptor blockers, including blockade by D₂-receptor blockers, boosting the cholinergic system (physostigmine, choline, deanol, lecithin), or using gamma-aminobutyric acid (GABA) agonists (valproic acid, baclofen, benzodiazepines, muscimol, γ-acyclic GABA).

2. Reduced levels of GABA and glutamic acid decarboxylase have been found in Huntington’s chorea (the sister-model to tardive dyskinesia) but not in tardive dyskinesia.

---

**TABLE II. PULMONARY REACTION INCIDENCE RATES**

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>World-wide</th>
<th>USA</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute reactions</td>
<td>7.7 x 10⁻⁴</td>
<td>2.1 x 10⁻⁴</td>
<td>6.4 x 10⁻⁴</td>
</tr>
<tr>
<td>Chronic reactions</td>
<td>1.3 x 10⁻⁴</td>
<td>5.2 x 10⁻⁴</td>
<td>7.8 x 10⁻⁴</td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to the number of courses of therapy theoretically required for 1 reaction to occur.
3. Reduced levels of GABA have not been found in anxiety states. If anxiety is considered to be a disturbance of arousal state\(^1\) one would, in view of the great effectiveness of the benzodiazepines in anxiety, concede that the GABA pathways are functionally relatively hypo-active in anxiety.

4. The patient under discussion did not experience relief from anxiety when on oxazepam 90 mg/d. She was probably undermedicated as regards both her anxiety and her tardive dyskinesia. Hollister\(^\text{a}\) describes the use of diazepam 20-40 mg/d for tardive dyskinesia, at which dose drowsiness and ataxia may ensue. Nevertheless, her failure to improve suggests that endogenous anxiety was not a factor. When first seen she had had an endogenous depression (biogenic amine depletion), which was at least partly relieved by amitriptyline, a 5-hydroxytryptamine repleter.\(^3\) She subsequently suffered a grief reaction.

5. The patient therefore suffered from both tardive dyskinesia and a disease caused by social circumstances. Correction of the latter removed the subjective discomfort in her experience of both grief and tardive dyskinesia. The objective signs remained unaffected by the oxazepam. Cole (quoted by Gardos et al.\(^3\)) describes a nine-point global scale for three distinct and clinically vital aspects of tardive dyskinesia: (i) global severity of abnormal movements as seen by the observer; (ii) global severity of the patient’s reaction to movement; and (iii) incapacity rating. My original letter\(^1\) dealt with the second aspect and not the first. Her improvement (becoming resigned to the involuntary movements) did not occur after medication but after Caplan’s\(^10\) phase I of the ‘mastery of stress’ — acting directly on the source of threat.

E. Freed

Department of Psychiatry
St Vincent's Hospital
Darlinghurst
New South Wales
Australia


Dacryohaemorrhoea

To the Editor: I was surprised to read in Theodore James’ interesting article on dacryohaemorrhoea\(^1\) that he could not find the slightest mention of this particular condition in Duke-Elder’s System of Ophthalmology, because Duke-Elder deals with the subject on pp. 1507-1508 of his Textbook of Ophthalmology, vol. 2.\(^2\) In his System of Ophthalmology (vol. VIII, part 1) he covers the weeping of ‘bloody tears’ (lacræmae cruentæ, dacryohaemorrhysis) on pp. 37-39.\(^3\) Like Homer (of the wine-dark sea), James (of the Tavel wine tears) sometimes nods.

S. Abel

308 Medical Centre
Heerengracht
Cape Town


Dr James replies: Dr Abel is quite right to express his surprise at my discourtesy to Duke-Elder in relation to ‘bloody tears’: I can offer no excuse, and it is most considerate of Dr Abel to find one for me — nodding in Homer’s company! Although none of the cases of bloody tears which have been reported compare with mine, I should like to state here with what keen interest I read Dr Abel’s own paper on the same subject which he delivered to a meeting of the Cape Town Group of the Ophthalmological Society of South Africa in June 1952 and which was published in the Transactions of that Society in the same year.

Important notice/Belangrike kennisgewing

Contributors to the correspondence column of the SAMJ are requested to provide 2 type-written copies of each letter submitted for publication, in triple spacing, and to ensure that any references are complete and presented in the Vancouver style (see articles in any issue of the Journal), since inaccuracy in this respect will delay publication.

Skywers wat bydraes vir die briewekolom van die SAMJ stuur, word versoek om 2 getikte afskrifte van elke brief wat voorgelê word, te voorsien. Bydraes moet in driehubbe-spasiëring getik word, en verwysings moet volledig en volgens die Vancouver-systeem aangebied wees (sien artikels in enige uitgawe van die Tydskrif), aangesien onakkuraatheid in hierdie opsig publikasie sal vertraag.