Multidrug resistant-tuberculosis in regions with high prevalence of HIV infection

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Introduction
The changing distribution of tuberculosis across the world presents a dangerous and challenging picture. After many years of declining prevalence tuberculosis is now on the increase in many places, not least some of the London boroughs. But it is in Africa, Eastern Europe (EE) and Central Asia (CA) where the most alarming rises are taking place. Figures 1a. and 1b. overleaf show tuberculosis prevalence for Africa and for EE/CA.

Tuberculosis in Africa
The cause of the dramatic rise in tuberculosis prevalence in Africa is well known, but the full consequences have yet to be revealed. The African HIV infection rate remains the highest in the world and with it comes inevitable co-infection with tuberculosis, a common opportunistic infection in immuno-compromised patients. In nearly all sub-Saharan countries between 60-70% of tuberculosis is related to HIV infection, and tuberculosis accounts for about 50% of all deaths in HIV-positive people. No HIV-related programme in sub-Saharan Africa can succeed without a strong component of tuberculosis control integrated within it.

Fortunately there is as yet very little drug resistance amongst new patients with combined HIV and tuberculosis in Africa, because the drugs have not been widely available for potential misuse. Although common and devastating, there is no bacteriological reason why the African tuberculosis epidemic should not be contained, if coupled with life-prolonging anti-retroviral treatment (ART). However, the problems are of course very far from simply resolved, due to under-investment in health infrastructure, lack of financial transparency and generally poor governance.

Tuberculosis in Eastern Europe and Central Asia
The cause of the dramatic rise in tuberculosis prevalence in Africa is well known, but the full consequences have yet to be revealed. The African HIV infection rate remains the highest in the world and with it comes inevitable co-infection with tuberculosis, a common opportunistic infection in immuno-compromised patients. In nearly all sub-Saharan countries between 60-70% of tuberculosis is related to HIV infection, and tuberculosis accounts for about 50% of all deaths in HIV-positive people. No HIV-related programme in sub-Saharan Africa can succeed without a strong component of tuberculosis control integrated within it.

The Soviet system of control seemed adequate. This system is (and is) based on rigidly vertical programmes of in-patient treatment in large isolated sanatoria, staffed by medical personnel trained exclusively to treat tuberculosis.

A decade later, the tuberculosis burden has almost tripled in these countries. Across the Russian Federation in 2001 the new patient incidence was 92/100,000 and in several members of the Commonwealth of Independent States (CIS) the figure was as high as 120/100,000.

The causes of this formidable increase in infection rate can be summarised as follows:

1. Marked decline in gross domestic product (GDP): Russia and Ukraine illustrate the scale of GDP decline, where in 2001 the GDPs were only 57% and 36% respectively of their levels in 1989. Some Eastern Europe countries (Poland, Slovenia) have managed to climb out of this economic trough, but only after several years of deprivation.

2. Substantial increase in poverty: it is estimated that in Eastern Europe some 50 million people live on less than US$ 2.15 per day and in the CIS the situation is probably worse.

3. Breakdown of social structures and social cohesion: this social breakdown contributes to the spread of sexually transmitted infections (STI), tuberculosis, suicide and drug dependency.

4. Massive increase in numbers of prisoners: this is fuelled by increased crime, which always accompanies poverty and social breakdown, together with harsh criminal justice systems traditional in many of these countries. The grossly overcrowded prisons
provide perfect conditions for the spread of tuberculosis, STIs and HIV. In many prisons there is no natural light and, during the long winter months, prisoners are in close confinement without exercise or fresh air. Tuberculosis incidence rates are often over 2,000/100,000 and in some prisons 40% of inmates may be infected. In Russia whole “colonies” are set aside for the detention of prisoners suffering from tuberculosis.

5. Breakdown in health infrastructure: the physical infrastructure is decrepit in nearly all the CIS countries, sometimes to the point of complete collapse (Figures 2a. and 2b. overleaf). Equally, and perhaps more damagingly, the morale of health workers has collapsed following years of non-payment of salaries and pensions. Dismal under-resourced hospitals and clinics contribute to the general gloom. It is not surprising that many of these facilities stand empty or are exceedingly underused. Bed occupancy in the hospitals of Georgia, for example, is around 30%. The general population is well aware of the lack of good medical care and also the likelihood that they may face high informal charges by health staff, who themselves are on the breadline.

All these factors have contributed to an epidemiological trajectory for tuberculosis which is amongst the steepest in the world at the present time and which is likely to continue along this course.

Problems in tuberculosis control leading to drug resistance

As already mentioned, tuberculosis control in most of the countries under discussion depends on systems more or less aligned to the previous Soviet methods. Patients are usually diagnosed through mass-radiology, almost never by sputum microscopy and culture. They are then isolated in distant sanatoria, their homes are “sanitised” by sanitary-epidemiological operatives and their treatment is prescribed according to a classification largely based on X-ray appearance. Surgery to remove diseased parts of the lung is still commonplace. However, the standard first-line tuberculosis drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) are included in the regimens in correct dosage, so in theory all hospitalised patients should be cured.

Yet many factors prevent the desired outcome. Adherence to the prescribed drugs is erratic, resulting in falling cure rates and a rising epidemic of drug resistant tuberculosis. The list of reasons behind this potentially disastrous state of affairs is a long one:

- Uncertain drug supplies.
- Administrative inertia.
- Scepticism about evidence-based World Health Organisation (WHO)-recommended practice.
- Cultural resistance to standardised practice.
- Reluctance to embrace sputum microscopy and culture as the chief diagnostic method.
- Unaffordable charging by local health staff.
- Lack of health education.
- Stigma.
- Lack of food and heating in sanatoria.
- Need to generate income for dependants.
- Lack of integration between civilian and penitentiary sectors, leaving many prisoners lost to follow-up when released.

All these contribute to a very high non-adherence rate, upwards of 60% in some countries. Where efforts are made to provide incentives such as food support, help with employment, and cash incentives, default rates can be much improved, even approaching the WHO target of an 85% cure rate for all patients starting on tuberculosis treatment.

Against this background it is easy to understand the rising incidence of multidrug resistant (MDR)-tuberculosis, both primary through drug mismanagement and acquired from existing cases. The percentage of MDR-tuberculosis amongst newly presenting patients with tuberculosis is now above 20% in many CIS countries and in the cities of Russia, and probably even higher in the prisons.
The deadly combination of MDR-tuberculosis in a region of high HIV prevalence

For obvious reasons this is the most feared disease coupling in the whole HIV arena. For a start, treatment of MDR-tuberculosis is difficult and costly, requiring the following:

- Excellent laboratory backing with facilities for mycobacterial culture, drug sensitivity testing, and preferably PCR-based rapid molecular assays for drug resistance patterns.
- Patients prepared to make frequent clinic visits for upward of two years, and to be totally reliable in taking complex mixtures of second-line drugs.
- Patients prepared to accept significant drug-related side effects over long periods.
- Clinical staff trained in use of second-line tuberculosis drugs, and possessing excellent clinical judgement (particularly in deciding when to alter drug regimes because of side effects or clinical deterioration).
- Reliable source of second-line drugs at affordable price.

Even in the few centres where all these factors can be brought together, there remains a strong risk of relapse after apparent cure in MDR-tuberculosis. For example 5 out of 18 patients relapsed within 8 months in a carefully conducted study in Ivanovo Oblast, Russian Federation.

Imagine now trying to put all the above ingredients in place in a setting of high HIV prevalence. The potential pitfalls are multiplied many times:

- The MDR-tuberculosis infection is likely to take an atypical rapid course, frequently a devastating total pulmonary infection.
- Sputum, if obtainable at all, is likely to be negative.
- Unless on life-long ART, patients will deteriorate and die despite appropriate second-line tuberculosis drug therapy.
- If on long term ART, patients will already need close clinical supervision and will be on another cocktail of drugs characterised by their own side effects.
- The possibility of drug interaction increases with the complexity of the regimen. (rifampicin, rifabutin and clarithromycin cannot be safely used in patients on ART, and no doubt other unfavourable interactions will be identified amongst the second-line tuberculosis drugs).

What of HIV?

Up to five years ago, HIV was a relatively mild problem in Russia and the CIS. It was limited almost exclusively to intravenous drug users (IUDs) and slowly spread amongst them by contaminated needles. The problem could be tackled and contained by programmes of clean needle provision, and HIV prevalence rates remained well below 1% of the population. In 1994 there were only 30,000 recorded HIV infections amongst the 450 million people of the region, whilst in Africa more than 400 times that number were infected. However, the last five years have seen prevalence rates in the general population rise, especially in the large cities of Russia. Moreover, this expansion is accelerating fast. By the end of 2002 a total of 229,000 cases had been diagnosed in the Russian Federation, of which almost one quarter had appeared in the previous year.

This pattern is almost a carbon copy of the early stages of the HIV epidemic in the now devastated countries of sub-Saharan Africa. In the Russian Federation the pattern is still patchy, with just 9 of the 89 administrative territories showing high HIV prevalence. The spread of infection emanates first from high-risk groups (sex-workers, homosexuals, truck drivers, prisoners, IDUs) and particularly affects towns along the major highways. This results in an uneven pattern of prevalence, with rural communities relatively spared. However, the infection eventually spreads into the less-at-risk general population and catastrophic HIV positive prevalence rates of 20% or more follow.

Why is the HIV epidemic likely to spread quickly in Russia and the CIS?

Russia and the CIS are now poised for the third and most disastrous phase. Social and economic deprivation provides fertile soil for rapid spread. Russia and many of the CIS also have extraordinarily high numbers of IDUs. There may be as many as 3 million IDUs in the Russian Federation and similar proportions relative to the total population in Ukraine and Kazakhstan. In Kyrgyzstan it is estimated that 2% of the adult population inject drugs. A survey of youths aged 15-18 in Moscow found that 12% of males had injected drugs.

Only the most active advocacy, insistence on protection, urgent treatment of STIs and removal of stigma stand any chance of halting this epidemic. Unfortunately, there is little evidence of a sense of urgency. Stigma excludes the groups most needing help – they are still regarded as “social deviants” in many quarters. The frail health systems and uncontrolled private practice may exacerbate rather than alleviate the problems, especially by increasing the numbers of partially or inadequately treated people at risk of developing multidrug resistance (both to tuberculosis drugs and to anti-retrovirals as they become available).

Figure 2a. Staining Bench Khurgan Tyube Tuberculosis laboratory

The possibility of drug interaction increases with the complexity of the regimen. (rifampicin, rifabutin and clarithromycin cannot be safely used in patients on ART, and no doubt other unfavourable interactions will be identified amongst the second-line tuberculosis drugs).
The average cost of treating a single case of MDR-tuberculosis in the UK is reckoned to be £2,000 for the drugs alone, not counting the cost of clinic attendance and staff salaries. The cost of triple ART chemotherapy for a typical UK patient is around £1,200 per year. Such costs would be completely unsustainable in the damaged economies of most CIS countries, just as they are in Sub-Saharan Africa.

Fortunately in resource-poor countries there are mechanisms to bring down the costs considerably: In the case of MDR-tuberculosis the Green Light Committee, administered by WHO, has successfully negotiated a 90% reduction in price for many of the commonly used drugs. For ART, the use of generic drugs has brought costs down typically to £250 per year. Even so the sheer logistical complexities in getting the drugs to countless patients, and in supervising them adequately, would tax the world’s finest health services.

Can the disaster be averted?

It is hard to be optimistic. Tuberculosis has been a problem in Russia since time immemorial. The long cold winters encourage physical crowding. Alcohol, social deprivation and poor nutrition play their part. Now the twin evils of HIV and MDR-tuberculosis have become entrenched, presenting a challenge that requires unimaginable investment in the health services. Readers may like to think through their own strategy if they were to be given the task of controlling and reversing the present catastrophe. For what it is worth, my own plans (given unlimited power and finance) would contain the elements shown in Table 1.

Table 1. Author’s suggestions for averting the disaster.

1. Laboratories would be upgraded to employ molecular diagnostic techniques to give rapid indication of drug resistance.

2. All patients with drug sensitive tuberculosis (and non-infectious tuberculosis) would be treated in the community through the primary health care service, leaving the tuberculosis specialist services to treat MDR-tuberculosis in isolation facilities.

3. Pharmaceutical companies would be compelled to invest in finding new anti-tuberculosis drugs and new sensitive diagnostic methods (many of the present problems lie in the practical difficulties of collecting suitable sputum samples, transporting, staining, microscopy, etc). They would also be required to research a more effective vaccine than the current Bacillus Calmette-Guerin (BCG) Vaccine.

4. Maximum effort would go into advocacy and health education, backed by appropriate legislation to halt the spread of HIV through drug dealing and unsafe sex.

5. A massive campaign would be launched to de-stigmatise the perception of HIV and tuberculosis by society at large.

6. The world would work towards a fairer global distribution of wealth, so that poverty (at the root of tuberculosis) would be relieved.

Recommended further reading


About Merlin

Merlin is a London-based medical non-governmental organisation (NGO), founded in 1992. It exists to provide an immediate and effective response to medical emergencies throughout the world. It is best known for its contributions to medical relief following disasters, both natural and man-made, and currently has programmes in 17 countries. It is also developing longer-term programmes in control of tuberculosis and HIV. These are based in sub-Saharan Africa and in the newly independent countries of the previous USSR, now known as the CIS.

Figure 2b. Khurgan Tyube Tuberculosis laboratory.
Liatrogenic risks associated with sporadic and variant Creutzfeldt-Jakob disease: inactivation of the unconventional causal agents

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Introduction

The transmissible degenerative encephalopathies (TDEs), otherwise known as transmissible spongiform encephalopathies (TSEs), are fatal neurological diseases of humans and other mammalian species that form a distinct group (Table 1). Their causal agents are unconventional because they are neither bacterial nor viral, and their true nature is the subject of debate. Nevertheless, there is little doubt that they are, at least partially, composed of post-translationally modified, disease-specific forms of the PrP protein that is expressed in its normal form in various tissues of mammalian species. The disease-specific, protease-resistant form of PrP is often referred to as PrPres, whereas the normal form is described as PrPsen. Regardless of the uncertainties about their precise molecular nature, it is well known that TDE agents are remarkably resistant to inactivation by procedures that inactivate conventional micro-organisms. TDEs are also known to have extremely long incubation periods that, in the case of the human diseases, can extend to decades.

Accidental transmission

Prior to 1996, concern regardingiatrogenic transmission of the human TDEs had focused upon sporadic Creutzfeldt-Jakob disease (sCJD) that affects around one in a million individuals worldwide per annum but has an unknown aetiology. However, there are regional variations in the incidence of sCJD. For example, Switzerland has had an incidence of around three in a million in recent years for unidentified reasons. The other human TDEs collectively have an incidence of between one and two cases per annum for every ten million of the worldwide population. There have been instances of accidental transmission of sCJD through the use of neurosurgical devices and instruments that were subjected to inappropriate decontamination and sterilisation procedures. A survey also showed that individuals who had undergone neurosurgery were at a higher risk of developing sCJD in later years compared with the controls. This might have resulted from the use of inadequate sterilising procedures for neurosurgical instruments but the study did not provide any information regarding the sterilisation procedures that had been used. Liatrogenic transmission has also occurred under circumstances where there had been, initially, no appreciation that specific inactivation procedures might need to be applied. These include the accidental transmission of CJD through:

- Corneal grafting.
- The therapeutic use of human growth hormone extracted from the pituitary glands of human cadavers.
- The use of commercially-processed, cadaveric-derived human dura mater for surgical repair procedures.

It was reported in 1996 that a new variant form of CJD (vCJD) had been observed in the UK. There was also confidence that vCJD was not occurring elsewhere within the EU at that time because an earlier initiative by the EC had established a network of centres for CJD diagnosis within which uniform standards for clinical assessment and laboratory diagnosis had been established. In 1996, none of the EU centres outside the UK had observed any TDE that had the characteristics of vCJD. Consequently Will et al. were driven to the conclusion that the emergence of vCJD was likely to be associated with the enormous epidemic of bovine spongiform encephalopathy (BSE) that had occurred in the UK, and that it had probably been acquired through the consumption of BSE-contaminated food products. Evidence that vCJD is caused by the BSE agent came from subsequent laboratory studies. With regard to the likely association between BSE and vCJD it is relevant to note that more than 183,000 cases of BSE have been identified to date in the UK. In contrast, the total number of cases identified collectively in other EU countries is around 5,000. By March 2004, the number of definite or probable cases of vCJD in the UK was 146, and cases had also occurred elsewhere – France 6; Italy 2; Canada 1; Ireland 1; USA 1. However, the cases that were diagnosed in Canada, Ireland and the USA had lived in the UK at a time when they were likely to have been exposed to the BSE.

Table 1. The transmissible degenerative encephalopathies.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Species affected</th>
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<tbody>
<tr>
<td>Scrapie</td>
<td>Sheep, goats, mouflon</td>
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<tr>
<td>Transmissible mink encephalopathy (TME)</td>
<td>Mink</td>
</tr>
<tr>
<td>Chronic wasting disease (CWD)</td>
<td>Elk, mule-deer*</td>
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<tr>
<td>Bovine spongiform encephalopathy (BSE)</td>
<td>Cattle, captive exotic ruminants</td>
</tr>
<tr>
<td>Feline spongiform encephalopathy (FSE)</td>
<td>Domestic cats, captive exotic felids</td>
</tr>
<tr>
<td>Kuru</td>
<td>Humans</td>
</tr>
<tr>
<td>Sporadic Creutzfeldt-Jakob disease (sCJD)</td>
<td>Humans</td>
</tr>
<tr>
<td>Familial Creutzfeldt-Jakob disease (fCJD)</td>
<td>Humans</td>
</tr>
<tr>
<td>Variant Creutzfeldt-Jakob disease (vCJD)</td>
<td>Humans</td>
</tr>
<tr>
<td>Sporadic familial insomnia (SFI)</td>
<td>Humans</td>
</tr>
<tr>
<td>Fatal familial insomnia (FFI)</td>
<td>Humans</td>
</tr>
<tr>
<td>Gerstmann-Straussler-Scheinker syndrome (GSS)</td>
<td>Humans</td>
</tr>
</tbody>
</table>

* Mainly in the USA and Canada but some cases in Korea through importation of infected animals.
agent in food products. In addition, one of the Italian cases was probably infected in France. It has been calculated that, before regulations were introduced in 1989 to remove specified risk materials from bovine carcasses in slaughterhouses, around half a million BSE-infected (but apparently normal) cattle were processed to provide meat and meat products in the UK. The current epidemiological data indicate that the incidence of vCJD in the UK may be declining, and this has resulted in a dramatically reduced estimate for the number of cases that might still occur. However, such estimates are complicated by the fact that all of the cases tested so far have been homozygous for methionine at codon 129 of their PrP genes. This codon also codes for valine, and all three possible codon 129 genotypes have been previously shown to be susceptible to various types of CJD-like disease. It is therefore possible that the other genotypes may be susceptible to vCJD but may simply have (possibly much) longer incubation periods. Revised estimates for the number of cases that might occur are discussed below.

Initially, concerns regarding the potential iatrogenic transmission of vCJD in the UK related to the large number of cases that might occur. Concern regarding accidental human-to-human transmission was heightened when it was reported that all of the cases tested were shown to have PrPres in their lymph nodes, tonsils and spleens; this was in contrast to the situation with cases of sporadic or iatrogenic CJD where no PrPres was detectable in such tissues. Also, the fact that lymphoid tissues could become infected before the onset of overt neurological disease was indicated by the finding of PrPres in the appendix of an individual eight months before they developed clinical vCJD. This is consistent with the situation in sheep with scrapie in which PrPres can be detected in the spleen at six months of age, even though they do not show any signs of neurological disease until they are around two years old. The potential presence of PrPres in the lymphoid tissues of humans that are silently incubating vCJD means that surgeons could be intentionally or incidentally traumatising vCJD-infected lymphoid tissues without any knowledge that these are infected.

Recognising this problem, the UK Department of Health carried out a study in which the tonsil or appendix removed from 3,000 individuals without neurological disease were examined for the presence of PrPres. One further appendix sample tested positive. In a somewhat larger study involving around 12,000 appendix or tonsil samples, three positives were detected. On face value, these findings were taken to indicate that there might be 4,000 cases of preclinical vCJD silently incubating within the UK but it was acknowledged that the PrPres distribution in these tissues was not typical. It was recognised that the small-scale nature of the studies carried out so far did not provide an adequate national estimate for either a) the possible number of pre-clinical cases of vCJD that might be in the pipeline or b) the extent of the problem relating to surgical procedures involving the lymphoid tissues of pre-clinical cases. To address these issues, a study was initiated in which the anonymised appendix or tonsillar tissue of 100,000 individuals without neurological disease will be tested for PrPres.

Although the distribution of infectivity in different tissues appears to be greater in cases of vCJD compared with sCJD, there is a more recent indication that previously unsuspected tissues such as those in the olfactory pathway might become infected in sCJD-infected individuals. If this was to be confirmed, it would suggest a potential route for accidental transmission either through the use of anaesthetic equipment, or by exposure to nasal secretions (or aerosols produced therefrom). However, there has been no indication in the past that sCJD has been transmitted from person-to-person through the use of anaesthetic equipment. Nor is there any indication that friends, family or nursing staff looking after individuals with clinical sCJD are at risk of developing the disease, despite their exposure to nasal secretions (and aerosols produced therefrom). It would seem that some time is needed to judge the relevance of recent claims regarding the distribution of infectivity in sCJD-infected individuals.

In the UK, further concern regarding the potential iatrogenic transmission of vCJD was raised by the much publicised occurrence of vCJD in an individual who had received a blood-transfusion from a healthy individual who eventually developed vCJD. The relevance of this finding will only become clear if there are further similar cases. In earlier studies, no infectivity was found in blood samples from vCJD-infected individuals that were injected into mice by the intracerebral route. However, only a small volume of blood (20 μl) could be injected into the brains of individual mice by this route of inoculation.

In addition, the "species-barrier" effect has to be considered. Although it can never be proven formally, it is realistic to assume that the transmission of human TDE agents to mice will be less effective than transmitting the same agents to humans. There are numerous publications that testify to the "species-barrier" effect, and it has been shown that the efficiency of transmitting BSE to cattle is around 500-fold greater than transmitting it to mice (GAH Wells personal communication).

A potentially more realistic appraisal of the risk associated with blood-transfusion in humans was obtained by studies in which 450 ml volumes of blood from sheep that had been experimentally infected with BSE, or were naturally infected with scrapie, were collected at various times before the onset of clinical disease and transfused into scrapie-free sheep. A number of the recipient sheep developed BSE or scrapie. Although these studies were not complicated by the "species-barrier" effect, their relevance with regard to vCJD and blood transfusion in humans is still an open question.

Table 2: Bovine Spongiform Encephalopathy (BSE).

- First identified in Britain in 1985; uniform distribution of neuropathological lesions in affected cattle.
- "Point-source" epidemic expanded by rendering practices.
- Currently 188,000 cases worldwide.

- Hypotheses on the origin of BSE.
  - Sheep-to-cow theory (involving changes in rendering practices).
  - Cow-to-cow theory (also involving changes in rendering practices).

- BSE has infected domestic cats, captive exotic ruminants and felids; mice, pigs, sheep and macaques have also been infected by experimental challenge.
Decontamination procedures

Regarding the inactivation of CJD-like agents that might contaminate medical devices and surgical instruments, the number of reliable and practical options is small. Until the mid-1990s it was considered that a number of procedures were completely effective. These included exposure to:

- 1M sodium hydroxide for an hour.
- Sodium hypochlorite containing 20,000 ppm available chlorine for an hour.
- Gravity-displacement autoclaving at 132°C for an hour.
- Or
- Porous-load autoclaving at 134-138°C for 18 minutes²¹.

Further studies indicated that only the hypochlorite treatment appeared to be completely effective whereas the other processes were able to substantially, but incompletely, inactivate these agents²¹ (Table 3). However, the use of strong hypochlorite solutions is not a product- or user-friendly process. These damage stainless steel and generate chlorine vapour that can be hazardous to operators if they are not wearing respirators. A further advance in the development of effective procedures was achieved by the discovery that TDE agents could be reliably inactivated when they are exposed consecutively or simultaneously to 1M sodium hydroxide and gravity-displacement autoclaving at 121°C. Although such methods of decontamination have been recommended in guidelines issued by the World Health Organisation²², there are practical problems associated with the use of these processes. For example, it has been reported that a variety of medical devices were irreparably damaged by their exposure to such procedures²³. On the other hand, studies at the Neuropathogenesis Unit in Edinburgh (UK) have shown that several grades of stainless steel are undamaged by this type of exposure (Taylor & Fernie, unpublished observations). Similarly, the WR2 company in the USA that uses hot alkali at a temperature of 150°C to dispose of animal carcasses has not experienced any degradation in the physical properties of their stainless steel reactor vessels that have been used for many years (G. Kaye, personal communication). It is clear that the nature of the materials that will survive alkaline autoclaving without significant damage needs to be better defined.

Another problem that has arisen with regard to autoclaving in alkali is the exposure of personnel to hydroxide-contaminated vapour in the general environment by its release through thermostatic steam-traps that vent to the normal environment before the condensate is discharged to the drainage system²⁵. Although sodium hydroxide solutions do not evaporate until they reach a temperature of 1,390°C, water and aqueous solutions tend to ‘bump and splutter’ during autoclaving. This means that aerosols containing sodium hydroxide can be produced and released, as described above. These types of problem would be overcome by using either of the types of containment systems recommended by Taylor²¹, or high-security autoclaves that are produced, for example, by the Fedegari company in Italy. High-security autoclaves retain all of the condensate that is produced during the autoclaving cycle, thus preventing the release of hydroxide-contaminated vapour into the general working environment. It is clear that the special methods described above could only be realistically applied to selected instruments or devices that were associated with a specific risk of contamination with CJD-like agents.

For practical reasons, the vast majority of surgical instruments and medical devices will still have to be processed by the production line systems that are customarily used in central sterilisation departments (CSDs). In this respect one observation is pertinent, at least with regard to the UK experience. This is that, for reasons of health and safety, nursing staff are being discouraged from carrying out the washing of instruments (that they previously carried out commonly) before sending them on for decontamination and sterilisation. Private conversations with the managers of CSDs have revealed that the decline of local washing has enhanced the problem of removing material that has dried onto the surfaces of devices and instruments.

However, CSDs in the UK have facilities for the option of hand-washing instruments and devices before these are processed through automated washer-disinfectors as a prelude to steam sterilisation. Generally, hand-washing is applied routinely to instruments and devices that are recognised to be difficult to clean, or to individual items that are contaminated with significant amounts of blood, mucus, pus or tissue. Although TDE agents tend to adhere tenaciously to surfaces²⁴, they can be removed by washing procedures²⁵. Thus, there is the possibility in washer-disinfectors that TDE infectivity washed off the surface of one instrument could become re-attached to the surfaces of other instruments²⁶. This makes it important to avoid processing instruments through washer-disinfectorsthat have any known TDE-related risk.

Clearly, it would be useful if effective decontamination methods could be developed that are less harsh than those used at present. In this respect, there are a number of ongoing studies looking at the combined effects of chaotropes, detergents, proteolytic enzymes, pH and temperature.

Table 3: TDE agent stability following exposure to various inactivation procedures.

<table>
<thead>
<tr>
<th>Little reduction in infectivity titres</th>
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<tbody>
<tr>
<td>– Organic solvents, aldehydes, hydrogen peroxide.</td>
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<tr>
<td>– Phenolic disinfectants, chlorine dioxide.</td>
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<tr>
<td>– Peracetic acid.</td>
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<td>– Most proteolytic enzymes.</td>
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<tr>
<th>Significant reduction in infectivity titres</th>
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<tr>
<td>– 1M or 2M sodium hydroxide at ambient temperatures.</td>
</tr>
<tr>
<td>– Sodium dichloroisocyanurate (20,000 ppm).</td>
</tr>
<tr>
<td>– Chaotropes such as guanidium thiocyanate.</td>
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<tr>
<td>– 95% formic acid or hot hydrochloric acid.</td>
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<tr>
<td>– Autoclaving at temperatures between 132°C and 138°C.</td>
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<tr>
<td>– Dry heat at 200-600°C.</td>
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<table>
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<tr>
<th>No detectable infectivity</th>
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<tbody>
<tr>
<td>– Sodium hypochlorite (20,000 ppm) ~30 minutes.</td>
</tr>
<tr>
<td>– Exposure to 1M sodium hydroxide during autoclaving at 121°C for 20 minutes.</td>
</tr>
<tr>
<td>– Boiling in 1M sodium hydroxide for one minute.</td>
</tr>
<tr>
<td>– Dry heat (incineration) at &gt;600°C.</td>
</tr>
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References are shown overleaf.
References