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Mortality and cancer from chemical weapons testing

Risk is not increased, but some health questions remain



KEYSTONE/STRINGER/GETTY IMAGES

RESEARCH, pp 749, 754

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The experimental studies of the effects of chemical warfare agents conducted on thousands of British military personnel over several decades at the Porton Down facility in the United Kingdom have been an ongoing source of controversy regarding the scientific, ethical, and moral environment in which they took place.¹ Concerns about effects on health increased following a coroner's finding in 2004 of unlawful killing regarding the death of a Porton Down subject in 1953 after cutaneous administration of a chemical warfare nerve agent in a non-therapeutic experiment. This finding understandably raised important questions about the longer term health of the 18 000 British veterans who took part in the Porton Down experiments.² To investigate this, two linked studies have assessed whether the risks of cancer or mortality are higher in veterans who took part in tests compared with those who did not.^{3,4}

Established in 1916 in response to the use of chemical warfare agents against British troops in the first world war, the Porton Down facility was later expanded because of the threat posed by Germany during the second world war; the use of chemical weapons by Iraq; and the later attacks by terrorists against civilians, such as the release of sarin in a subway in Tokyo in 1995. In response to increasing public concern, the UK Ministry of Defence commissioned an epidemiological study to investigate a range of health outcomes in the military personnel who took part in the Porton Down chemical weapon experiments.

More than half of the Porton Down veterans were exposed to known or probable human carcinogens, most commonly dermal exposure to sulphur mustard,⁵ so Carpenter and colleagues' study on cancer morbidity is of considerable scientific and public interest. The authors found no significant differences in the overall incidence of cancer nor in the incidence of most cancer types in Porton Down veterans compared with non-veterans.³ Although a few subgroups had some isolated excesses of specific cancer types—such as excess of cancer of the trachea, bronchus, and lung in Porton Down veterans exposed to Lewisite—the lack of smoking data and the large number of analyses make it difficult to draw any firm conclusions about the causal nature of these few findings.

Venables and colleagues' study of mortality reported a small excess of overall mortality in the Porton Down veteran group.⁴ However, this overall excess was mainly the result of excesses in non-cancer causes of death, such as deaths from infectious and parasitic diseases, circulatory diseases, genitourinary causes, and exter-

nal causes. Some of these excess deaths are probably related to the longer period of service of Porton Down veterans compared with that of the comparison veteran group in the study, rather than to their involvement in the Porton Down experiments. Importantly, the authors found no increase in cancer mortality, consistent with the main finding in the cancer morbidity paper.³

The authors acknowledge that their studies have some limitations. Because UK cancer data have been available only since 1971, cancer rates in the early years of the Porton Down programme could not be studied. Also, it was not possible to adjust their findings for important confounders, such as cigarette smoking. One of the major strengths of these studies was the painstaking and time consuming attention to detail in the assessment of exposure, which is not easy when extracting data from records that are several decades old.⁶

The overall findings are consistent with other studies of veterans with short term or intermittent exposure to chemical weapons. These include the study of US navy veterans from the second world war, who participated in mustard gas chamber tests, which found no excess in any cause specific mortality.⁷ Also, the mortality study of US army Gulf war veterans who were potentially exposed to nerve agents during the March 1991 chemical weapons demolition at Khamisiyah in Iraq, reported no significant findings, apart from a borderline excess of deaths from brain tumours.⁸

The findings of the two studies should provide some reassurance to Porton Down veterans and their supporters that they have no excess risk of cancer or major causes of death. Although human carcinogens such as sulphur mustard and benzene were used in the Porton Down experiments, it should be remembered that the level and duration of exposure are important determinants of future cancer risk. In this study, the veterans took part in the experiments for only one to four weeks, for an average of two days a week. Therefore, the cumulative doses received were probably small compared with industrial exposure in manufacturing facilities, and—as the studies found—too low to cause a measurable excess of cancer.

Although these findings are reassuring for cancer and mortality outcomes, we need to take a more global view of the health of Porton Down subjects. This research group has previously published results for some other outcomes, which—although they have some methodological limitations—showed excess reporting of symptoms and poorer quality of life in a subgroup of Porton Down veterans.⁹ The finding of excess symp-

toms has some similarities with reported effects in many other veteran groups after deployment to areas of high personal threat.¹⁰ Although the nature of the threat to Porton Down veterans was different from that experienced by other veterans, non-fatal and non-cancer health outcomes in Porton Down veterans remain an important area of future research and public interest.

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Treatment of depression in primary care

Incentivised care is no substitute for professional judgment



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Patients with chronic depression commonly present to general practice,¹ and they often have other important (physical) diseases.² Although effective treatment is available, evidence suggests that patients and practitioners make insufficient use of it.³ These are important reasons to improve general practitioners' care of depression, as pursued by the World Health Organization action to integrate mental health into primary care.⁴ In England and Scotland, the quality and outcomes framework (QOF) identifies evidence based interventions and provides financial incentives to practices that implement these interventions. This exciting and innovative approach to improving performance is followed with interest outside the United Kingdom.

Two linked studies look at the QOF system and the management of depression in primary care. Kendrick and colleagues assess whether rates of prescribing antidepressant drugs and referrals to specialist services vary according to patients' scores on incentivised depression questionnaires.⁵ Validated screening instruments to assess the severity of depression include the hospital anxiety and depression score, the Beck depression inventory, and the patients' health questionnaire. Kendrick and colleagues report that practitioners usually administered these questionnaires, but that some patients whose scores qualified them for treatment did not receive antidepressants or referral to specialised services—notably elderly patients and those with comorbidity. In addition, two of the questionnaires gave very different severity grades—83.5% of patients were classified as moderately to severely depressed and in need of treatment by the patients' health questionnaire, whereas only 55.6% were classified as such by the hospital anxiety and depression score. This difference casts doubt on the validity of these scales and their usefulness in general practice. At first sight these results suggest that the QOF approach may not be as useful as hoped in this situation, but it is important to understand the other factors that come into play.

The first of these factors is the nature of the intervention. Prescription of antidepressants and referral to specialised services are “procedural” aspects of performance. Evidence based criteria can be applied to prescribing and referral, but successful care of patients with depression is determined by a combination of correct clinical procedures and a trusting doctor-patient relationship.⁶ This shifts the focus from treating just symptoms to treating the patient as a whole. The general practitioners in this study may therefore have opted to forfeit the incentives and work personally with their patient, rather than refer or prescribe. This is especially likely because many of the practices had a special interest in mental health, and because the number of follow-up appointments increased with the severity of depression. The second linked study by Dowrick and colleagues, which assessed how general practitioners and patients valued questionnaires, confirms the importance of a holistic patient centred approach.⁷

The surprise finding that older patients and those with comorbidity were less likely to be treated for depression brings us to the second factor. Intuitively, we would expect these patients to receive intervention more rather than less often. But comorbidity is as common as it is poorly investigated. General practitioners rely to a large extent on their clinical judgment, and they may be reluctant to prescribe antidepressants because of potential interactions with other drugs.⁸ Generic interventions such as empowerment and lifestyle changes may be more attractive because they may treat more than one condition at the same time.⁹ Given the limited research, this is an area where general practitioners' experience is well ahead of scientific evidence. Exploration of this experience could further improve the QOF process.

Validated questionnaires can assess the severity of depression, but Kendrick and colleagues show that they were less robust than expected. In their qualitative interview study, Dowrick and colleagues show that patients appreciated the use of these questionnaires.⁷ It would be

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interesting to know if this was the questionnaire as such or the explicit unambiguous questions asked about their condition, which could easily be incorporated into the general practitioner's history taking. General practitioners were at best ambivalent about the questionnaire, and they often used their professional judgment rather than the results of the questionnaire to guide management. Again, it would be interesting to know if this was related to the nature of the questionnaires or the fact that they were less robust than had been assumed. The hospital anxiety and depression score for instance is designed to identify possible depression but further assessment is needed to confirm the diagnosis. This confirmation could possibly come from the general practitioners' professional judgment.

General practitioners prescribe treatment that is not always in accordance with guidelines or with the QOF system. These studies provide evidence that patients' needs are better assessed by general practitioners' professional judgment than by guided care. The two linked studies did not look at the course of the patients' depression, however, so we do not know how well the patients fared. Further analysis of general practitioners' experience is therefore warranted for a more robust analysis of the QOF.

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Tocolytics and preterm labour

Whether to treat or not is the real dilemma, not which drug to use

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Preterm labour is still the main cause of perinatal morbidity and mortality in the developed world. Despite a better understanding of the pathophysiology, and the recognition that it is a syndrome with multiple causes, rates continue to rise.¹ In the linked cohort study, de Heus and colleagues assess the incidence of serious maternal complications with the use of tocolytic drugs for the treatment of preterm labour.²

Corticosteroids given to women at risk of preterm birth increase fetal lung maturity and can reduce fetal death, intraventricular haemorrhage, and respiratory distress by up to 50%.³ In contrast, it is still unclear whether tocolysis improves neonatal or longer term outcomes.⁴ Thus, the Royal College of Obstetricians and Gynaecologists' clinical guideline on tocolysis concludes that, "it is reasonable not to use tocolytic drugs."⁵

Despite the lack of evidence, several tocolytic drugs are commonly used worldwide. They are used primarily to delay delivery for up to 48 hours to allow for administration of corticosteroids or transfer to a unit with neonatal intensive care facilities (or both). Little consensus exists as to which tocolytic agent is the best. Beta agonists, atosiban, and indometacin all reduce the incidence of delivery within 48 hours compared with placebo, but none has been shown to improve neonatal outcomes.⁴ Nifedipine has not been studied in placebo controlled trials, but it is more effective at delaying delivery than β agonists, and has been associated with improved neonatal outcomes.⁶ Atosiban and

nifedipine have not been directly compared.

The study by de Heus and colleagues assesses maternal safety. They recorded adverse maternal effects in an unselected population of 1920 consecutive women given tocolytic drugs in routine clinical settings in the Netherlands and Belgium over an 18 month period. The most commonly used agent was atosiban (42%), followed by nifedipine (34%), β agonists (14%), and indometacin (8%).

The overall incidence of adverse effects was reassuringly low, but the study highlights the dangers of multi-drug regimens, which have no proven benefit either sequentially or in combination. Four women needed intensive care after being subjected to such regimens—three of which included β agonists. But before such practices are condemned outright, a thorough analysis of each case is warranted, so that further research into safer combination treatments is not compromised.

Because of the definitions used in the study design, postpartum haemorrhage was not included as a maternal adverse event. Some people may think this a surprising omission considering the basic mechanism of action of all tocolytics.

Consistent with previous studies, the β agonists had a higher incidence of serious adverse drug reactions (1.7%) than nifedipine (0.9%); no such reactions were reported for atosiban.

Hypotension was the most serious adverse drug reaction associated with nifedipine, which is not surprising



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considering its licensed indication. Hypotension was defined as a systolic blood pressure of <100 mm Hg and a drop of more than 20%. Associated symptoms did not need to be treated. It is debatable whether this reaction would be considered “life threatening” according to the Council for International Organizations for Medical Science definition used as a guideline in the article, and no justification is given for using these particular values. Indeed, the authors themselves question the importance of these events and point out that no associated episodes of fetal compromise occurred.

These findings highlight the relative maternal safety of tocolytics, although β agonists have the highest adverse event rate and their continued use is hard to justify. Atosiban stands out as the drug with the safest maternal adverse event profile, but it has not been shown to improve neonatal outcomes and is considerably more expensive than nifedipine. Using the number needed to treat analysis provided in the article, we calculated that 108 patients would need to be treated with atosiban to prevent one serious adverse drug reaction associated with nifedipine. This means that, allowing for the spread across the confidence intervals, an extra £30 000 (€33 000; \$44 000) to £45 000 would need to be spent for each serious adverse drug reaction prevented (costs sourced from *British National Formulary*, September 2008). Clearly a detailed cost-benefit analysis is warranted.

This study also serves as a timely reminder that the decision to use tocolysis should not be taken lightly, especially as we have no good test for differentiating “true” from “spurious” preterm labour, so many women are treated unnecessarily.⁴

After more than 30 years of research we still do not know whether tocolysis benefits the fetus, so the choice of which drug to use remains a secondary question. The real dilemma is whether or not we should treat at all. Not only may tocolysis lack any real benefit, but it could be harmful, as highlighted in the recent publication of the long term outcomes of the ORACLE II trial.⁷ In the original study, antibiotics were given to women with

intact membranes who were at risk of preterm labour, and no improvement was seen in neonatal outcomes. But of major concern is the increased incidence of cerebral palsy at 7 years seen in the recently published follow-up data.

We agree with de Heus and colleagues that a randomised controlled trial of nifedipine and atosiban is needed; however, any such study should include a placebo arm. Accumulating evidence such as that from the ORACLE II trial and from groups examining the associations between infection, inflammation, preterm labour, and brain injury,⁸⁻¹¹ alongside improvements in neonatal care, mean that the old assumption that “keeping the baby inside longer must be a good thing” can no longer go unchallenged.

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Environmental waste in health care

Must be reduced for the overall carbon reduction strategy to succeed

In the linked analysis article, Hutchins and White describe an audit of anaesthetic waste collected from six theatres in one teaching hospital in the United Kingdom and identify potential improvements in the management of such waste.¹ Around 540 kg of solid anaesthetic waste was produced (about 2300 kg per theatre per year), 40% of which was potentially recyclable paper, card, plastic, and glass. Analysis of five sharps bins found that only 4% by weight was true sharps waste (needles and broken glass)—57% was glass and 39% was “other” (packaging, plastic, metal, and fluid).

Last year’s World Health Assembly adopted a powerful resolution on climate change, which not

only warned of the stark consequences for human health but also identified how the health sector should respond to the profound changes taking place in the global ecosystem.² The direct contribution of the health sector to environmental degradation is however less well analysed and debated. It is clear that the scale of carbon reduction needed to limit the effects of global warming cannot be achieved without the health sector playing its part.

Analysis of the carbon footprint of the NHS in England gave surprising results.³ About 18% of the NHS carbon footprint came from staff and patient travel, 22% from energy usage, and 59% from procurement, including equipment and pharmaceuticals. This is

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unlikely to be an atypical finding, and in countries such as the Netherlands and Denmark, with a less car based transport system, the proportion attributable to procurement may be higher.

To tackle the problem, medical industries will need to review their processes and supply chains and adapt their purchasing approaches to make carbon reduction a priority. In some areas of health care, such as pharmaceuticals, the avoidance of unnecessary prescribing or treatment will help. But in other areas, including where single use devices are common, reducing, reusing, reprocessing, and recycling waste will cause intense debate.

The World Health Organization estimates that 20% of the total waste arising from healthcare activities is potentially hazardous.⁴ Concerns about transmission of agents such as the prion responsible for variant Creutzfeldt-Jakob disease and viruses that can spread via body fluids have driven much of the recent growth in single use equipment and the consequent increase in waste classified as potentially hazardous. However, evidence shows that items intended for single use are often reused without sterilisation.⁴

The WHO reports that worldwide about 16 million hepatitis B infections, 4 million hepatitis C infections, and 160 000 HIV infections occur annually from improper reuse of syringe needles.⁴ Concern about injecting practices has led some countries to advocate a shift back to reusable glass syringes. From the perspective of carbon reduction, the importance of tackling the volume of clinical waste is reinforced by the estimated high fossil carbon content of clinical waste compared with general municipal waste.⁵

The importance of reducing healthcare waste is heightened by the steadily reducing landfill capacity in many countries and the sometimes vociferous opposition to the construction of incineration plants. Healthcare systems need to embrace a holistic

approach to minimising waste but also encourage commitment and innovation among healthcare professionals in individual specialties. Hutchins and White's audit of waste is an example of how healthcare professionals can take into account the environmental consequences of their work and minimise the amount of clinical waste while recognising that patient safety is paramount.¹ Their approach is valuable and would make a substantial contribution if it became the norm. To be fully effective it must however be linked to rigorous procurement practices that have environmental concerns at their heart. If they operate in an organised manner, clinicians are well placed to become environmentally discerning customers and demand clinical supplies that are much less wasteful.

Healthcare professionals are no different from other members of society, and many are making the necessary changes in their homes to reduce their ecological footprint. They should be encouraged to bring the same concerns into play in their professional lives. Thomas Berry, the American theologian, has said that you cannot have well humans on a sick planet.⁶ The goals of healing people and healing the planet will increasingly need to go hand in hand.

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Managing research data for future use

The *BMJ* is now asking authors for data sharing statements

For some time the *BMJ* has been watching other journals' efforts to encourage authors to make raw research data available. Now we are taking part too, by asking authors to include a data sharing statement at the end of each original research article. The statement will explain which additional data—if any—are available, to whom, and how. Those data could range from additional explanatory material to the complete dataset. People allowed access to the data might range from fellow researchers to everyone. And data might be available only on request, accessible online with a password, or openly accessible to all on the web with a link on bmj.com.

We understand that many authors wish to guard data until they have published all their own papers, and we know that data sharing is hard to do. But we hope that

authors will, increasingly, set the data free, perhaps after a set period of personal use.

Data sharing means more than the open access publication of articles and the posting in online registries of

Sharing medical research data: ethical and editorial barriers and proposed solutions¹

Ethics committees: encourage researchers to include plans to publish data in trial information sheets and discuss the safeguards in place to protect the privacy of patients

Research funding agencies: give greater scrutiny to data sharing plans and monitor their enforcement

Journal editors and publishers: recommend that authors prepare data in line with an agreed standard (which requires further consideration). Encourage deposition of data in the journal or suitable third party repository as part of the submission process, potentially via an accession number system, as for trial registration

Trialists: obtain explicit consent for publication of suitably anonymised raw data as part of patient recruitment procedures

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study protocols and main results. Sharing allows other researchers—and perhaps scientists, clinicians, and patients—access to raw numbers, analyses, facts, ideas, and images that do not make it into published articles and registries. At its fullest extent, data sharing means free access for everyone. Many people would call this a moral obligation because most research is publicly funded and involves the public as participants. Other potential benefits include quicker scientific discovery and learning, better understanding of research methods and results, more transparency about the quality of research, and greater ability to confirm or refute research through replication.

Such sharing raises important questions about who owns the data,¹ who gives permission to release the data (including funders, research participants, owners of the intellectual property, and copyright holders), where and how the data should be stored (in electronic repositories managed locally, nationally, or internationally; or in subject specific databases), how the data should be stored and managed and made compatible across repositories, how the data should be accessed and mined, who should have access and when, and what limits may be needed to prevent misuse and mishandling of data. Yet, despite these and other complexities, the movement to free the world's vast swathes of untapped research data is gathering speed.

This momentum is coming not just from a few open access advocates and proponents of making the web a searchable network of data as well as articles.² As delegates at the UK Research Data Service (UKRDS) conference in London heard last month, many researchers would also like access to unpublished raw data.³ Yet academic, technology, publishing, and business interests currently conspire—deliberately or not—to keep data hidden away. Researchers lack the incentives and the means to analyse all the data that they generate, to manage data after funded projects have ended, and to share data other than informally with certain collaborators. A recent UKRDS study on the logistics and costs of developing and maintaining a national shared digital research data service concluded that such a service is feasible and worth funding, and that it could greatly increase UK universities' potential for research and innovation and their global competitiveness.⁴ Meanwhile, many other countries are already on the case.

Data sharing is hardly a new idea. Physicists, environmentalists, and researchers in the basic biomedical sciences have been doing this for years. Funders such as the UK Medical Research Council,⁵ US National Institutes of Health,⁶ and Wellcome Trust⁷ already mandate sharing of data from research in basic science and genetics. The US National Heart, Lung, and Blood Institute has opened up to researchers worldwide its collection of genetic and clinical data from three asthma research networks and the Framingham Heart Study.⁸ Even GlaxoSmithKline has opened up its “patent pool” so that data relevant to finding drugs for neglected diseases can be explored by other researchers.⁹

Numerous science journals mandate data sharing

too. For example, a condition of publication in a *Nature* journal is that “authors are required to make materials, data and associated protocols promptly available to others without preconditions. Data sets must be made freely available to readers from the date of publication, and must be provided to editors and peer-reviewers at submission, for the purposes of evaluating the manuscript. For the following types of data set, submission to a community-endorsed, public repository is mandatory.”¹⁰ These data sets include those containing DNA and protein sequences, macromolecular structures, microarray data, and chemical compound screening.

For most medical journals, however, sharing of clinical research data is a new and difficult concept. Last week the editors of the open access BioMed Central journal *Trials* spelled out the main ethical and editorial barriers to data sharing in medicine and, partly drawing on discussions with scientists and other editors (including TG), proposed some solutions (box).¹¹ The maintenance of patient confidentiality is a major challenge, because the combination of clinical data and personal data and the place of research can be enough to reveal a research participant's identity. Hence clinical research data need to be anonymised carefully before sharing and, if a risk of identification remains, patients should be asked for consent to data sharing as well as consent to taking part in the research.

Since 2007, the *Annals of Internal Medicine* has been asking authors to make a “reproducible research statement” at the end of each research paper.¹² Authors state whether and within what limits they will share the original study protocol, the dataset used for the analysis, and the computer code used to produce the results. We gladly acknowledge that we are emulating this policy in introducing data sharing statements for *BMJ* research articles and bringing data sharing to authors' and readers' attention. We hope authors and readers will now join us in this debate and will help journals to set data free.

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