Links with the tobacco industry

In their article on how the tobacco industry withheld data on the toxicity of environmental tobacco smoke (published online Dec 11, 2004),[1] Pascal Diethelm and colleagues make some misleading comments about my research work.

My contacts with the tobacco industry go back to 1965, a time when to receive funding from the industry was acceptable. I acknowledged the funding in my published work,[2] negating Diethelm and colleagues' argument that my contacts were secret. Additionally, from 1974 I was a scientific adviser to INBIFO (Institut für Industrielle und Biologische Forschung), an association also disclosed.[3] Contrary to what the authors claim, there was never a formal contract for consultancy and my financial remediation was in form of a per diem.

The authors imply that I helped to try to minimise the effects of environmental tobacco smoke, using circumstantial evidence and citations from senior Philip Morris executives to support their case. On the contrary, several of my early publications draw attention to the differences in toxicity between the vapour and the particulate phase in cigarette smoke, and indicate they have different toxic properties.[4] That environmental tobacco smoke contains a higher proportion of volatile agents and has a higher inflammagenic activity in relation to the amount of total particulate matter than directly inhaled smoke is neither new information nor particularly surprising. The most awry accusation is that my study on the relation between drinking green tea and lung cancer[5] was an attempt to steer attention away from the risks of environmental tobacco smoke. My study was an in-vitro assessment of the mutagenicity of tea extract, designed to test the notion that drinking large amounts of green tea increases the risk for lung cancer. For those not wanting to draw attention away from the main but simplistic message of tobacco smoke toxicity, such information is undesirable and can be discredited by assigning it to tobacco industry attempts to dilute the health risk.

Over the years, various claims were being made about the effects of environmental tobacco smoke and some of them, such as the risk of carbon monoxide poisoning, were based on results of tenuous research. As scientists, our role is to assess risks with a healthy scepticism, not to ignore them because of preconceived notions. Diethelm and colleagues are trying to discredit my research activities yet rarely do they base their assertions on direct analysis of my work.

I believe the individual researcher should be able to decide whether or not to collaborate with the industry. The assessment of resulting research results should be based on an analysis of actual data and not circumstantial evidence or guilt by association as in the article by Diethelm and colleagues.

We are still facing an important health problem caused by smoking. I had chosen to work with the industry to explore the hazards of exposure to smoke. This collaboration may be retrospectively criticised, yet I have probably contributed more to the knowledge of the risk associated with tobacco smoke than any of the antitobacco activists who refuse money from that industry.

I have previously worked as an independent scientist to the tobacco industry as well as to the cotton and petroleum industries.

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Authors' reply

Ragnar Rylander does not seek to refute our central argument—that Philip Morris maintained and sought to conceal a testing programme that provided evidence of the harmful effects of passive smoking. Instead, he accuses us of trying to harm his research reputation by means of selective use of information, and alleges that our article is scientifically dishonest.

Rylander's work has been scrutised by three independent bodies: a Swiss court[1] ruled that the term "unprecedented scientific fraud" was appropriately used to describe his work on tobacco; the University of Geneva[2] concluded that Rylander "was guilty of scientific misconduct in hiding the real extent of his links with the tobacco industry and in aligning his activity as a scientific investigator and expert with the strategic objectives of his industrial sponsors"; and most recently he has been removed from one of the European Commission's advisory committees after failing to disclose his links with the tobacco industry.

The reports of these inquiries paint a different picture of his research to that set out by Rylander. For example, the University of Geneva found that:

> "Many items of correspondence between Rylander and Philip Morris scientists, as well as lawyers representing the tobacco industry, show that Rylander hardly took any initiative in the tobacco area without extensive consultation with industry. Rylander's epidemiological studies on the effects of environmental tobacco smoke followed industry's leads and were meant to support a sceptical message on the effects of passive smoke, in line with an industry defined strategy".[2]

Rylander's statement that he never had a formal contract with Philip Morris does not tell the whole story. On Dec 7, 1972, he signed a "consulting agreement" with the company, as a conse-

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quence of which he received payments (covering "Fees [including travelling expenses]") of US$2500–85 000 per year between 1972 and 1997 as well as research support of $40 000–80 000 between 1985 and 1997.[3] These payments supported monthly visits to INBIFO and an extensive range of other activities for Philip Morris. He also received other payments from, for example, Shook, Hardy and Bacon, a law firm representing the tobacco industry (http://www.shb.com). Rylander also fails to tell the whole story when he states that information about his links to the tobacco industry had been published. The article he refers to was in response to one[4] that pointed out he had declined, despite extensive inquiry, to reveal these links.

In our paper and in this letter we have been able to portray only a very small part of the role that Rylander has played in the tobacco industry's efforts to conceal the evidence on the harmful effects of passive smoking. Rylander argues that an assessment of his work should be made on the basis of actual data. We agree and note that this has been done in the rulings by the Swiss court and in the report by the University of Geneva, both of which are now in the public domain.

In a 1997 letter to Richard Carchman, at Philip Morris, Rylander states that

> "Whilst I will help out as much as possible, I see a potential conflict in the task . . . I have never been involved with any Philip morris executive in meetings or contacts with outside persons, to retain as far as possible the image as an independent scientist. So far this has worked well . . ."[5]

We contend that this image is no longer sustainable.

PAD is president of OxyRomandie, a Swiss-based association for the prevention of passive smoking, which receives subsidies from the local government; JCR is physician-in-charge of CIPRET-Genève, an organisation responsible for smoking prevention financially supported by the local government; MM's work on tobacco control is supported by the National Cancer Institute, US National Institutes of Health, grant number 1 R01 CA91021-01. Following the release of a press statement by two of the authors (PAD and JCR) in Geneva in 2001 relating to Ragnar Rylander's conduct and links with the tobacco industry, Rylander took legal action against PAD and JCR alleging libel. MM appeared as a witness in the case. In December, 2003, the Geneva court found the statements by PAD and JCR, some of which are mentioned in this letter, to be true. Full details of the legal process, including judgments, can be found at http://www. prevention.ch/rylanderpm.htm.

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Possible explanations for the results of CRASH

The findings of the CRASH investigators (Oct 9, p 1321),[1] showing increased mortality at 2 weeks for patients with head injury treated with high-dose corticosteroids, are surprising and potentially practice-changing. However, they might be the result of systematic bias and an inadequate protocol.

The team did not take into account the predictable hyperglycaemia in patients treated with high-dose steroids during the early and critical phase of their illness. As such, and in view of their simple trial design, we doubt their claim that investigators were unaware of treatment allocation. Uncontrolled hyperglycaemia is strongly and linearly associated with increased mortality from head injury in particular[2] and critical illness in general.[3,4] Progression to organ failure and increased institution-acquired infection are plausible causes for excess mortality at 2 weeks.

Tight glycaemic control with insulin is associated with a profound survival improvement in critical illness, including head injury.[3,4] This great benefit is seen even during fairly short, 3-day periods of critical care.[3] Neither the protocol nor the published findings indicate that any effort was made to monitor the occurrence of severe hyperglycaemia, anticipate unblinding, or formalise therapeutic efforts to regulate glycaemic control. Thus, variable efforts are likely to have been made to monitor and manage blood sugar, resulting in unassessed imbalances between groups.

Systematic, though unintentional, unblinding and neglect of concomitant hyperglycaemia in patients on active treatment might have negated any beneficial effects of high dose corticosteroids. Assuming tight glycaemic control had prevented a conservative 1·6% (n=83) of hyperglycaemia-associated deaths in the high-dose steroid group, the overall relative risk for death would have been statistically comparable between groups at interim analysis (relative risk=1·1, 95% CI 0·9–1·2). If, as is more likely, uncontrolled hyperglycaemia accounted for 10–25% of the excess deaths, survival might have accrued in the group treated with steroids.

I declare that I have no conflict of interest.

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1 CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004; **364:** 1321–28.
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The authors of the CRASH trial[1] state that administration of prednisolone did not reduce mortality within 2 weeks after head injury, and comment that the

cause of the rise in risk of death within 2 weeks was unclear. Their protocol involved administration of a loading dose of 2 g methylprednisolone (or placebo) over 1 h in a 100 mL infusion followed by a maintenance dose of 0·4 g methylprednisolone (or placebo) per h for 48 h in a 20 mL per h infusion. We believe that secondary adrenal insufficiency, due to suppression of secretion of corticotropin-releasing factor and adrenocorticotropic hormone by high doses of methylprednisolone, might explain their results.

Contrary to popular belief, short-term, high-dose glucocorticoid treatment impairs reactivity of the hypothalamic pituitary adrenal axis. In 2000, Henzen and co-workers[2] reported adrenal suppression in nearly half of patients who received short-term treatment with a high dose of corticoid, which persisted for weeks in some. In our experience[3] in patients with Cushing's syndrome—a hormonally active adrenal tumour—treated with surgery, suppression of the hypothalamic-pituitary-adrenal axis (HPA) by long-term hypercortisolaemia depended on the individual.

A head injury is a stressful experience. A large increase in cortisol secretion might, therefore, be necessary for survival during the days and weeks after the accident. Agha and colleagues[4] have confirmed a high prevalence of undiagnosed early post-traumatic anterior pituitary hormone abnormalities with relatively frequent HPA insufficiency in survivors of traumatic brain injury. The experimental data[5] indicate an important role for corticosteroid substitution in regulation of expression of regional neurotrophic factors after traumatic brain injury. The neuroprotective characteristics of these factors are possibly responsible for favourable outcomes after traumatic brain injury. We believe that a routine substitutive therapy with hydrocortisone for 7–10 days after the initial methylprednisolone course could reduce mortality within the 2 weeks after head injury.

We declare that we have no conflict of interest.

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1 CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial). *Lancet* 2004; **364:** 1321–28.
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The 3% excess of deaths among the head injury patients in the CRASH trial[1] who were allocated active methylprednisolone is significant (p=0·0001, if no allowance is made for the data-dependent stop halfway through the study). But, if the results of this trial are considered together with those from the other randomised trials of such treatment, which collectively indicate no hazard,[1] then the excess becomes 2%, and the p value becomes 0·001, which is ten times less extreme. Hence, the apparent excess of deaths in these studies could be largely or wholly due to an extreme play of chance that was made to seem still more extreme by the data-dependent halt to recruitment to CRASH. If so, the accompanying Comment[2] should not have described the apparent increase in mortality as indisputable. In my view, the cautious conclusion of the CRASH investigators is more appropriate: they review all the randomised evidence, and then claim only that the evidence shows that such treatment does not materially reduce mortality.

I declare that I have no conflict of interest.

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Author's reply

The results of the CRASH trial of corticosteroid treatment reliably refute any reduction in mortality in the 2 weeks after head injury. The effect of corticosteroid allocation was a significant 18% (95% CI 9–27) increase in the risk of death from all causes within 2 weeks (1052 [21%] corticosteroid deaths *vs* 893 [18%] placebo deaths; p<0·001).

Ivor Douglas suggests that corticosteroid induced hyperglycaemia unblinded the treatment allocation, leading to bias in outcome assessment. We believe this scenario is unlikely. First, because death was the primary end point, knowledge of treatment allocation should not have affected outcome assessment. Second, hyperglycaemia is common in patients with head injury whether or not they receive corticosteroids. In the German Ultrahigh Dexamethasone Study,[1] 30% of patients in the placebo group were hyperglycaemic compared with 48% of those receiving corticosteroids. The German trial was relatively small, however, and the precise contribution of corticosteroids to hyperglycaemia after head injury is unknown.

Douglas suggests that variable efforts might have been made to manage hyperglycaemia, resulting in "unassessable imbalances between the randomisation groups". If corticosteroids did cause an excess of hyperglycaemia in the group treated with corticosteroids, this would not be a confounding factor, rather, it would be an effect of a policy of administering corticosteroids to

patients with head injury, which is what the trial sought to quantify. Any hyperglycaemia that was unrelated to corticosteroid use should have been balanced by randomisation. We accept that tight glycaemic control might in theory modify the effect of corticosteroids on mortality in patients with head injury. However, until such evidence is available we believe that our recommendation that corticosteroids are best avoided in the treatment of head injury should stand.

We note with interest the hypothesis offered by Anna Kasperlik-Zluska and colleagues that secondary adrenal insufficiency due to corticosteroid administration accounts for the apparent increase in mortality in the corticosteroids treated group. They also suggest that routine replacement therapy for 7–10 days after corticosteroid administration might lead to reduced mortality with corticosteroids. Again, in view of the results of the CRASH trial we would caution against such a treatment regimen in the absence of new evidence from a large scale randomised controlled trial.

We declare that we have no conflict of interest.

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1 Gaab MR, Trost HA, Alcantara A, et al. Ultrahigh dexamethasone in acute brain injury. Results from a prospective randomised double-blind multi-centre trial. *Zentralblatt für Neurochirurgie* 1994; **55:** 135–43.

Clinical predictors of bioterrorism-related inhalational anthrax

Demetrios Kyriacou and colleagues (July 31, p 449)[1] nicely describe the differences in various symptoms and signs between a substantial series of cases with inhalation anthrax and cases with community-acquired pneumonia or influenza-like illness. Mediastinal widening or pleural effusion on chest radiography was the most accurate predictor of anthrax compared with the other clinical syndromes. Kyriacou and colleagues state that "Limitation of the effects of such an attack [of anthrax] requires rapid and accurate recognition of early victims . . ." and note their findings could be used in syndromic surveillance systems although with caveats related to limitations of their study. The accompanying Comment (p 393)[2] tends to support this view.

We do not believe these findings would be useful for syndromic surveillance—eg, "to enable earlier detection of [bioterrorism-related] epidemics and a more timely public health response, hours or days before disease clusters are recognized clinically, or before specific diagnoses are made and reported to public health authorities . . .".[3] Outside of a recognised exposure situation—eg, laboratory accident or bioterror attack—inhalation anthrax is an extremely unlikely diagnosis and the pretest probability of anthrax is very low; hence, although the likelihood ratios in the study are high for some signs and symptoms, particularly the aforementioned chest radiographic findings, the post-test probability of anthrax given the signs and symptoms is extremely low.

As a crude example, in 2001 in the USA an estimated 4·5 million Americans sought medical attention for community acquired pneumonia[4] and 11 cases of inhalation anthrax were diagnosed.[1] The pretest probability of inhalation anthrax is, therefore, 0·0000024 and, given mediastinal widening, the post-test probability is 0·00003.[5] In 2000, 2002, and 2003, with no cases of inhalation anthrax, the pretest and post-test probabilities are zero.

At such miniscule or absent post-test probabilities, cases with the signs and symptoms described by Kyriacou and colleagues are unlikely to be recognised as (potentially) anthrax unless there was substantial clustering—ie, the aim of rapid and accurate recognition of cases will probably not be met. This likelihood is exacerbated by the third limitation mentioned by Kyriacou and co-workers, that signs and symptoms that are indicative of anthrax might well present fairly late in the clinical evolution of the case and, hence, not be helpful in early recognition.

We declare that we have no conflict of interest.

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1 Kyriacou DN, Stein AC, Yarnold PR, et al. Clinical predictors of bioterrorism-related inhalational anthrax. *Lancet* 2004; **364:** 449–52.
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Demetrios Kyriacou and colleagues[1] address the issue of clinical predictors of illness due to bioterrorist deliberate release. They conclude that the most accurate predictor of anthrax infection is mediastinal widening in combination with pleural effusion on a chest radiograph, and state that the sensitivity of mediastinal widening and pleural effusion for inhalational anthrax infection, in their study, was 100%.

Their calculation of sensitivity, though correct, is misleading. The relevant calculation here is for the positive predictive value (PPV). From the figures given, mediastinal widening in combination with pleural effusion is a poor predictor of disease caused by inhalational anthrax (PPV [anthrax]=22/80 [22 anthrax+53 community acquired pneumonia+5 influenza like illness]=27·5%). The combination is in fact a better predictor of community acquired pneumonia (PPV 53/80=66·3%). A better predictor of inhalational anthrax infection in this study is mediastinal widening alone; however, the PPV is still less than 50%—ie, 18/37=48·6%).

The PPV of a test is not a constant, and reduces as the condition tested

becomes rarer than other conditions causing positives. In this study population, the relative prevalence of anthrax cases was high; this situation is unlikely in real life. The true PPV will, therefore, be even lower than predicted by Kyriacou and colleagues.

I declare that I have no conflict of interest.

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1 Kyriacou DN, Stein AC, Yarnold PR, et al. Clinical predictors of bioterrorism-related inhalational anthrax. *Lancet* 2004; **364:** 449–52.

Author's response

Martin Tepper and Jeff Whitehead do not believe information with respect to the clinical predictors of inhalational anthrax would be useful for syndromic surveillance of this potential bioterrorism-related disease. My colleagues and I respectfully disagree. The correspondents are correct in noting that an extremely low pretest probability of inhalational anthrax in a single patient would still result in a low, albeit higher, post-test probability (unless the individual clinical characteristic used to calculate the post-test probability is close to 100% sensitive and 100% specific). However, when used in combinations, clinical characteristics that discriminate inhalational anthrax from more common acute respiratory illnesses can be extremely helpful to frontline clinicians—eg, emergency and primary care doctors, infectious diseases specialists, and public-health officers—who are responsible for the identification and reporting of patients with potential bioterrorism-related diseases.

The chest radiograph finding of widened mediastinum in an emergency department patient, for example, is uncommon but not rare, and can be caused by several pathological processes. Widened mediastinum seen in a patient with fever, vomiting, and altered mental status would greatly narrow the list of potential causes. A small cluster of these patients in the same emergency department, or even the same city, within a limited time would suggest an outbreak of only a few potential diseases, including inhalational anthrax. Thus, improving doctors' abilities to detect inhalational anthrax in clinical settings would enhance surveillance methods for the early detection of a bioterrorism anthrax attack.[1]

Syndromic surveillance systems use indicator data types that reflect events that precede a clinical diagnosis, such as constellations of medical signs and symptoms in persons seen in various clinical settings.[2] These systems are not meant to make the definitive diagnosis, which often depends on expensive, time-consuming, or rarely available laboratory testing. Instead, these systems are meant to trigger a public-health response more rapidly than would be the case if definitive laboratory diagnoses were needed. In fact, the Centers for Disease Control and Prevention have described outbreak detection as the over-riding purpose of syndromic surveillance for terrorism preparedness.[3] Unfortunately, little effort has been made to ascertain which specific clinical characteristics maximise the effectiveness for detection of inhalational anthrax cases. Furthermore, bioterrorism surveillance systems in the USA do not have standard case definitions for syndromes under surveillance and most systems do not report the sensitivities and specificities of their case definitions for detecting bioterrorism-related victims.[4]

In response to Richard Gair, we note that our study did not calculate positive and negative predictive values because we had arbitrarily set the number of patients with community-acquired pneumonia or influenza-like illness that were compared with the historically reported inhalational anthrax cases. This method is typical of a case-control study of a rare disease. However, it does not preclude the use of our estimated sensitivities and specificities of the clinical characteristics when attempting to discern inhalational anthrax from more common acute respiratory illnesses. For an individual patient, one should always ascertain the positive and negative predictive values based on the pretest probability of inhalational anthrax. The pretest probability would change radically if there is known exposure to aerosolised anthrax endospores or if a cluster of patients with similar clinical characteristics, suggesting inhalational anthrax, are seen.

I declare that I have no conflict of interest.

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China's infamous one-child policy

Your Sept 11 Editorial (p 909)[1] refers to China's "infamous one-child policy", without acknowledging that without it conditions of life for the country's 1·3 billion people would have been much worse. In theory, one-child families should only be necessary in certain circumstances. These are: (a) that a community has outgrown the carrying capacity of its ecosystem or is about to do so, and (b) that there is nowhere for people to migrate to, and (c) that a country has too few exports to exchange for food and other essentials. Known as demographic entrapment, these circumstances invariably result in severe

poverty, starvation, and violence; the only response is for a community to limit its fertility radically. As such, China's one-child policy saved 200–400 million people, and was the only rational solution to what the country perceived as its "grain problem" in the face of its rapidly increasing population.[2]

China's response to demographic entrapment was only possible because the taboo that surrounds the one-child policy in Europe and North America does not operate there. A tight population policy lockstep[3] ensures the taboo is maintained and that entrapment is never discussed here. China understood that ecological constraints do not, alas, respect human rights.

Unfortunately, the Great Lakes region of central Africa—especially Rwanda[4] and North Kivu—is gravely trapped. Fortunately, however, the notion of demographic entrapment is not taboo, and I have been able to discuss the idea freely in Malawi, Kenya, Uganda, and the Congo:

> "Should one, or should one not, say to one's friends in Africa that, if they don't reduce their fertility radically, if necessary to one child only, they must expect the direst poverty, starvation, and violence? I argue that one has to, and that not to do so is the gravest dereliction of duty in public health. If my friends want to lynch me, they are more than welcome. I trust that I will proceed to my martyrdom with a good courage! Much better, than, say, carcinoma of the rectum!"

Mercifully, this speech has always been well-taken, allowing me to at least open the dialogue on one-child families in Africa.[5]

China was fortunate in that it was able to "disentrap itself" not only by its one-child policy, but also by its rapid economic development. The absence of rapid economic development in Africa means that fertility reduction is essential (for more information see http:// www.leeds.ac.uk/demographic.disentrapment).

I declare that I have no conflict of interest.

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Greek kleroteria: the first randomisation technique?

Assignment of individuals to a particular group of interest owes much to R A Fisher[1] who, working in agricultural science, introduced the term randomisation in 1926. Random sampling had an earlier origin, however, within social science research. Kiaer[2] proposed in 1897 that a representative (purposive) sample rather than a census be used to gather data about an existing population.

More recently a variant of these original approaches, the aim of which is to assign groups of people to different interventions, has been proposed.[3] Cluster randomisation has gained a wide acceptance in medicine because of its simplicity and because of the ease with which it can be applied to naturalistic settings—eg, a family doctor's practice.

The ancient Greeks of Pericles introduced with their kleroteria (figure) a form of cluster randomisation used to pick members of the public for jury service. Kleroteria were made from slabs of wood or stone, into the face of which were scored five to 11 columns of narrow slots usually aligned in 50 horizontal rows. Into the slots were inserted the bronze identification tickets (pinakia) carried by citizens who had volunteered themselves for jury service. On the lefthand side of the kleroteria there ran a tube, the top of which was funnel shaped and the bottom of which was moveable by means of a crack-driven device.

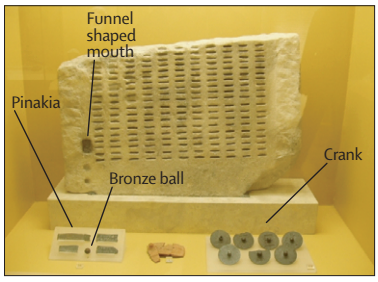

Figure: **Greek kleroteria**

Citizens would submit their pinakia to an official who would place them in the slots of the kleroteria, filling as many rows as possible. A mixture of white (as many as rows of people needed to sit on the jury) and black (enough to make up the total number of balls to the number of rows of tickets) balls would then be pored down the funnel, to be released one by one onto the stone or wood via the crank mechanism. Dependent on whether the ball relesed was white or black, all citizens on that row were accepted or rejected for jury service that day.

Kleroteria stood at the entrance of every court.

I declare that I have no conflict of interest.

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