e-mail submissions to
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Muller's ratchet hypothesis

The situation in WHO's Regional Office in Africa (WHO/AFRO), which you describe in your Aug 7 Editorial (p 475)[1] is not unique. As a former staff member of WHO/Europe I would say that almost all the weaknesses you identify for WHO/AFRO in your fourth paragraph now apply to the European office, most notably that the agency acts as a political rather than a technical one.

For several years, I have been concerned about financial maladministration that has affected my programmes. I have pursued this issue through all available channels, including the United Nation's Office of Internal Oversight Services (OIOS) (which after nearly a year of consideration claimed to have no mandate to oversee WHO). I can, hence, confirm there is no effective financial oversight for WHO as a whole or for its regional offices.

Although the health issues in Europe are not on the same scale as in Africa, there are serious issues to be addressed. As I noted last year,[2] progress in environmental health, particularly by WHO/Europe, since the late 1980s, has been impressive, but the low priority given to environmental health by the present Regional Director (and the present Director General and his predecessor in Geneva) is surprising given the increasing problems from pollution, as well as global climate change. In Europe there are many serious environmental problems, which are a legacy from the past, and which need tackling at a supranational level. For the future there is the need to maintain the gains made against the relentless pressure of economic growth.

That there was no contest for the prestigious and well rewarded post of Regional Director, WHO/Europe, in September, was therefore surprising. The incumbent was returned unopposed, presumably because the post is regarded as unimportant. There is a genetic effect, known as Muller's ratchet, whereby a lack of selective pressure (competition) leads to an irreversible build-up of deleterious mutations in descendents, so weakening the organism. If WHO's most senior management is to be appointed through elections it would seem that the Organization, like organisms, needs competition to stay healthy. As such, the reasons why the Regional Director's position was not challenged for the next 5 year term should be identified. An unopposed succession, by default an endorsement of policies based on reasoning, which some might describe as over-simplistic, combined with a lack of financial oversight, cannot be healthy.

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1 The Lancet. WHO's African regional office must evolve or die. *Lancet* 2004; **364:** 475–76.
2 Baverstock K. A time to ask what you want of WHO. *BMJ* 2003; **327:** 111.

AD2000: design and conclusions

Contrary to the rather pessimistic conclusions of the AD2000 study group (June 26, p 2105),[1] we find the results of this ambitious study rather encouraging. Despite recruiting only a fifth of its intended numbers from a limited catchment area and using idiosyncratic diagnostic procedures, dosing, and delivery routines, including repeated wash-out periods, the trial managed to produce positive results in cognition and function on a par with other clinical trials.[2] These findings were achieved in the face of high drop-out rates, which must have detrimentally affected the power of the study, and statistical modelling to replace large amounts of missing data. This problem becomes worse after the first phase, making interpretation of data beyond that point difficult.

Measuring quality of life in patients with dementia and in their carers is fraught with difficulty. However, conclusions drawn by the AD2000 Collaborative Group about the negative results in the treatment of neuropsychiatric features are also problematic, since the investigators started by including large numbers of patients with zero or low scores on the scale used and then restricted the analysis to patients with much higher scores; here the numbers are so low (n=41) that the power is inadequate to show any difference between groups.

Although tolerance was excellent, Lon Schneider, in his accompanying Commentary (p 2100),[3] expresses concerns about deaths and serious adverse events on donepezil. His concerns reflect the numbers shown in the flow chart, which are different to those presented in the text. The death rates reported are fairly low, and perhaps support the relative safety of donepezil in view of the fact that the group taking donepezil had more vascular dementia and co-morbidity.

So, despite these positive results, we feel that the methodological difficulties noted from design through to analysis preclude the study from making a great contribution to the published work. The results should be considered along with those of other trials and not instead of them. We hope the findings will not unduly affect reappraisal of this class of drugs by the National Institute for Clinical Excellence (NICE), since the results of this study are atypical and are on just one drug. The suggestion that these drugs have not been a help to people with Alzheimer's disease is offset by the expansion of dementia services since the drugs became available, following the NICE guidance of 2001[4] and the subsequent National Service Framework for Older People.[5]

We recognise that this study was complex and difficult to deliver and, as such, does not reflect clinical practice. However, the shortcomings suggest that any attempt to inflate the importance of this data set, as has been done by the media, is ill founded. Many doctors already use cholinesterase inhibitors cautiously,

suggesting that this report will have little effect on routine clinical practice.

All authors are members of the Alzheimer's Society and have received grants from pharmaceutical companies that manufacture cholinesterase inhibitors, including donepezil.

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1 AD 2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004; **363:** 2105–15.
2 Burns A, Rosser M, Hecker J, et al. The effects of donepexil in Alzheimer's disease: results from a multinational trial. *Dement Geriatr Cogn Disord* 1999; **10:** 237–44.
3 Schneider LS. AD2000: donepezil in Alzheimer's disease. *Lancet* 2004; **363:** 2100–01.
4 National Institute for Clinical Excellence. Donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease. http:// www.nice.org.uk/article.asp?a=14487 (accessed Aug 23, 2004).
5 Department of Health National service framework for older people. http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4003066&chk=wg3bg0 (accessed Aug 23, 2004).

Eisai and Pfizer have great concerns about the design and conclusions of the AD2000 trial.[1] We believe that numerous components of the methodology raise issues that limit the importance and generalisability of its findings to patients being considered for or currently treated with donepezil for mild-to-moderately severe Alzheimer's disease.

Difficulties include methods for patients' selection, sample size, attrition rate, randomisation procedures, and the effect of multiple washout periods. First, patients were selected on the basis of the uncertainty principle; those with a definite indication for or against donepezil treatment were not eligible. Instead, only patients for whom the doctor was "substantially uncertain whether or not a particular patient would derive worthwhile benefit from donepezil" (protocol p 7)[2] would be eligible for randomisation to donepezil or placebo. Furthermore, enrolment was based not on well defined entry criteria but was "left entirely to the responsible physician. Even within one participating hospital different doctors may decide differently" (protocol p 8).[2] By deliberately disallowing patients for whom donepezil has been proven efficacious, the investigators introduced bias into their results.

The study was designed to recruit 3000 patients to provide 90% power to detect a 20% reduction in either the severe disability rate or loss of activities of daily living. However, only 566 patients were enrolled. Therefore, the study was underpowered. By our calculations, using the number of patients enrolled, the likelihood of a type 2 error is about 70%. Furthermore, the investigators' justification for sample size seems to be derived from post-hoc power calculations and hypotheses.

Additionally, there was substantial attrition. Within 1 year, 48% of patients had discontinued; less than 20% remained by the end of the second year. Statistically, this small sample is not sufficient to refute the findings of other studies[3,4] that lend support to the view that acetylcholinesterase inhibitors can decrease risk for, or time to, institutionalisation. Also, the effect of the limited geographic location on selection and doctor practice patterns further decreases the generalisability of the results.

The investigators included washouts at the end of each study phase. When the protocol was developed (April, 1998), data had been published,[5] indicating that such washouts were associated with loss of donepezil treatment benefit. This design would be expected to lead to a decreased benefit on cognition, and could affect factors important for institutionalisation.

In conclusion, one anomalous study that contains substantial methodological limitations should not outweigh the wealth of sound studies that have proven the efficacy and safety of donepezil and other acetylcholinesterase inhibitors approved by regulators around the world and supported by the NICE guidance. To dissuade patients from seeking assessment and treatment for Alzheimer's disease on the basis of this study would be a distinct disservice to them, their families, and their doctors.

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2 AD2000 Protocol Development Group. A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's disease protocol. http:// www.ad2000.bham.ac.uk/ further.htm (accessed Aug 31, 2004).
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4 Thomas P, Ingrand P, Lalloue F, et al. Reasons for informal caregivers for institutionalising dementia patients previously living at home: the Pixel study. *Int J Geriatric Psychiatry* 2004; **19:** 127–35.
5 Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; **50:** 136–45.

The results of the controversial AD2000 trial[1] question the importance of treatment of Alzheimer's disease with donepezil, the first acetylcholinesterase inhibitor licensed in the UK. We feel the findings of this study in 565 patients should be considered alongside the wealth of evidence-based data and clinical experience of approved drugs, involving thousands of patients.

Although there are questions about study design (including entry criteria) and reasons for poor recruitment, we wish to challenge, as the licence holders of galantamine (Shire Pharmaceuticals, Basingstoke, UK), the investigators' extrapolation of their findings with donepezil to the class of cholinesterase

inhibitors. Indeed, we note that the media have reported this study in terms of a class effect.

The medical community would not accept that results from a study of an individual statin, non-steroidal anti-inflammatory drug, proton-pump inhibitor, or angiotensin-converting enzyme inhibitor could be extrapolated in a blanket fashion as a class effect for each respective group. Neither should this general principle be accepted here.

The cholinesterase inhibitors approved for Alzheimer's disease do not all share the same pharmacology. Their efficacy and safety profiles vary. Galantamine is unique in that it is a positive allosteric modulator of nicotinic acetylcholine receptors in the brain, not only reducing breakdown of acetylcholine but also rendering nicotinic acetylcholine receptors in the presynaptic nerve terminals more sensitive to available acetylcholine.[2]

The results of large randomised, double-blind, placebo-controlled studies[3–5] in patients with mild-to-moderate Alzheimer's disease show that treatment with galantamine slows cognitive decline when compared with placebo, with cognition being maintained above baseline levels for up to 12 months.[4] Galantamine exhibits broad efficacy in these studies across all areas of assessment (not just cognition).

The AD2000 Collaborative Group makes some bold claims against the use of donepezil in the management of patients with Alzheimer's disease, but inappropriately extrapolates them to other drugs with cholinergic effects.

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1 AD 2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004 ; **363:** 2105–15.
2 Samochocki M, Zerlin M, Jostock R, et al. Galantamine is an allosterically potentiating ligand of the human α4/β2 nAChR. *Acta Neurol Scand* 2000; **Suppl 176:** 68–73.
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4 Raskind MA, Peskind ER, Wessel T, Yuan W, the Galantamine USA-Study Group. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. *Neurology* 2000; **54:** 2261–68.
5 Wilcock GK, Lilienfeld S, Gaens E, on behalf of the Galantamine International-1 Study Group. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ* 2000; **321:** 1445–49.

As a consultant working for the UK National Health Service (NHS) in old age psychiatry, and an active prescriber of cholinesterase inhibitors, I welcome the AD2000 report, despite the authors' conclusion that a "rational strategy" for use of such drugs in Alzheimer's disease is either to "treat all" or "treat none", exclusively.[1]

In his Commentary,[2] Lon Schneider emphasises the unusual omission criteria and the subsequent difficulties with recruitment in this study, compared with drug-company sponsored trials in Alzheimer's disease to date. The criteria in this study included prior certainty that the patient would benefit from treatment with donepezil, an adverse drug reaction, or the patient electing for NHS prescription of the drug in the run-in phase. The later increasingly available (and presumably attractive) option of NHS open-label prescribing resulted in withdrawal of considerable numbers of patients and censoring of their treatment centres' data throughout the course of the main trial. Despite these drawbacks, long-term benefit was identified in cognitive (mini mental state examination [MMSE]) and functional (Bristol activity of daily living scale) components of the disease over a 2 year duration.

Such persistent outcome benefit is noteworthy, particularly in a non-industry sponsored study intent on scrutinising efficacy and costs of a cholinesterase inhibitor in a naturalistic setting, and with the difficulties mentioned above. Schneider has already unfavourably compared one of the few alternative reports[3] that describe a drug trial in Alzheimer's disease of similar duration, despite its positive outcome. Interpretation of another lengthy trial,[4] a 3-year comparison of galantamine against placebo, was also handicapped by use of a historical and mathematically modelled control group, by contrast with the present study. The investigators' reluctance to accord their treatment findings the status of "worthwhile clinical and social benefits" should, therefore, not overshadow the importance of the result.

The Collaborative Group exclude any association between donepezil response and pretreatment with aspirin. A priority now should be to properly assess the efficacy of other rational combination pharmacological (and non-pharmacological) therapies for the disease. Potential drug candidates include cholinesterase inhibitors, statins, antioxidant vitamins, and non-steroidal anti-inflammatory agents. Memantine cotherapy with each cholinesterase inhibitor particularly needs to be assessed. The results of a trial[5] of memantine therapy in 404 donepezil–treated patients with moderate-to-severe Alzheimer's disease, showed significant benefit in favour of the combination of the cholinesterase inhibitor with this moderate affinity CNS glutamate receptor antagonist, compared with the former alone.

Given the difficulties discussed in the AD2000 report in undertaking publicly funded independent research, I call upon pharmaceutical companies to collaborate together in trials of rational combination therapies for Alzheimer's disease, despite the risk of commercial disadvantage should a drug compare unfavourably with its rival compounds. Alternatively, we could wait decades for the relevant drug patents to expire before this paradigm is tested.

I have received honoraria for chairing a meeting organised by Shire/Jannsen-Cilag, for attending advisory groups for Bayer, Shire, and Novartis, and from Pfizer/Eisai for lecturing. I have received expenses to attend conferences from Pfizer/Eisai, Shire/Jannsen-Cilag, Novartis, and Zeneca.

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1 AD 2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004; **363:** 2105–15.
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Authors' reply

Some correspondents misunderstand eligibility based on uncertainty; participating doctors were uncertain whether an individual patient would obtain a worthwhile clinical benefit from donepezil, not uncertain whether the patient fitted into a diagnostic category for which donepezil use was licensed. This fact is evident from the characteristics of patients entered: all had the licensed indications for donepezil—ie, DSM IV diagnosis of mild-to-moderate (MMSE 10–26) Alzheimer's disease.

The attrition rate was in fact lower than in any previous study, with only 13% of the 486 patients randomised to long-term donepezil or placebo stopping protocol treatment in the first 48 weeks, 14% opting not to continue into a second year of treatment, and 2% stopping during year 2. The attrition rates cited by Latif Akintade and colleagues are misleading, since they include patients who did not complete the run-in as well as those who were institutionalised, dead, or censored. Similarly, there was less missing data than in any previous study, thereby minimising drop-out bias; an issue in many of the reports cited.

To clarify data queries, the flow chart lists deaths on treatment; the death analysis also includes deaths after stopping treatment, institutionalisation, and centre withdrawal.

Although AD2000 did not meet its original pragmatic recruitment target—mainly because of difficulties arranging funding for treatment and research support—the study is the largest study of donepezil in person-years of placebo-controlled treatment. The numbers randomised provided greater than 90% power to detect, or refute, the 50% reduction in institutionalisation needed for cost neutrality, and greater than 95% power, at $p<0·01$, to detect an effect size of 0·3 SD on the secondary outcome measures. The results thus provide statistically convincing evidence to refute the primary cost-effectiveness hypothesis that donepezil use is cost-neutral, and to rule out minimally clinically relevant improvements in the secondary outcome measures—ie, AD2000 has not produced a false negative result.

The negative findings are not explained by an irreversible loss of benefit after the washout periods—for example, patients who entered a second year of treatment declined 1·45 MMSE points more in the donepezil group than in the placebo group during the preceding 6-week washout, but then improved 2·84 MMSE points more than controls after 12 weeks of re-treatment. Similar post-washout recovery has been seen in other studies.[1] Results would have been little different if all patients had received 10 mg of donepezil given the small, non-significant difference between doses. We would also anticipate similar findings with other cholinesterase inhibitors. Indirect comparisons[2,3] show similar benefits on cognitive, functional, and behavioural outcomes, as do the few direct randomised comparisons[4] between different cholinesterase inhibitors.

The results of AD2000 are anomalous when compared with methodologically unsound studies, such as those cited by Akintade and colleagues as supporting a delay in institutionalisation with cholinesterase inhibitors, which have been rightly criticised.[5] The apparent benefits from long-term treatment in these non-randomised, open treatment studies are refuted by AD2000, and must be explained by selection and other bias—eg, doctors and carers stop treatment of patients who do not seem to be benefiting. Our findings are, however, typical of those seen in the randomised double-blind trials with a small improvement in functional ability equivalent to the average patient's decline in 10 weeks. This improvement is too small to be noticeable in an individual patient and can only be measured statistically through methodologically rigorous studies such as AD2000.

We concur with Nick Clarke that trials comparing cholinesterase inhibitors against other drugs such as memantine, and against combinations of cholinesterase inhibitors with other drugs, are needed—these could be undertaken now if publicly funded. As noted by Clive Holmes and colleagues, the main contribution of cholinesterase inhibitors to people with Alzheimer's disease has been the welcome expansion of dementia services, making independent clinical trials such as AD2000 more feasible. On present evidence, however, we believe that cholinesterase inhibitors are overpriced considering their minimal benefits.

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1 Rogers SL, Friedhoff LT. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicentre open label extension study. *Eur Neuropsychopharmacol* 1998; **8:** 67–75.
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The Cochrane Library, Issue 3, 2004. Oxford: Update Software.

4 Jones RW, Soininen H, Hager K, et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatric Psychiatry* 1999; **19:** 58–67.

5 Finucane TE. Another advertisement for donepezil. *J Am Geriatr Soc* 2004; **52:** 843.

Monkey malaria in man

Balbir Singh and colleagues (Mar 27, p 1017)[1] report interesting data on the occurrence of *Plasmodium knowlesi* malaria in a human population in Malaysian Borneo.

Cross-species transmission of infectious agents is among the most important public-health threats facing humanity. Man's increased use of forested areas for hunting, road construction, mining, logging, etc, brings them into close proximity with non-human primates and other animals, heightening the potential for transmission of zoonotic infections. Wolfe and others[2] have reported naturally acquired simian foamy virus infection in a population of hunters living in central Africa who had direct contact with non-human primates.

Future studies need to identify the anopheline vector of *P knowlesi* infection in the human population of Kapit.[1] An understanding of the biology and feeding habits of the vector is necessary to ascertain whether transmission is occurring so that effective control methods can be deployed. Additionally, the prevalence of *P knowlesi* parasitaemia in the general population and in macaques in the Kapit region should be estimated.

Furthermore, pathogen exchange can occur from non-human primates to people, and vice versa. Therefore, in environments where human and non-human hosts overlap, both modes should be considered in epidemiological models to determine if and how transmission of the pathogen can be contained in the population.

Most *P knowlesi* infections reported by Singh and colleagues were in adults (91·5%), and almost all were men (67%). There was no evidence of clustering of cases within long house communities.[1] These results suggest that transmission is occurring away from home, probably because of occupational exposure or journeys to the jungle in search of game.

As a clinician, the relevance of the results of this report is that *P knowlesi malaria* is a differential diagnosis for *P malariae* or *P falciparum* malaria in individuals with a fever and relevant travel history to jungle areas or wildlife reserves in southeast Asia, the natural habitat of *Macaca fascicularis* and *M nemestrina*.

This differential diagnosis would be of greater clinical importance if *P knowlesi* malaria was associated with greater severity or resistance to conventional antimalarials. However, *P knowlesi* malaria is not fatal in human beings and is responsive to conventional anti-malarial drugs.

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1 Singh B, Sung LK, Matusop A, et al. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet* 2004; **363:** 1017–24.

2 Wolfe ND, Switzer WM, Carr JK, et al. Naturally acquired simian retrovirus infection in central African hunters. *Lancet* 2004; **363:** 932–37.

Mercury in vaccines and potential conflicts of interest

In their 2002 Article on mercury concentrations and metabolism in infants receiving vaccines containing thiomersal,[1] Michael Pichichero and colleagues' conflict of interest statement read: "None declared."

Despite such a claim, Pichichero published in the journal *American Family Physician*[2] in 2000 the statement: "The author has received research grants and/or honoraria from the following pharmaceutical companies: Abbott Laboratories, Inc.; Bristol-Myers Squibb Company; Eli Lilly & Company; Merck & Co.; Pasteur Merieux Connaught; Pfizer Labs; Roche Laboratories; Roussel-Uclaf; Schering Corporation; Smith Kline Beecham Pharmaceuticals; Upjohn Company; and Wyeth-Lederle."

On the basis of this disclosure by Pichichero, he clearly did have a conflict of interest that he did not disclose to the readers of *The Lancet*.

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1 Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet* 2002; **360:** 1737–41.

2 Pichichero ME. Acute otitis media, part I: improving diagnostic accuracy. *Am Fam Physician* 2000; **61:** 2051–56.

Authors' reply

In their letter, Mark Geier and David Geier contend that Michael Pichichero's previous work in vaccine development constitutes a conflict of interest with respect to our recent description of mercury concentrations in infants. We disagree.

Our descriptive study was a study of thiomersal, not a study of a particular vaccine or pharmaceutical product. We did not assess, or draw conclusions about, the safety, immunogenicity, or efficacy of any vaccine. Instead, we simply described the concentrations of detectable mercury in blood at intervals after the parenteral administration of vaccines formulated with thiomersal to healthy infants. These data are important, because exposure guidelines based on oral ingestion of methyl mercury might not be appropriate when applied to parenteral administration of ethyl

mercury. The study was funded entirely by the US Federal Government, and there was no role of any industrial entity in the design of the study, measurement of mercury, analysis of the data, or publication of the results. Neither of us had (or have now) any direct or indirect financial interest in the outcome of this study, and neither of us have received financial support from industry to undertake other studies of thiomersal or mercury, nor been asked to advise industry with respect to the use of thiomersal or other preservatives in vaccines. Therefore, we do not believe that we have a conflict of interest relevant to our *Lancet* publication.

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Sir Arthur, Sir James, Sir Percivall, soot, and skin cancer

The Correspondence letter by Keith Denkler (Aug 14, p 582)[1] about soot and cancer of the hand is interesting, but probably incorrect. Sir James Earl (Sir Percivall Pott's son-in-law) speculated that a cancer on the hand of a patient who attended him in 1800 was due to "frequent exposure to soot vapours".[2] His patient worked as a gardener and often carried a bucket containing soot in that hand, the contents of which he spread around young plants in the garden "to preserve them from the slugs". The lesion started as a wart, ulcerated, and extended on the dorsum of the left hand. The major exposure to soot was, however, to the patient's right hand, as Sir James clearly recorded that this was the hand used to spread the soot on the ground. He also noted that the onset of the growth was in the spring and that the lesion increased in size and ulcerated the next spring.

Wellcome Library, London

Illustration of basal cell carcinoma
Image from the report by Jacob in 1827,[3] showing an advanced lesion in a 50-year-old woman, which commenced on the temple. Jacob describes the smooth and glossy edges of the ulcer, its slow relentless progression with comparatively inconsiderable suffering, and its ability to dissect out the eye-ball and destroy bone without involving the lymph glands.

Rather than being the first case of occupational soot cancer of the hand, this malignant growth was probably a cancer more closely related to the patient's occupation—ie, a sun-induced skin cancer due to his constant exposure to ultraviolet light as a gardener. Soot might have contributed as a cocarcinogen but seems unlikely, since the main exposure occurred on the other hand.

Denkler's contention that Sir James gave the first description of basal cell carcinoma is difficult to sustain in the absence of supporting histological evidence. I believe the cancer on the gardener's hand (in view of its location and the clinical features of the accompanying illustration) was a squamous cell carcinoma of the skin.

Sir Arthur Jacob (1790–1874), the Irish surgeon and ophthalmologist, is credited with the first description of basal cell carcinoma in 1827.[3] His report was important because he not only accurately described "the peculiar condition of the edges and surface of the ulcer, the comparatively inconsiderable suffering produced by it, its incurable nature unless by extirpation" (figure), but also because he recognised its lack of potential to metastasise. This latter point was a major distinguishing feature from other cancers, including scrotal carcinomas, which Sir Percivall described as ". . . frequently indurating and spoiling the inguinal glands".[2]

Sir James might have unwittingly described another occupational cancer—ie, ultra violet light induced squamous cell carcinoma on the exposed skin of an outdoor worker. Sir Arthur's remains the original and definitive description of basal cell carcinoma.

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1 Denkler K. Sir Percivall Pott, Sir James Paget, and soot cancer of the hand. *Lancet* 2004; **364:** 582.
2 Earle J. The chirurgical works of Percivall Pott, FRS: a new addition with his last corrections. To which are added a short account of the life of the author, a method of curing the hydrocele by injection, and occasional notes and observations. London: Wood and Innes, 1808.
3 Jacob A. Observations respecting an ulcer of peculiar character, which attacks the eye lids and other parts of the face. *The Dublin Hospital Reports* 1827; **4:** 232–39.

Department of Error

Iida K, Procter RN. Learning from Philip Morris: Japan Tobacco's strategies regarding evidence of tobacco health harms as revealed in internal documents from the American tobacco industry. Lancet *2004;* **363:** *1820–24*—In this Public Health article, the Conflict of Interest statement should have read "RNP has worked on several occasions as an expert witness in plaintiff's lawsuits, including USA vs Philip Morris Inc et al. KI has no potential conflict of interest."

Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. Lancet *2004;* **363:** *1751–56*—In this Article (May 29), the Methods section of the Summary should have read: "In this population-based retrospective cohort study we identified NSAID-naive individuals aged 66 years or older, who were started on rofecoxib (n=14 583), celecoxib (n=18 908), and non-selective NSAIDs (n=11 606), and randomly selected non-NSAID users as controls (n=100 000)."