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TOXINS AND INTOXICATIONS

CONTENT

TOXINS AND INTOXICATIONS

In this issue, we give examples of toxins and intoxications that occurred in the (recent) past or that are ongoing. Some affect the individual, others affect many; some are intentional, most are unwanted; some have a clear correlation with health, for others it is not yet clear. What is abundantly clear is that these threats to human health cannot and should not be ignored and deserve the same kind of attention as other conditions.

Human health is threatened by many factors that may originate internally in the body such as myocardial infarction or diabetes mellitus as well as by external factors. The latter include infections, trauma, or exposure to environmental factors with often serious consequences. Examples are domestic smoke (leading to COPD), stimulants such as betel nut (a carcinogen), khat (cardiovascular disease), coca leaves (oral carcinoma), or local brews containing methanol (may be fatal). A particularly serious category is exposure to teratogenic drugs such as thalidomide (Softenon™) in the 1960s leading to, among others, phocomelia (absence of limbs) in babies born to mothers who had taken this drug to combat morning sickness during pregnancy.

A special category is accidental or intentional administration of a toxin in the context of homicide or suicide. These are often culturally determined as was the case in the (mostly) intentional acetic acid overdosing among citizens of the Netherlands Antilles and Surinam in the 1970-1980s. A similar suicide drug is para-phenylene diamine (PPD) that is used as a basis for hair dyeing and intensifying henna painting of the hands in women who are getting married. When swallowed, it leads to severe morbidity and mortality. Organophosphate poisoning (accidental or intentional) is common in low- and middle-income countries (LMICs), and clinical as well as epidemiological findings are presented in this issue.

Large scale exposure to toxins may occur as in toxic olive oil scandal in Spain in the 1980s and the Bhopal industrial disaster in India (1984) with immediate and long-term effects on health.

Other health risks include environmental pollution as was the case in the oil leakage scandal in the Niger River delta (Nigeria, starting in 1958). The oil destroyed the source of clean water and arable land for decades, threatening the means of existence of many living in the delta. Disasters due to radioactivity have also occurred, such as the Chernobyl disaster (Ukraine, 1986), where people died of radiation with large-scale environmental pollution. Similar damage to the environment with health risks resulted from the mining of uranium in Niger for example.

In some cases, there is only a (strong) suspicion of a culprit; in the case of the increasing numbers of patients worldwide with Parkinson's disease, only circumstantial evidence exists linking the use of pesticides to the occurrence of this disease. Neurologist Bas Bloem, Radboud Medical Center, Nijmegen, the Netherlands, is a world expert and advocate on this disease and co-author of a paper that we include in this issue. It is no coincidence that he was recently awarded the Stevin price of 2.5 million euros to stimulate research on this topic.

Investment in research on the (long-term) health effects of exposure to toxins and intoxications, access to clinical care and psychological support, and support for justice being done and obtaining financial compensation are among the priorities in this neglected field of tropical medicine and global health.

Ed Zijlstra
Olga Knaven

Exposure to toxins – past and present

Epidemiology, clinical features, socioeconomic impact and liability

In this overview, we discuss various industrial disasters that affected the lives of many as well as individual exposure to toxins, either accidental or intentional. All have a dramatic effect on (planetary) health as well as a socio-economic impact that may result from environmental pollution or persisting disability. Lastly, we highlight the main issues in obtaining financial compensation.

MASS EXPOSURE – INDUSTRIAL DISASTERS

THE BHOPAL GAS TRAGEDY / DISASTER – THE WORLD'S WORST INDUSTRIAL DISASTER

On the night of 2-3 December 1984, a gas leak occurred at the Union Carbide Indian Limited pesticide plant in Bhopal, Madhya Pradesh, India. Over 500,000 people were exposed to methyl isocyanate (MIC) gas, the worst industrial disaster ever. The official immediate death toll was 2,259. In 2006, the Government of Madhya Pradesh stated that the leak caused over 550,000 injuries including 38,000 temporary partial injuries and 3,900 severely and permanently disabling injuries.[1,2]

The initial effects were coughing, severe eye irritation, and breathlessness. Children were more affected as the gas tends to fall toward the ground.

The following day, thousands had died mostly because of choking, circulatory collapse and pulmonary oedema. Autopsies revealed renal injury, cerebral oedema, liver necrosis and necrotising enteritis.

In the immediate aftermath, the health services became overwhelmed; there was no plan on how to deal with a disaster of this magnitude and there was no awareness of appropriate treatment methods. Mass funerals and cremations took place. 170,000 people were treated in hospital or temporary facilities. Trees in the vicinity became barren and thousands of animals were collected and buried. Long-term effects include eye disease (cornea scars, opacities), respiratory disease (pulmonary fibrosis), neurological disorders (memory loss), psychological problems (Post Traumatic Stress Syndrome: PTSS), cancers, and child health damage (risk of peri- and neo-natal death). The stillbirth rate was up by 300% and neonatal mortality by around 200%. Those who did not die suffered severe socioeconomic consequences in addition to health problems.[1,2]

Extensive litigation followed; Union Carbide agreed to pay USD 470 million for damages and was ordered to fund a hospital in Bhopal to specifically treat victims of the disaster at a cost of USD 17 million. The Indian Supreme Court ordered the Indian Government to purchase a group medical insurance policy to cover 100,000 persons who might later develop symptoms.[1]

YELLOW CAKE ("URANIA")

Yellow cake is a type of uranium concentrate powder that is a step in the processing of uranium before fuel fabrication or uranium enrichment. It is produced by in situ leaching, in which acid, alkaline and peroxide solutions are pumped through the uranium deposit. Yellow cake is what remains after drying and filtering.[3] It is used for uranium fuel for nuclear reactors. Uranium can be enriched to the isotope U-235. Low-enriched uranium, with up to 20% of U-235, is suitable for electro-power reactors. Highly enriched uranium (>20% U-235) is suitable for compact nuclear reactors used in naval warships and submarines. Uranium with levels of U-235 > 90% is suitable for nuclear weapons.[4]

Niger has the world's fourth largest uranium reserves. When France discovered uranium in its former colony, it was felt as a blessing for the country, which ranks 187 out of 188 countries on the United Nations Development Index. Areva, a French state-owned mining company, extracted uranium in open pits as well as in mines. Niger has benefited only marginally but suffers from tremendous pollution, leading to chronic exposure to radiation in miners who work without even minimal personal protection such as face masks. The long-term effects are not well known, but deformed babies, high death rates, and lung cancer are among the commonly perceived consequences. Yellow cake mining in Niger leaves Niger in the dark (90% have no electricity), while in France one in three light bulbs is lit thanks to Niger's uranium being used in nuclear energy: a classical example of ruthless (colonial) exploitation of a poor country's resources.

NUCLEAR RADIATION

The Chernobyl disaster (Ukraine, 1986) occurred because of poor maintenance and mismanagement. Thirty operators and firemen died within 3 months as a result of the accident. Around 20 people died as a result of acute radiation syndrome. More than 335,000 people were evacuated. A large cloud of radioactivity spread over Europe across an area of 160,000 km2 where radioactive caesium (^{137}Cs), one of the common fission products of the fission of U-235, was detected in the air.[5,6] For some time, the consumption of crops of vegetables was discouraged. Despite the exposure to high levels of radiation, no major long-term health effects were noted.[7] The feasibility of resettlement and agriculture are subject to examination; in 2011 Chernobyl was declared a tourist attraction. Wildlife is thriving in the absence of humans despite exposure to radiation.

The Fukushima disaster (Japan, 2011) was triggered by a tsunami caused by an earthquake off the coast of Japan. The tsunami destroyed the reactor's cooling system. No casualties resulted directly from exposure to radiation; all deaths were due to the impact of the tsunami. A large area surrounding

Figure 1: Plaque to the victims of the Toxic Oil Syndrome. ahttps://en.wikipedia.org › wiki › Toxic_oil_syndrome

the nuclear plant, with a diameter of 20 km², was evacuated, including 154,000 people. Large quantities of radioactive water were released into the Pacific ocean, which continued for years thereafter.[8] The incident caused a great scare world-wide and increased existing negative sentiments against the use of nuclear energy. In Germany, former chancellor Merkel put in place the ''Atomausstieg'' (nuclear power phase-out), a decision that has serious consequences now that the supply of Russian gas as a source of energy is decreasing because of the Ukraine war.

THE SHELL OIL DISASTER IN NIGERIA

Since 1958, oil has been commercially produced by the Shell oil company in the Niger River delta in Nigeria. Multiple oil leakages due to poor maintenance and in some areas, sabotage, have occurred with deleterious impacts on farmlands, fishponds, rivers, and residential areas. While the local population hardly benefits from the oil production, they suffer from a lack of clean drinking water, poor housing, poor health, and poor health care. It is a matter of a handful of poor farmers fighting for justice against a powerful multinational and a dysfunctional Nigerian Government, which has failed to regulate the oil industry and protect the rights of the local population. In 2020, Amnesty International and other NGOs reported that no more than 11% of polluted areas had been cleaned. In 2021, a Dutch court ruled that Shell is liable for damages and must offer compensation. In addition, Shell needs to do more to prevent further damage and renew pipes and other infrastructure.[9]

MASS EXPOSURE – BY INGESTION – THE TOXIC OIL SYNDROME (BAD OLIVE OIL)

In 1981 in Spain, 25,000 people in or around Madrid became ill within a short period of time, and hundreds died. About 100,000 were exposed to a toxin, long-term mortality is estimated at 5000 people, and 20,000 have survived with poor quality of life. [10,11,12] The cause was shown to be rapeseed oil adulterated with 2% aniline (phenylamine) and sold illegally by street vendors as "olive oil".[11] It started with flu-like symptoms and a morbilliform rash. In the first months, deaths were due to a chemical pneumonia with very high eosinophilia. Later, deaths were mainly from unremitting pulmonary hypertension and chronic cor pulmonale (right-sided heart failure due to pulmonary hypertension); many developed a scleroderma-like illness with neuromuscular and cutaneous manifestations. Studies showed degeneration of the conduction system leading to conduction disturbance, arrhythmias and sudden death. In addition, fibromuscular dysplasia in the coronary arteries could lead to ischaemia. [11] The implication for rapeseed caused considerable discussion as this oil was thought to be beneficial for lowering cholesterol. While rapeseed oil has been used for centuries in the Orient, it was only introduced in the Western world several decades ago. However, growing rape plants and producing rapeseed oil has developed into a multibillion dollar industry. The result was a bitter trade and tariff dispute between French and Canadian farmers; the Canadian product was called canola oil and contained only a few percent of erucic acid, the perceived culprit compound of rapeseed oil. In 1989, after the longest trial in Spanish history, judges dismissed charges for murder or intentional injury against distributors; some were given prison sentences for importing and tampering, but many of the accused were acquitted, causing an uproar. [10]

MASS EXPOSURE – ARSENIC IN THE ENVIRONMENT

The WHO estimates that > 200 million people across 70 countries are chronically exposed to concentrations of inorganic arsenic (As) in drinking water.[13] Bangladesh, India, Taiwan and Peru are among the worst affected countries. [14] The health risks include lung, bladder and skin cancer, ischemic heart diseases, and skin lesions. There is increasing evidence for the development of neurodevelopmental deficits in children and adolescents after exposure to As in drinking water as well as to cadmium (Cd). It is not clear to what extent genetic polymorphisms play a role that could result in differences in detoxification enzymes, DNA repair, and tumour suppression proteins. Epigenetics may play a role whereby arsenic exposure induces different gene expression leading to predisposition to cancer and other diseases. [15]

INDIVIDUAL EXPOSURE

ACETIC ACID INTOXICATION – A CULTURALLY DETERMINED INTOXICATION

Concentrated acetic acid (also called glacial acetic acid) has an 80-85% content of acetic acid (also known as

ethanoic acid) and needs to be diluted to 4% before consumption, e.g. as a salad dressing; it has a pungent, vinegar-like odour. In a report from 1977, 100-200 cases of acute intoxication with concentrated acetic acid were reported to occur annually in Surinam in a population of 350,000. [14] Similar cases (25-30 annually in a population of 160,000) were reported in 1982 from Curacao, Netherlands Antilles. [15] The female to male ratio was 3:1 to 5:1. In both countries, the cases mainly involved suicide attempts.

The clinical features include erosions on the mucosa of mouth, oesophagus and stomach. In severe cases, haematemesis occurs with perforation of the oesophagus, stomach, or jejunum, leading to mediastinitis or peritonitis. Aspiration leads to bronchopneumonia. General complications include haemolysis, renal failure, and circulatory insufficiency, likely to be caused by myocarditis. Intravascular coagulation has been described. Long-term complications include oesophagus stenosis leading to aspiration pneumonia; repeated dilatation of the oesophagus may be needed. Treatment is supportive. Antibiotics are indicated for 4-8 weeks if perforation is suspected. The role of steroids in the prevention of long-term stenosis is controversial. The increasing number of cases was a reason for calling for political action to prohibit the sale of concentrated acetic acid.[17]

THE SOFTENON™ SCANDAL

Softenon™ (thalidomide) had been used world-wide since 1957 for sleeping problems and as a sedative and pain killer. Later, it was also used to treat pregnancy-induced vomiting. In 1961, it became clear that it caused severe abnormalities in newborns. More than 100,000 children have been born with abnormalities of the eyes, kidneys, or genitals, and in particular short or absent limbs (focomelia).[18] Before Softenon™, focomelia was a rare condition; it was caused by inhibition of angiogenesis – the growth of blood vessels of limbs. In the late 1980s, the drug was reintroduced for several indications, including mouth ulcers in HIV infection, leprosy, Behcet's syndrome and other rheumatic diseases; inhibition of angiogenesis was thought to be of importance in the treatment of cancer. It is on the WHO list of essential medicines.[19]

Only in 1982 did Chemie Grünenthal (Stolberg, Germany) apologize for the production of Softenon™. There is information that suggests that, as early as 1959 (two years before it was banned), the side-effects were already known but were covered up. The media played an important role in finding the truth. The scandal led to more stringent rules for drug research and registration.[18]

DOMESTIC SMOKE

In low- and middle-income countries (LMICs), many households use a mixture of fuels for cooking, including charcoal and wood. In addition, various other smoky means of lighting, such as paraffin, tin lamps and candles, are used. This causes exposure to particulate material by inhalation. If these particles are larger than 0.5 mm in diameter, they are deposited in the muco-ciliary lining of the trachea and bronchi. This mucus is constantly swept towards the throat, where it is swallowed.[20,21]

The effect of smoke on the ciliary function has been the subject of study. One study from Malawi suggested that smoke exposure is a risk factor for reduced lung function and COPD. This mechanism may be similarly impaired by cigarette smoking, which is an important risk factor for pneumonia. This has not been studied in LMICs, where smoking is less common. Domestic smoke is also a risk factor for lung carcinoma of the lung, nasopharynx and oesophagus, as was shown in a study from Zambia. [22,23] In a review paper, Gordon et al describe the scope of the problem and outstanding issues for research. Solutions that have been proposed are the use of high-efficiency cookstoves and the use of charcoal instead of wood, which reduces the exposure to smoke. Outdoor cooking is promoted, which also reduces the occurrence of burn injuries.[22]

The result of exposure to smoke and large particles can clearly be seen in fluid obtained from a bronchoalveolar lavage (Figure 2).

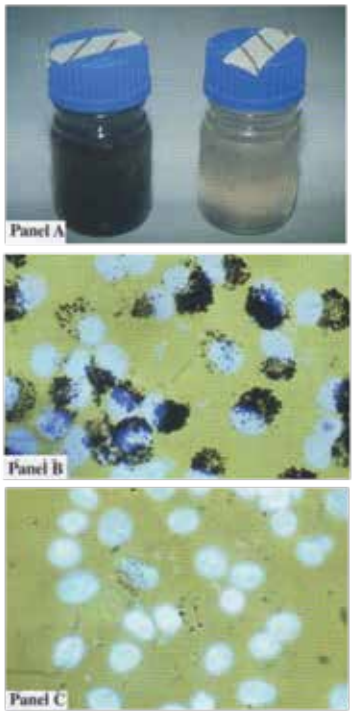


Figure 2. From: Fullerton DG, Gordon SB. Hidden risks for pneumonia in Malawi. Malawi Med J 2003 Jun;15(2):68-71. Reproduced with permission.

Panel A. Bronchoalveolar washing from individuals exposed (left) or not (right) to domestic smoke.

Panel B. Domestic smoke exposure: Macrophages in a BAL samples have phagocytosed numerous carbon particles.

Panel C. No domestic smoke exposure: few carbon particles have been phagocytosed.

PARA-PHENYLENE DIAMINE POISONING (PPD) – A COSMETIC PRODUCT THAT MAY BE USED TO COMMIT SUICIDE

Para-phenylene diamine (PPD) has traditionally been used as a dark-coloured hair dye. It may be used alone or in combination with colouring extracts such as henna for dyeing the hair or the skin (Figure 3,4). It is popular in African countries such as Sudan, Morocco, and Egypt and is also used in India. Chronic as well as acute intoxications have been described. In the ENT hospital in Khartoum, Sudan, each year 300 cases are seen with 10% mortality. [24]

Acute intoxication occurs because of accidental or intentional (suicidal or homicidal) exposure to pure PPD. Suicide accompanied by filicide has been reported; a Sudanese woman killed herself and poisoned her 4 children of whom 1 died, 1 recovered after dialysis and 2 others recovered without intervention.[25] In Sudan, PPD is readily available on the local market and is very cheap. The clinical syndrome after ingestion includes laryngeal oedema, rhabdomyolysis and subsequent renal failure, neurotoxicity (paraplegia) and toxic hepatitis (Figure 5).

There is no antidote and management is supportive.

LEAD POISONING – OCCUPATIONAL AND RECREATIONAL EXPOSURE

Lead poisoning commonly results from occupational exposure in workers employed in a battery recycling plant; other sources are the use of Ayurvedic products to which lead is added or opium-chewing.[26] Other less common cases include a history of gunshot and residual bullets in the bone marrow. Another case had a history of prolonged usage of ritual pills and holy paper incineration. Clinical features include colicky abdominal pain, renal failure, and anaemia.

In acute intoxication, the classic form of lead neuropathy may present as weakness of the wrist and finger extensors, and later spread to other muscles. There is only minimal sensory involvement.

Chronic exposure leads to a more typical toxic neuropathy with distally accentuated sensory and motor involvement. Axonal degeneration may occur. In children, there may be a link with neuropsychological disorders.

On clinical examination, Burton's line should be looked for [Figure 6]. This is the result of a reaction between lead in the blood and degradation products of oral bacteria. Management includes immediate termination of exposure; chelation therapy to bind and remove lead from the blood should be tried in acute poisoning but is controversial in neuropathy.[27,28]

Figure 3. PPD as raw material can be bought on the market. Source: Archives Rotterdam Center for Tropical Medicine

Figure 4. Henna fortified with PPD is used for hand painting in women before marriage. Source: Archives Rotterdam Center for Tropical Medicine

CARBON MONOXIDE (CO) POISONING

At least 21 teenagers died in a tavern in East London, South Africa, on an early Sunday morning in late June 2022. As the Electricity Supply Commission (ESCOM) of South Africa is unreliable in providing an uninterrupted electricity supply, private houses or businesses often have to depend on their own generator. In this case, a petrol generator was placed inside the tavern that had all its doors locked. It is likely that carbon monoxide accumulated, which has no smell, taste or colour and causes headache, dizziness, coma and death.[29]

CO binds to haemoglobin with much greater affinity than oxygen, thus reducing the oxygen carrying capacity of the blood. Diagnosis is done by measuring the carbon monoxide level in the blood. Standard pulse oximetry (SpO2) not reliable, as it cannot differentiate between carboxyhaemoglobin

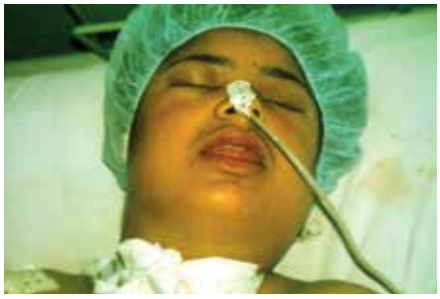


Figure 5. Laryngeal oedema after swallowing PPD in a suicide attempt.
Source: Archives Rotterdam Center for Tropical Medicine. Source: Archives Rotterdam Center for Tropical Medicine

and oxyhaemoglobin. Treatment is with high-flow oxygen through a non-rebreather mask; hyperbaric oxygen may be considered in severe cases.

Long term sequelae include myocardial toxicity and neuropsychiatric syndrome with personality changes, focal neurological deficits, and cognitive effects.

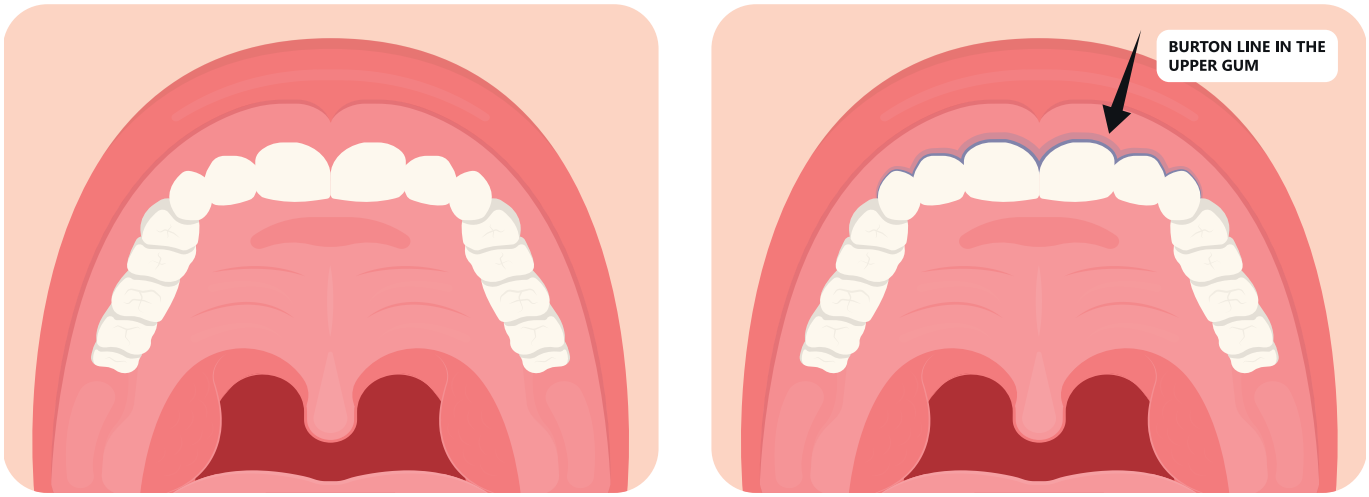
It is sad to realize that, even in South Africa, mismanagement and corruption have affected safe and uninterrupted electricity supply by ESCOM, leading to tragedies such as this one. In general, adequate ventilation and well-tuned engines, such as generators that burn clean with minimal CO production, are helpful in preventing such disasters.

* At the time of print, other factors such as combined exposure to methanol or another unidentified substance were still under investigation.

MICROPLASTIC – THE NEW THREAT TO HUMAN AND ANIMAL HEALTH?

World-wide pollution with plastic is a major reason for concern, and not only for the environment, as (macro) plastic has been demonstrated in various animals resulting in serious morbidity such as gastrointestinal obstruction. Potential toxic effects for humans are not known. Recently, it became possible to measure microplastic in human blood samples that probably have been absorbed from the gut.[30] The mean concentration in the blood was 1.6 microgram per millilitre and the particle size varied from 700 nanometre to 0.5 millimetre. It is estimated that, during life, an individual consumes the equivalent of 3 credit

LEAD POISONING



NORMAL GUMS

BURTON'S LINE IN LEAD POISONING

Figure 6a. Burton's line – a blue line immediately above and below the teeth as the result of lead poisoning

Figure 6b. Published by Oxford University Press on behalf of the Association of Physicians. Reproduced with permission.

cards of plastic. The significance of these findings is not clear. The methodology used is still a subject of study, but research is focused on the potential role of microplastics in inflammatory processes, such as inflammatory bowel disease (Crohn's disease, ulcerative colitis) or irritable bowel syndrome.[30,31]

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Culture related substance abuse – a selection out of many

Since ancient times, many types of (psychoactive) substances have been used by mankind. Of course, some of these substances, like tobacco, cannabis and cocaine, have become well-known globally, and there is an increasing body of knowledge about their use and health effects. However, there are also many psychoactive substances which are far less known and whose use is more confined to specific cultural or religious groups. In this article, we highlight some of these substances and their (adverse) effects on health.

BETEL NUT

Betel nut, or areca nut, is the seed of the fruit of the areca palm which grows in the tropical Pacific, Southeast Asia and South Asia, and parts of east Africa. In these areas, betel nut chewing is a common cultural practice. There is evidence that betel nut usage is increasing.[1] It is estimated that more than 10% of the world's population consumes betel nut in some form.[2] Betel nut is most commonly used by slicing it into thin pieces and rolling it in a betel leaf with slaked lime, hereby forming a package known as a betel quid or betel paan.[3] Over the years, an increase has been seen in the addition of tobacco to the betel quid, which further increases the health risks of individuals using it.[1]

The effects of betel nut are caused by the alkaloids inside the areca nut, of which arecoline is the most important one.[4] Arecoline has several effects on the central nervous system. It causes an increase in sympathetic activity, thereby increasing adrenaline and noradrenaline levels. This leads to tachycardia, increase of skin temperature, and reduction in hunger. It also stimulates the parasympathetic system, causing euphoria and enhanced alertness.[4] Habitual betel nut usage can cause a variety of adverse health outcomes, of which induction of oral precancerous lesions is the most important one. Depending on the type of lesion, these can turn malignant over several years to decades. Betel nut has been classified as a Group 1 carcinogen by the International Agency for Cancer Research (IACR).[1] Other described health effects are periodontal disease, oral submucous fibrosis (a chronic lesion of the oral cavity), decreased fertility, enlarged prostate, elevated risk of other chronic diseases such as cardiovascular diseases, diabetes mellitus and chronic kidney disease, and increased risk of developing other malignancies such as liver cancer and breast cancer.[4] In 2012, the World Health Organization (WHO) published a report which highlighted the need for effective measures to discourage the use of betel nut, including policies, education and clinical services.[1] Unfortunately, until now, little information is available on evaluations of educational strategies aimed at reducing betel nut use.[4]

KHAT

Khat, also called qat, kaht and several other similar names, is a plant (Catha edulis) of which the buds and leaves are chewed for their stimulant effects. Its use is embedded in cultural and social traditions in parts of Eastern Africa, such as Somalia and Ethiopia, and in parts of the Middle East, such as Saudi Arabia and Yemen.[5] The psychoactive effects of khat are caused by the active substances cathinone and cathine, which are amphetamine analogues.[6] They cause feelings of happiness, and increase alertness, energy and self-esteem. Unfortunately, long-term use of khat can cause a large variety of adverse health effects, as shown by a recent review of Alshoabi et al.[7] Within the cardiovascular system, it can cause increased blood pressure and an increased risk of myocardial infarction. Described adverse effects on the digestive system are, among others, dental caries, gastritis, risk of hepatoxicity and gastrointestinal tract cancers. Within the nervous system, khat may cause insomnia, hallucinations and stress, and it increases the risk of stroke.

Most countries do not have a clear policy with regard to khat use. There are several international initiatives in the field of khat research, of which the National Institutes of Health (NIH) funded Khat Research Program is the largest. The goal is to gain knowledge in order to develop evidence-based harm-reduction, prevention, and treatment strategies.[8]

COCA LEAVES

Coca (*Erythroxylum coca*) is an indigenous plant of western South America. For thousands of years, the leaves of this plant have been of great importance in the lives of native Andean people, who use the leaves (either by chewing or making tea) for cultural and religious motives. Chewing coca together is of great importance in acknowledging and supporting social relationships.[8] But the leaves are also used for medicinal purposes. Historically, and still today, coca has been and is used to support physical labour, as it has a stimulating effect and reduces fatigue and appetite. It also works as a local anaesthetic, reduces gastrointestinal complaints when ingested as tea, and helps against high-altitude sickness.[9]

The coca plant contains several alkaloids, of which the psychoactive component cocaine is the principal and best known one.[10] Most of the research has been done on cocaine and not on the other alkaloids, which has led to a scarcity of scientific knowledge about the effects of whole coca leaves. A recent case report from Molina-Àvila (2022) presented four cases of patients, known coca leaves chewers, developing oral squamous cell carcinoma (OSCC) in the absence of the typical known risk factors for OSCC like smoking, excessive alcohol consumption, areca and betelnut, HPV or chronic mechanical irritation.[11] The authors state that

Figure 1. Ingredients of a betel quid

Figure 2. Coca leaves

this could indicate a pathophysiological relationship between chronically chewing coca leaves and developing OSCC, but further studies are needed to establish this. As mentioned above, studies on the adverse effects of coca leaves are scarce and controversial. Until now, no genetic damage within the oral mucosa caused by coca has been found, contrary to what is known about the betel nut ingredients.[12] Dental and periodontal lesions have been described as a result, and the lesions themselves could lead to oral carcinogenesis.

METHANOL

Although possibly less linked to a *specific* culture, methanol should not be absent from this article, as methanol abuse and poisoning is an issue within various cultural groups globally. Methanol is a toxic alcohol that is legally used industrially as a solvent, pesticide, and alternative fuel source. This toxic alcohol is sometimes also used as a cheaper alternative for ethanol (consumable alcohol). When ingested by humans, it can cause methanol poisoning with fatal consequences. Industrial methanol is either added to legal alcoholic beverages, or is derived from inappropriate home brewing of alcohol. Both these types of 'illegitimate alcohol drinks' are consumed within several cultures and countries. The highest consumption is in Europe, followed by South America and Africa.[13] Home-brew beverages with methanol are often the result of financial motives, but homebrews can also be more culturally embedded with unintended methanol content, for example in the case of local medicinal herbal drinks.

A study by Nili-Ahmadabadi et al. (2016), analysing medicinal herbal drinks marketed in Hamadan, Iran, found that 50% of the drinks were contaminated with methanol. Outbreaks of acute methanol poisoning have been reported worldwide. One example is an outbreak in Uganda in 2017, caused by drinking adulterated 'Waragi' (a Ugandan gin), with a very high case fatality rate of 80%.[14] Methanol is rapidly absorbed after oral ingestion and is metabolized by alcohol dehydrogenase enzyme (ADH) to toxic metabolites. These metabolites cause retinal damage and necrosis of basal ganglia, which can lead to irreversible neurologic damage and death.[15] Besides general emergency management, treatment involves ADH inhibition therapy with, for example, ethanol. Ethanol has a higher affinity for ADH then methanol, thereby blocking the metabolism of methanol to the toxic metabolites.

Unregistered alcohol is produced without supervision or regulations, resulting in a lack in quality control and safety. At a policy level, the formulation of mitigation strategies to address this public health issue is challenging. Policymakers need to target measures in different areas, including access to alcohol, financial motives, knowledge and information, culture, community norms, and behaviour.[16]

CONCLUSION

Globally, there is a great variety of substances which are being used and/or abused within different cultures and communities. Unfortunately, many of these substances can have adverse health outcomes. When working as a doctor in an unfamiliar setting, it can be useful to gain knowledge about local cultural and traditional substance use. On a policy level, addressing the use of these culture-related substances comes with challenges. First of all, there is a lack of evidence-based research on health effects. Second, many of these substances are deeply embedded in a culture, and policymakers need to take this into account when devising policy measures.

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Parkinson's disease in the African environment

Parkinson's disease (PD) is a neurodegenerative disease which afflicts ageing individuals regardless of gender, ethnicity or geographic background. In recent decades, we have seen a steep increase in new numbers of persons affected by PD. In fact, PD is the world's fastest growing neurological condition, which has led to the introduction of the term 'Parkinson Pandemic'.[1] This rapid growth can be ascribed in part, but not wholly, to ageing of the worldwide population.[1] Importantly, the growth of PD persist even after correction for the ageing effect, suggesting that other factors are also at play. In fact, the question remains whether ageing per se is a sufficient cause of PD, because the disease appears to have been utterly rare prior to the year 1817, when the disease was described for the first time in London by James Parkinson, at a time when air pollution was becoming significant due to the industrial revolution.

People obviously didn't live as long in those days, but even then there were enough elderly individuals to allow the disease to become manifest. Perhaps the ageing effect is merely the result of prolonged exposure to toxic chemicals in our environment, as we shall discuss later. Neither are better diagnostics a very good explanation, because the diagnosis of PD is established today as it was done two hundred years ago, namely based on a good interview and a proper neurological examination. The Parkinson Pandemic [1] affects Sub Sahara Africa (SSA) like everywhere else, but solid neuro-epidemiological data from SSA are scarce.[2] It begs the question whether the nature and magnitude of risk factors for PD are the same in SSA.

Various demographic and cultural factors contribute to a lesser visibility of PD in SSA. Delayed or missed diagnoses are common because of the low density of neurologists and limited access to neuro-diagnostics in SSA, which will slowly but steadily improve in the next decades. By necessity, other medical professionals have to take medical responsibility, but they understandably lack the professional training to reliably identify parkinsonism. In many SSA countries, most neurological conditions are not even treated by non-neurological disciplines such as internal medicine specialists and paediatricians, but by assistant medical officers (AMO's)/ clinical officers, healthcare workers who follow an abridged medical curriculum and run most of the healthcare in SSA. An example is the United Republic of Tanzania with one neurologist per eight to ten million inhabitants and six MRI scanners throughout the country.[3] Presently, eight percent of Tanzanian citizens have healthcare insurance and can afford access to neurological care, diagnostics and treatment. The cost of levodopa-carbidopa medication taken three times daily amply exceeds the average daily income of a Tanzanian. This medication is only available in the six major cities of the country, which may take several days of travel.

Due to better healthcare, nutrition and infectious disease control, life expectancy in SSA is increasing, and neurodegenerative disease (such as PD and dementias) are therefore being seen more often every year. There is, however, still a 'treatment gap' for PD with a majority of patients never seeing a neurologist.[2] Neurological conditions, especially movement disorders, bear a sociocultural stigma. [3,4] This causes diagnostic delay and a tendency to seek refuge in alternative medicine and spiritual healing methods. Finally, in various cultures in SSA, PD is regarded as a natural consequence of ageing rather than a disease.[4]

The aetiology of PD is a combination of intrinsic susceptibility and environmental risk factors. The genetic predisposition ranges from monogenic mutations (which often lead to young-onset PD) to genetic polymorphisms which raise genetic susceptibility to PD. Environmental risk factors include a range of exogenous toxins which by themselves can produce a PD phenotype, such as the party drug MPTP and pesticides. Pesticide use as a risk factor in PD has been extensively studied in higher-income regions of the world. For example, heat map studies performed in France, Canada and the USA have shown that PD is not evenly distributed across the country, but appears to be concentrated in clusters which in turn are tightly associated with the presence of farmland or vineyards and more intense use of pesticides. In keeping with this finding is the fact that farmers appear to have a significantly increased risk of developing PD. However, the raised risks are not limited to farmers but also affect people living in the immediate vicinity of farmland or vineyards where pesticides are used. It thus affects rural populations at large, presumably because pesticides contaminate food and water and spread via the air.[1]

Presently, 16% of the world's citizens and its youngest population live on the African continent (one fifth of the world's land surface), which drives up the pressure on food production.[5] Climate change in Africa comes with droughts, floods and erosion, challenging an already underpowered food production. In rural SSA, the majority of people are involved in farming at least part of their working hours and live at or near farming grounds. Education regarding pesticide use is minimal and knowledge regarding longer-term effects is lacking. Protective equipment is typically not available, and even when there is access, it is not used faithfully. Recent studies have in fact even questioned the efficacy of protective equipment in protecting against the toxicity of pesticides, so more work is needed to better protect those working with pesticides.

Organic vegetables grown with minimal pesticide usage are very rare, because

the lower yield per acre makes organic farming less popular. 'Agrovet' stores are found down to the smallest villages, where farmers can buy pesticides and livestock medicine without restrictions. What is really disconcerting is that many toxic chemicals, which are associated with a clear risk of developing PD, and which have consequently been banned in more developed countries, are still being used on the African continent. For example, organophosphates, paraquat, rotenone, warfarin and arsenic are sold over the counter in 1 to 4 litre wholesale containers. In Tanzania, the local farmers' cooperative has shopkeepers wearing dungarees and caps sponsored by a well-known pesticide brand.

The exposure to herbicides, fungicides and insecticides of the average SSA inhabitant is ubiquitous, but exact figures are not well known. Accidental intoxications (most commonly pesticides and kerosene) are in the top-10 of paediatric emergencies of a large referral hospital in Northern Tanzania.[7] Deliberate ingestion of such compounds is commonly seen in patients who attempt suicide and is associated with high mortality. Insidiously and unnoticed, more gradual exposure to pesticides crossing the blood brain barrier over several years is likely to co-occur in many individuals. Small epidemiological studies on the relation between PD and pesticide exposure in SSA exist, but larger-scale neuro-epidemiological data are lacking. At present, large-scale eradication programs for parasitic diseases (such as sleeping sickness, malaria, onchocerciasis and schistosomiasis) have not shown an association with PD, but the pre-symptomatic period might be too long to really answer this question.

If we extrapolate the epidemiological and in-vitro evidence of a causal link between pesticide exposure and PD and take into account improved life expectancy, we can expect a rise in numbers of PD patients in rural SSA. It goes without saying that a vast global region with a population at the lowest median age will lead to a very long exposure duration to environmental pesticides, so that a further surge in patients with PD can be expected.

An ongoing study in the Tanzanian referral hospital shows a striking percentage of early onset PD in age group below 50 years. A minority of patients has not grown up in farms or rural regions and not one patient grows or consumes organically grown vegetables. Further associations between PD and pesticide exposure in Tanzania are currently being studied. With the 'PD Pandemic' striking SSA, this could shed more light on the role of pesticides in PD.

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Organophosphate poisoning in two pediatric patients

CASE

In a district hospital in South Africa, two previously healthy siblings of three (male) and five (female) years old were brought into the Emergency Department with confusion, increased breathing, rhinorrhoea, drooling and muscle tremors. According to their mother, they were both in good health and playing in the garden before they were found there approximately one hour prior to presentation. Mother suspects the children might have ingested pesticides which were stored in soda bottles.

The physical examination showed hypersalivation, rhinorrhoea, confusion, crying, pinpoint pupils, decreased reflexes and decreased breath sounds on auscultation. The clinical condition of the three-year-old boy was worse compared to his older sister as he also had a reduced Glasgow Coma Scale (CGS) of 10. His vital signs upon arrival were a heart rate of 170-180 beats/minute and a respiratory rate of 36 breaths/minute with an oxygen saturation of 93-96%; his random blood sugar was 8.3 mmol/L. He weighed 15.9 kilograms.

The provisional diagnosis was organophosphate poisoning based on clinical presentation and the relatively high incidence in this rural area.

SETTING

This case is from a rural district hospital in South Africa. The hospital has approximately 400 hundred beds with capacity to conduct laboratory tests, X-rays, and (mostly obstetric) ultrasounds. Specialist advice is possible through telephone consultations with a specialist in one of the other hospitals in the area.

EMERGENCY MANAGEMENT

The siblings were immediately started on intravenous (IV) fluids with normal saline, oxygen support, and IV atropine. They received 0.5 mg, 1 mg, 2 mg, and 4 mg of IV atropine at 5 to 10-minute intervals. The older sister responded well on four repeated bolus of atropine. However, the boy needed a last bolus of 8 mg atropine IV and had three seizures during the resuscitation, lasting less than thirty seconds. The seizures were stopped with two doses of 3 mg IV diazepam. His oxygen saturation remained above 93%, and he maintained his own airway. The symptoms waned after the fifth dose. His secretions decreased, pupils were normalized and reactive, and his chest had good air entry bilaterally. The drowsiness and confusion persisted during observation in the Emergency Department, but his tachycardia improved and remained between 110-130 beats/minute.

Blood gas facilities were unavailable, and therefore emergency blood samples were sent off to the laboratory. The brother's and sister's initial investigations, including complete haemogram, renal function, coagulation and liver function tests were normal, except for their bicarbonate of 18 and 20 mmol/L and anion gap of 20 and 21 mmol/L, respectively, thus indicating a mild metabolic acidosis with an increased anion gap.

FOLLOW-UP

The patients were treated with continuous atropine infusion for 24 hours. The boy received a loading dose of phenytoin 18 mg/kg. Once they were clinically stable, they were admitted to the ward for further management: vitals monitoring, pupil size checks, mental status observation, and supportive management in case of seizures, bronchospasms or hypotension. Within 24 hours, the children improved considerably and the atropine administration was discontinued. The next day, they were discharged home. Further outpatient evaluation of the siblings two weeks later showed normal clinical findings and no residual symptoms.

BACKGROUND

Incidence - Organophosphates are commonly used in agricultural products such as pesticides and herbicides, and also as therapeutic agents, including ecothiopate used in the treatment of glaucoma. However, many products containing organophosphates are sold illegally for domestic use, such as the 'street pesticide' terbufos.

Organophosphate poisoning results in significant morbidity and mortality in low- and middle-income countries and is therefore an important public health problem. The incidence of organophosphate poisoning is estimated to cause 250,000 to 350,000 fatalities per year worldwide.[1,2]

Pesticide poisoning is a major component of poisoning accounts in children, particularly in low- and middle-income countries with large agricultural communities. Pest proliferation is partly caused by poor social circumstances such as overcrowding, unhygienic living conditions, and lack of housing, causing individuals to look for cheap and sometimes illegal solutions. This increases the risk of accidental exposure in children.[3]

PATHOPHYSIOLOGY

Organophosphates are rapidly absorbed through multiple routes of exposure, such as skin, mucosa and the respiratory and gastrointestinal tracts. They irreversibly inhibit acetylcholinesterase and plasma cholinesterase enzymes. Acetylcholinesterase is responsible for hydrolysis of acetylcholine to choline and acetic acid. Inhibition of these enzymes causes overabundance of acetylcholine at cholinergic synapses. This results in an acute clinical syndrome of cholinergic overstimulation at the neuromuscular junction of the sympathetic and parasympathetic nervous systems and the central nervous system. The clinical significance of inhibition of plasma cholinesterase enzyme remains unclear.

CLINICAL FEATURES

Symptoms and signs of organophosphate poisoning through oral or respiratory exposure usually manifest in thirty minutes to three hours, while symptoms of toxicity from dermal exposure may take up to twelve hours. The onset and duration of symptoms and clinical features and their severity vary depending on the type of organophosphate agent, route of absorption, and dosage. Patients with severe poisoning will typically present with excessive salivation, pinpoint pupils, declined mental state, and respiratory depression. The clinical features can be explained by the cholinergic overstimulation and can be broadly classified as secondary to the (a) muscarinic effects (b) nicotinic effects and (c) central nervous system effects (see Table 1). Ultimately, the clinical features may be determined by a multi-system manifestation involving the gastrointestinal, respiratory, cardiovascular and nervous systems, as well as involvement of skeletal muscle and other organs and metabolic effects.

Table 1. Clinical effects of organophosphate poisoning

MUSCFARINIC EFFECTS	Respiratory	Bronchospasm, hypersecretion
	Cardiovascular	Bradycardia, hypotension
	Gastrointestinal	Hypersalivation, vomiting, abdominal pain, diarrhoea
	Ocular	Lacrimation, miosis
	Other	Bladder hyperacitivity, excessive sweating
NICOTINIC EFFECTS	Cardiovascular	Tachycardia, hypertension
	Neuromuscular	Fasciculations, muscular weakness, paralysis, respiratory paralysis, cramps
CNS EFFECTS	General	Respiratory and circulatory depression, anxiety and confusion, seizures, declined mental state, decreased reflexes, ataxia, dysarthria

DIAGNOSIS

Diagnosis is made on the basis of history of exposure, recognition of clinical signs of cholinergic overstimulation, the typical garlic or petroleum-like smell, or improvement of symptoms after initiating appropriate treatment. Diagnostic tests are direct measurements of red blood cell acetylcholinesterase activity and plasma cholinesterase activity in the blood. Unfortunately, these laboratory tests are rarely available in rural hospital settings.[4]

TREATMENT

Management should start by checking the airway, breathing and circulation, and decontamination of the patient. Supportive care of the respiratory, cardiovascular and neurological systems is required by providing oxygen or a secure airway and obtaining IV access to start fluid infusion. The main aim of treatment is reversal of muscarinic effects with atropine, enzyme reactivation by an oxime such as pralidoxime (which is an antidote that binds specifically to organophosphate-inactivated acetylcholinesterase), and stopping seizures via diazepam.

A bolus of IV atropine should be administered and subsequent doses should be doubled every 5 minutes if there is no response until respiratory and muscarinic signs and symptoms are relieved. To maintain the effects, continuous atropine infusion may be required for a couple of days.

Atropine does not bind to nicotinic receptors and therefore is ineffective in treating neuromuscular dysfunction. Oximes can be given as these are effective in treating both muscarinic and nicotinic effects, but this was not available in our hospital. An IV bolus must be administered slowly in 30 minutes, also followed by continuous infusion. Oximes should only be given with concurrent atropine.[4]

Unfortunately, accidental ingestions of poisonous agricultural agents are common in children in low- and middle-income countries. Successful recovery from organophosphate poisoning is based on time from ingestion to initial presentation, rapid resuscitation, stabilization, and treatment with atropine.

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Global Health residency programme

The Global Health and Tropical Medicine program (GH&TM, 27 months duration) for physicians is offered in the Netherlands by the training Institute International Health and Tropical Medicine (OIGT) with support of the NVTG. The program is concluded by a Global Health Residency of six months duration in a low-resource setting.

Residents undertake two research projects, aimed at tackling locally relevant public health problems. Attaining knowledge of the social determinants of health, the epidemiology and burden of particular diseases, and familiarizing themselves with how local health systems address these are part of the learning objectives. Since the introduction of the training programme in 2014, a large variety of public health research projects have been conducted. In this section, MT*b* offers a platform for GH&TM trainees to present the findings of their projects.

Organophosphate poisoning – a major public health problem in rural India

Many patients present at the Emergency Department of hospitals in India with organophosphate (OP) poisoning. While the condition is well known and treatment is available, most patients die or spend a long time in the Intensive Care Unit. Organophosphates are highly toxic nerve agents which act by inhibiting the enzyme acetylcholinesterase, located throughout the central nervous system, causing severe cholinergic toxicity.[1,2] Intoxication can occur after cutaneous exposure, inhalation, or ingestion and causes a variety of symptoms that can progress to paralysis and respiratory arrest.[3] The mortality of OP poisoning is estimated to be between 10 and 20% and is probably higher in India due to lack of access to healthcare.[4] Death usually occurs because of respiratory failure.[2,5]
According to the WHO, unintentional poisoning caused the loss of over 10.7 million years of healthy life (disability adjusted life years, DALYs) and almost 200,000 deaths in 2012, of which 84% in low- and middle-income countries. The estimated number of deaths from deliberate ingestion of pesticides is even higher, about 370,000 per year.[6] As India is one of the countries where organophosphates are easily available, it is estimated to be responsible for a large proportion of the global burden. This article aims to provide an overview of the public health burden of organophosphate poisoning in India.

RESULTS AND DISCUSSION

The literature makes it clear that OP poisoning can be a public health hazard in three ways, namely acute unintentional poisoning, intentional poisoning, and chronic exposure.

ACUTE UNINTENTIONAL POISONING

A tragic example of unintentional poisoning occurred in 2013 in the eastern state of Bihar. At least twenty-three Indian school children, aged 4 to 12, died after eating a school lunch contaminated with monocrotophos, an insecticide containing OP. It turned out that cooking oil had been stored in an empty monocrotophos container at the school.[7-9] Although this particular incident made it to the global news, it is not a stand-alone incident.

According to the WHO World Bank, the mortality rate attributed to unintentional poisoning in India was 2.4 (male 2.8 vs female 1.9) per 100,000 people in 2016, compared to 5.2 in Burundi (male 6.8 vs female 3.7) and 0.1 (male 0.1 vs female 0.1) in the Netherlands, Switzerland and Singapore.[10] These numbers are not specified by type of poison.

The numbers from the National Accidental Deaths and Suicides Report of the government of India[12] are more specific. For the years 2014 and 2015, the numbers of reported fatalities from accidental pesticide poisonings were 5915 and 7060 respectively.[12] Boedeker et al (2020) conducted a systematic review on the global distribution of unintentional acute pesticide poisoning (UAPP), based on available literature from 2006 – 2018 and supplemented by mortality data from the WHO.[13] They estimated that there are a total of 385 million cases of UAPP per year worldwide, including around 11,000 fatalities. Most of these occur in South Asia.[13] Based on these numbers,

Table 1. From the National Accidental Deaths and Suicides Report 2015 (Table 1.10), showing number of cases and number of deaths from accidental insecticide/pesticide poisoning over the years 2014 and 2015.[12]

Cause	Number of cases			Number of persons died								
	2014	2015	% var.	2014				2015				% var.
				Male	Female	Trans.	Total	Male	Female	Trans.	Total	
Poisoning (total)	25351	27657	9.1	13133	7453	1	20587	17555	8617	1	26173	27.1
Accidental intake of Insecticides/ pesticides	7365	7672	4.2	3932	1983	0	5915	4912	2147	1	7060	19.4

the amount of accidental deaths due to UAPP in India would be almost 60% of the total amount globally. As organophosphate pesticides are mainly used in agriculture, it is likely that the most common source of exposure to OP lies within the occupational domain and involves agricultural workers and pest control exterminators. Other exposure could be environmental and would likely occur in the public places and areas close to farms.

Boedeker et al (2020) estimate that, based on a worldwide farming population of approximately 860 million, about 44% of farmers are poisoned by pesticides every year. The same estimate for India resulted in a prevalence ratio of 62%.[13]

INTENTIONAL POISONING

As mentioned above, about 370,000 people per year die of intentional OP poisoning worldwide[6]. According to Patel et al (2012), 187,000 people died of suicide in India in 2010, although this is likely an underestimate[14]. The main method of suicide was poisoning, mostly from use of organophosphate pesticides, corresponding to about 92,000 deaths.[14] A sensitivity analysis accounting for underreporting of suicides in India done by Mew et al (2017) resulted in an even higher estimate of 168,000 pesticide self-poisoning deaths annually.[15] This accounts for 19.7% of global suicides and about 45% of total self-inflicted OP poisoning deaths worldwide.[15]

Although the majority of deaths due to suicide in India occurred in men (61% men vs 39% women), Indian women seem to be more vulnerable when compared to international numbers. The age-standardised suicide rate in Indian women aged 15 years or older is more than 2.5 times greater than it is in women of the same age in high-income countries. For men, this was 1.2 times.[14]

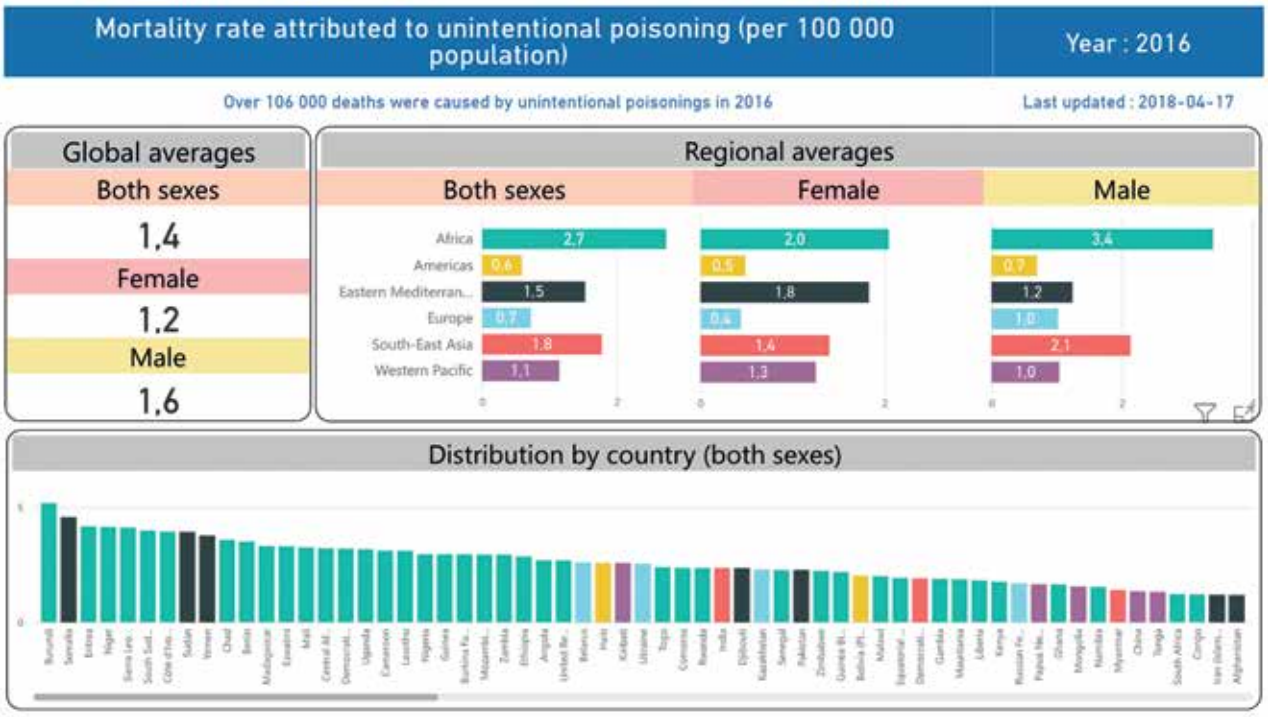

Figure 1. World Health Statistics data visualizations dashboard – unintentional poisoning.[11]

A Global Burden of Disease study performed between 1990 and 2016 came to the same conclusion.[16] The researchers found that the suicide death rate for Indian woman was 3 times higher than would be expected for geographies with a similar Socio-Demographic Index. The largest portion of suicide deaths in their study was from married woman.[16] The reason for this high suicide rate in women might be due to cultural aspects. Multiple studies from India confirm that domestic violence and gender disadvantage – especially for women in rural areas – are predictors for attempted suicide.[14,17,18] In the Global Burden of Disease study, the authors suggest a correlation with domestic violence, economic dependence, arranged and early marriage, and young motherhood.[16] Furthermore, the lack of treatment for mental illness, especially in rural areas, also contributes the number of suicides.

Homicide by intentional poisoning with OP is not common. This is probably due to the obvious smell and taste and the planning and preparation needed to kill someone compared to shooting or stabbing them. According to a review by Sikary (2018), the prevalence of homicidal poisoning in India varied from 0.03% to 3.7% based on poisoning among other homicidal deaths or other nature of poisoning. Agrochemicals, including organophosphates, accounted for the majority of these cases, but exact numbers were not presented. In almost all of the reviewed cases, the perpetrator was a first degree relative[19].

CHRONIC EXPOSURE

Another factor contributing to the public health burden of OP poisoning that was identified in the literature is chronic exposure to pesticides. While high-level exposure to organophosphates can lead to death in the short term, several studies have suggested that chronic low-level exposure can also have serious health consequences.

A literature review performed by Muñoz-Quezada et al (2016) concluded that evidence suggests an association between chronic exposure to OP pesticides and neuropsychological effects, although there is no consensus about the specific cognitive skills that are affected.[20]

Other research suggests an association between exposure to OP and several types of cancer, immunological abnormalities and Parkinson's disease.[21] However, special concern lies with pregnant woman and unborn babies. There is compelling evidence that prenatal exposure to even low levels of OP is detrimental for the unborn child's brain development, putting the baby at risk of cognitive and behavioural deficits and neurodevelopment disorders like autism and ADHD.[22]

Children are also more vulnerable than adults. Because their organ systems have not fully developed, they eliminate toxins more slowly from their bodies compared to adults; because their nervous system is still developing, children are believed to be at increased risk for long-term sequelae following organophosphate exposure. However, the long term consequences are not fully understood.[23]

Chronic exposure routes for OP appear to be the same as for unintentional poisoning: occupational and environmental exposure. Evidently, farmers and crop sprayers are at high risk due to their occupation.[21,24] Furthermore, people can be exposed to environmental intake through diet, inhalation, or dermal resorption. [25,26]. Little research exists about how much each path of intake contributes to total exposure to OP. However, people in Punjab were found to use empty containers of pesticides to store food, which also played a role in the mass casualty event at the school in Bihar.[26]

CONCLUSION

OP poisoning contributes to the burden of disease in three ways: unintentional acute exposure, intentional exposure, and chronic exposure. Each of these have their own specific causes and associated demographics. Unintentional poisoning with OP mostly affects farmers and pest control workers living in rural areas. Intentional poisoning with OP mostly occurs as an impulsive way of committing suicide.

Contributing factors to the high suicide rate in India are a combination of social problems and mental health issues, with gender inequality greatly contributing to the number of suicides under women. Women are especially at risk in rural areas, due to their perceived inferiority, poor access to (mental) healthcare, and easy access to pesticides.

The evidence on chronic exposure to organophosphates is not as clear as on the other types of exposure, although multiple routes of exposure have been identified and various adverse health effects described. People working with pesticides, like farmers and crop sprayers, are most at risk for adverse health effects due to cumulative exposure. However, even low concentrations of OP can be dangerous to unborn babies and children.

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A patient with painful legs

SETTING

This case is set in Paam Laafi, a small hospital at the edge of Ouagadougou, Burkina Faso. This hospital provides mostly primary care and has 2 medical doctors and 9 beds in the ward. It has a basic laboratory and a possibility to perform ultrasounds by a radiologist once a week. It is possible to refer patients to a bigger hospital in the capital, but these are almost always full and cannot provide enough care for most patients.

PHYSICAL EXAMINATION

On physical examination he looks ill. The vital signs show a pulse rate of 108 beats per minute and a temperature of 40 °C. The blood pressure cannot be measured because of lack of a working device. The SpO2 is normal. Examination of the heart, lungs and abdomen and skin is normal. The legs look symmetrically normal on inspection; palpation of the lower legs and especially the soles of the feet is symmetrically very painful. The muscle tone is normal, as is the temperature of both legs.

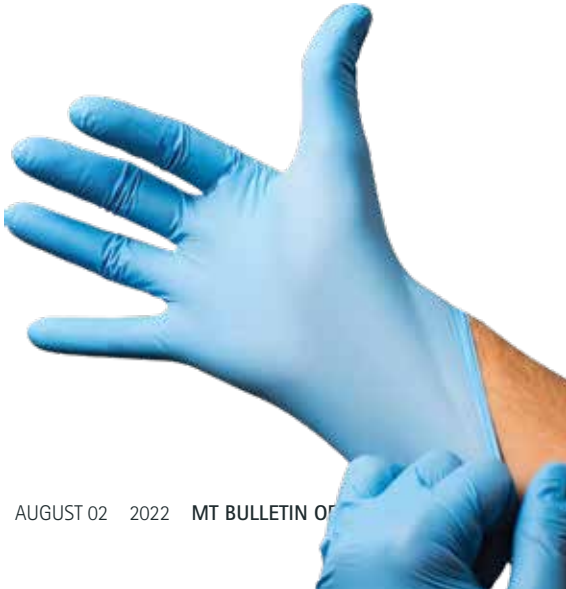
Neurological examination of the legs shows an intact distinction between cold and warm objects, as well as normal vibration sense, but he could not differentiate between blunt and sharp objects. The muscle power and gait could not be tested because of the pain.

In the following two weeks, multiple additional tests were performed. An ultrasound of the abdomen showed a bilateral microlithiasis of the kidneys and a splenomegaly.

Laboratory investigations showed a haemoglobin level of 7.6 mmol/L;

CASE

A 19-year-old man with no prior history of disease presents with general malaise, a fever and progressive pain in his lower legs in the last 4 weeks. Furthermore, he has a headache, is mildly short of breath on exertion, and has a mild stomach ache. He has been vomiting after the consumption of food and has pain on passing urine. For 3 days, he has been unable to walk because of the pain. The patient says he has been working in Ivory Coast as a gold digger for the last 15 months. He received various treatments there including metronidazole injections, ciprofloxacin, tinidazol, anti-malaria treatment, metopimazine for nausea and unknown medication for the cough and the stomach ache. These had no effect, and he is now back in Burkina Faso for medical consultation.



there was a thrombocytosis of 547 x 10^9/L and a mild hyponatraemia of 129 mmol/L. CRP, leukocytes, potassium, liver function tests, glucose and creatinine were all normal. The urine culture showed no growth of bacteria. A CT-scan of the brain was performed in a private clinic which showed no abnormalities. HIV and malaria tests were both negative. The medical doctors in charge could not make a clear diagnosis and asked our specialist panel for help. In the meantime, the patient was admitted to the ward and received paracetamol and vitamin B1, B6 and B12.

SPECIALIST ADVICE

The specialist panel suggested an extensive list of differential diagnoses, which are summarized in 3 groups:

1. Neuropathy, triggered by intoxication (alcohol, drugs, botulism, exposure to toxin such as arsenic, acrylamide, mercury [Hg]) or by deficiency (vitamin B1, B6, B12 {subacute combined neuropathy}).
2. Vascular causes, including vasculitis, arterial obstruction or thrombosis. Since a more extensive physical examination showed no explicit signs for this, these seemed less likely.
3. Infection of unknown origin, although this was considered less likely, considering the low

Table 1: Overview of mostly described symptoms of mercury (Hg) intoxication

MERCURY INTOXICATION	ACUTE	CHRONIC
Metalic / elemental	**Inhalation** · Cough, chills, fever, dyspnoea, tachypnoea, chest pain · Hypoxemia, altered CO diffusion and ventilatory patterns · GIT complaints **Higher concentrations** · Necrotizing bronchitis, bronchiolitis, pneumonitis · Pulmonary oedema, respiratory failure, death **Ingestion** · Only problems if existing mucosal damage of GIT **Subcutanous injection** · Local abscess, granuloma formations **Intravenous injection** · Acute pulmonary or systemic micro-embolism with respiratory failure	**Severe pulmonary complication** · Interstitial fibrosis, residual restrictive pulmonary diseases **Neurologic disorders** · Cognitive impairment · Psychomotor retardation · Personality changes
Inorganic	**Ingestion** · Gastro-enteritis with nausea, vomiting and bloody diarrhoea; metallic taste, local oropharyngeal pain, colic abdominal pain **Inhalation** · Dyspnoea, chest pain, tightness, dry cough · Acute chemical pneumonitis and bronchiolitis **Renal dysfunction** · Polyuria and proteinuria · Nephrotic syndrome	**Gastro-intestinal problems** · Stomatitis, hematemesis, haematochezia, gingivitis, gingival bleeding · Corrosive damage to mouth and throat · Tremor of the lips, tongue, severe salivation, losing teeth, anorexia, weight loss **Neurologic abnormalities** · Tremor, ataxia · Sensorimotor neuropathy · Other neurological symptoms **Renal dysfunction** · Immune complex nephritis. immunological glomerular disease and mercury-induced nephropathy **Cardiovascular** · Hypertension, tachycardia · Coronary heart disease, myocardial infarction, increased carotid intimal medial thickness, carotid obstruction
Organic	**Mild exposure** · No severe symptoms **High exposure** · Acute GIT symptoms · Delayed neurotoxicity regional destruction of neurons	**Placenta** · Neurological and developmental disorders in unborn children
Any form via the skin	**Contact dermatitis** · mild swelling, vesiculation, scaling, irritation, urticaria and erythema	· Allergic contact dermatitis · Pain, acrodynia · Mucocutaneous hyperpigmentation · Purpura

CRP and leukocytes. There were no signs of leprosy; the tests for HIV and malaria were negative.

Because of the history and physical examination, neuropathy seemed most likely. Electromyography for a definitive diagnose was not possible. As happens so often in clinical practice in a resource-limited setting, no final diagnosis could be established.

However, for teaching purposes we discuss the clinical features of mercury (Hg) intoxication, as he had been working as a gold digger, and to emphasize the importance of inquiring about occupational exposure.

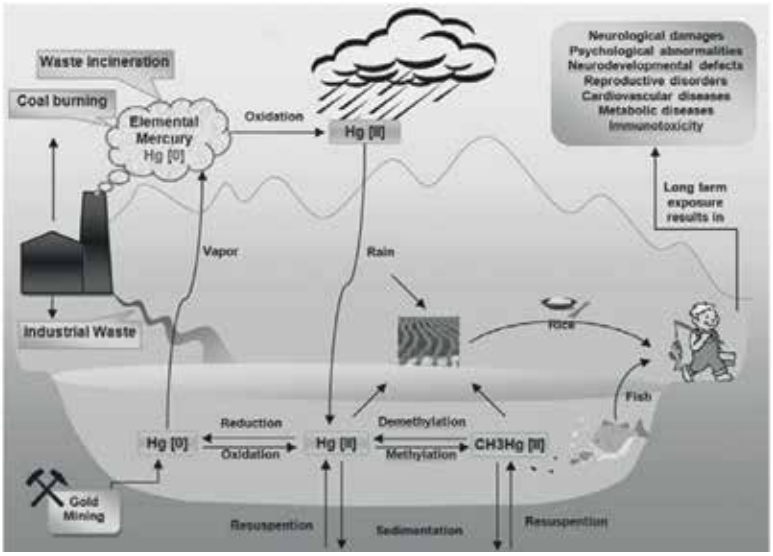


Figure 1. Mercury in the environment. Source: Rafati-Rahimzadeh M, et al. [2]

MERCURY INTOXICATION

Mercury (Hg) has long been admired by humans, as it is not only attractively bright but also the only metal that remains fluid at room temperature. However, mercury is very toxic and may affect many organ systems, including skin, nervous system, cardiovascular, musculoskeletal, genitourinary, and respiratory systems. This broad and non-specific presentation may make it difficult to diagnose a mercury intoxication. [1,2] Since mercury is used for extracting gold, there is a serious risk for mine workers of developing an intoxication. There is also a possible risk of exposure via tooth fillings, vaccines, or eating seafood because of mercury accumulation in fish and shellfish.[3] The chemical form, dosage and duration of exposure to mercury determine the profile of toxicity.[1,4] The different forms are elemental or metallic (Hg 0), inorganic (Hg II) and organic (CH_3Hg II) compounds.[1-4] See Figure 1 for an overview of mercury in the environment. The most important clinical features of mercury intoxication are summarized in Table 1.

DIAGNOSIS AND TREATMENT

Measurement of mercury (concentrations) is possible in plasma, urine, stool and even hair samples. Again, the form of mercury determines the sample: urine for elemental or inorganic mercury, but stool for organic mercury (e.g. methyl mercury).[2]

Treatment is mainly supportive,[1,2,4] and activated coal can be used after acute ingestion.[1] Mercury-specific chelating agents are D-penicillamine (DPCN), dimercaptosuccinic acid (DMSA), 2,3-dimer captopropane-1-sulfonate (DMPS), and dimercaprol (British Anti-Lewisite; BAL).[1, 2, 3] It is important, given the side-effects of these drugs, for the Hg intoxication to be confirmed.[3] Lastly, prevention of exposure to Hg in the environment is of paramount importance.[4]

FOLLOW UP

The patient was admitted, and after 5 days the body temperature normalized and the pain in his legs was almost gone. He kept having poor appetite and vomited after the consumption of food. A gastroscopy was performed and pangastritis with gastroparesis was visible. The specialist indicated this could be part of a combination autonomic/peripheral neuropathy and advised erythromycin. The patient left the hospital feeling better after 1 week. Later biopsies of the stomach showed evidence of *H. pylori* infection but no atrophic cells. At follow-up one year later, he was well and asymptomatic. He did not return to Ivory Coast to work as a gold digger.

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Interview with Albertine Baauw and Barend Gerretsen

In this section, we would like to introduce you to colleagues in global health and tropical medicine. They can include those who already have considerable experience and are looking back at their career or those in a much earlier stage of their professional life – basically anyone who has a story to tell.

In this issue, we had the pleasure to interview Albertine Baauw and Barend Gerretsen, the current and previous head of the training institute for physicians in Global Health and Tropical Medicine (PGHTM) respectively. They shared with us their personal experiences, their views on the role of the PGHTM, and some advice for Global Health professionals.

PERSONAL SKETCH

Barend: "I studied medicine at the VU, where I was one of the first to be able to do a research internship abroad. I had the option of going to either Indonesia or Bangladesh and chose the latter, a choice which, looking back, has had quite an impact on my life. I have developed a weakness for Bangladesh and have been back many times. I was happy I got to work together with a local organisation, a so-called grassroot organisation. This inspired me to continue my career in international healthcare, and I decided to follow the tropical doctor training, together with Albertine.

After the Netherlands Course in Global Health and Tropical Medicine (NTC), I went to Zambia for a couple of months and after that briefly to Mozambique. Eventually, I went to St. Francis Hospital in Turiani, Tanzania, which was quite exciting since my predecessors were well-known tropical doctors. Unfortunately, the collaboration between the hospital and Cordaid Memisa stopped, which highlighted the problems with the sustainability of the hospital and the program that had been set up.

I eventually ended up in public health, working as an educator for KIT (Koninklijk Instituut voor de Tropen, Royal Tropical Institute), as team lead Health Systems Strengthening, and of course as head of the training in Global Health and Tropical Medicine (GH&TM), which I did for seven years. Right now I am on the supervisory board of Amref, a very different role that I enjoy a lot. Due to all my previous experiences, I have a helicopter view of the workings of such an organisation."

Albertine: "I would like to describe my career by means of all the different roles you can have as a PGHTM. My first experience was in Sri Lanka, in gynaecology and obstetrics, where I worked for Doctors without Borders in a big team on the frontline. My role was an *Emergency Aid physician*, which I think is a function that a PGHTM is suitable and prepared for, since they can fulfil many different roles in a big team, which is needed in case of war or natural disasters. Another role I had was in *Public Health* and as a *Clinician* when I worked in Malawi for Cordaid. I was a medical officer but also a public health supervisor. This combination of work is what a PGHTM is trained for. You simultaneously work in the villages with prevention programs and as clinician in the hospital, both of which reinforce one another. As PGHTM, you are trained to be more aware of the social determinants of health and that benefits individual patient care as well.

Another role was in *Advocacy*, as a paediatrician for refugee children in the Netherlands, where I had to think from many perspectives. *Communicator* is an important role since you learn to 'speak the language of many' when you have worked in different settings and locations, and you learn to recognize the patterns that are similar overall. As an *Educator* you have to adjust to the group you work with. In the Netherlands, I would follow a training with only paediatricians, but as PGHTM you learn to involve the whole team in a training. For example, in a LMIC we would teach ETAT (Emergency Triage Assessment and Treatment) to the whole team, including the night watchman, since he will have to alert the doctor if necessary. And there are many more roles a PGHTM can have. Barend, do you have some additions?" Barend: "Initiator!" Albertine: "Yes, as head of the training institute for PGHTM, I love to work with this group of people since they are so energetically devoted as doers starting initiatives. They are able to identify problems and work to solve them. For instance, they look for ways to implement PGHTM in the care for refugees from the Ukraine war, and to connect the public health sector with the curative health care in this setting."

YOUR CONTRIBUTION TO LMICS

Barend: "First of all, the individual patients: being able to save them is quite rewarding although a bit of old-fashioned tropical doctor sentiment. I realized the impact as a doctor in a hospital is quite limited, so this motivated me to do a master's in health systems management and continue my career in Public Health. In my seven years as head of the training institute for PGHTM, I did my best to promote the program since I believe that doctors who are going to work in an LMIC need proper preparation. I think it is unethical to go abroad and work in an unknown setting, unprepared, leading to unsafe situations. Of course, the program still has its shortcomings, but it does teach doctors what not to do in those situations as well."

WHAT INSIGHTS HAVE YOU GAINED THAT ARE USEFUL FOR THE DUTCH HEALTHCARE SYSTEM?

Barend: "I promoted the GH&TM program because I am convinced it

has added value for healthcare in the Netherlands as well as abroad. The PGHTM works in the service of both the Dutch and international healthcare using a lot of skills gained abroad, including intercultural communication. A very obvious role for them is of course during a pandemic, when healthcare problems are not confined within borders and you need doctors with outbreak experience.

We try to develop all those other roles that Albertine mentioned in PGHTM as well, roles that they bring back to the Netherlands with them. What we must keep in mind is that we cannot quantify the added value of a PGHTM for the Dutch healthcare. We must focus on the fact that experience abroad expands your personal skills, knowledge and other competencies which are of value for the Dutch healthcare system."

Albertine: "The NTC has made quite an impact on me, because you focus more on Health Systems and projects. In the course, you have the health resource allocation game, where you construct a health system and see what the impact is on the individual health care. Actually, during the whole GH&TM training, you learn to look at many different perspectives, and implement them in individual health care, which is also of high importance in Dutch healthcare."

FUTURE OF THE PHYSICIAN GLOBAL HEALTH AND TROPICAL MEDICINE

Barend: "Nowadays, we are focusing more and more on other non-clinical competencies such as intercultural communication during the internship abroad. This competency, in particular, is quite a challenge for PGHTMs in training as they start with a lot of clinical work.

I must admit that it remains a challenge to shape the training in the current teaching culture and that we need some goodwill to be able to continue. We have achieved a lot over the years but are in a vulnerable position since we do not receive structural funds. However, I do believe that the training is in a stronger position than before, and I see a bright future for it."

Albertine: "As mentioned before, PGHTMs are very well trained to identify and solve problems that are broader than only one specific interest. For example, right now we are discussing with a PGHTM how this group in the Netherlands can step in to help with the Ukrainian refugees. This crisis also highlights that it is unclear who is responsible in this context. Is it the municipal health services? I believe the PGHTM can act as a bridge between public health and curative health, something that is still lacking in the Netherlands. Additionally, the advocacy role will also become a more important role for the PGHTM abroad and in the Netherlands. Finally, globalisation and global developments demand that we adjust the GH&TM training to the needs abroad and in the Netherlands."

M. Ariaans
D. Krijnen

ADVICE FOR YOUNG PROFESSIONALS IN GLOBAL HEALTH:

"ALWAYS STAY MODEST AND CURIOUS"

"DO NOT THINK YOU ARE GOING TO CHANGE AND IMPROVE EVERYTHING; SMALL STEPS ARE ENOUGH"

"LEARN AS MUCH FROM OTHER CULTURES AND TAKE THIS WITH YOU ABROAD AND BACK TO THE NETHERLANDS"

The Nile

Original title: Nilen. By Terje Tvedt. H. Aschehoug & Co. (W. Nygaard), Oslo, 2021

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English edition: The Nile. History's greatest river. Bloomsbury Publishing Plc 2021, 400 pages

The Greek poet Hesiodus, who lived between 700 and 600 BC, gave the river its name, Nilos (Νείλος), because the numerical value of the Greek letters was 365 – symbolizing ''everything'' as a description of the impact of the giant river not only on geography but also on imagination.

The Nile is the world's longest river (6400 km) as measured from the origin of the White Nile, which originates in Uganda, to the delta at the Mediterranean Sea. The main reservoir is Lake Victoria, to which important tributaries contribute water originating in Kenya, Tanzania, Rwanda, Burundi and Congo. The Blue Nile begins in Lake Tana in the Ethiopian highlands, 2500 km from Khartoum, Sudan, where it joins the White Nile to continue as the Nile (Figure 1). Other important tributaries that receive water from Ethiopia are the Atbara River and the Sebat River. The Blue Nile contributes 80% of all water that eventually reaches Egypt; the water flow is highly seasonal as 90% of all the water flows through the river during 3 months in autumn, which illustrates the need for regulation of flow and reservoirs of water. The Nile has shaped the geographical history and lives of people who live in countries through which the river flows. While its early significance during the pharaonic times was thought to be ''divine'' and a source of life, later Egypt became the granary of the Roman Empire. The river kept its central position in the development and political history of all countries in the region up to the colonial times and after independence. Control

Figure 1. Geographical map of the Nile (Source: Map of the Nile Basin, World Bank, 2013)

of the flow of water has become the subject of political and (threatened) military conflict, as is still the case today. Terje Tvedt has extensively researched the Nile from all angles (historical, geographical, political, economic), and travelled widely to see and experience all major sections of the river in all the countries involved. He starts his travels in Egypt, and from there he travels upstream.

One geographical issue that was only solved in the late 1890s was the origin of the (White) Nile, an enigma that was already mentioned by early writers and historians such as Herodotus. Explorers such as David Livingstone, Henry Stanley and Richard Burton all failed to be the first to see where the White Nile begins its epic journey to flow through Uganda, South Sudan, and Sudan, where it joins with the Blue Nile to continue as the Nile to Egypt and the Mediterranean Sea (Figure 2). It was John Hanning Speke who discovered in 1862 that the White Nile originates at what is now called Jinja in Uganda, where the only outlet of Lake Victoria is located. This is called the Victoria Nile (Figure 3). Stanley reported in 1870 that all other connections of Lake Victoria with rivers are inlets that contribute water to the lake. In 1864, Samuel and Florence Baker discovered that the Victoria Nile described by Speke

Figure 2. The Blue Nile and White Nile join at Khartoum, Sudan to form the Nile (© Archives Rotterdam Center for Tropical Medicine)

flows into Lake Albert to continue as the Albert Nile in north Uganda, which upon entering South Sudan changes its name to the White Nile (Figure 1).

These were colonial times and, while the expeditions were supported by the Royal Geographical Society, the discoveries were important for the British Empire to establish control of the Nile for geopolitical purposes. Often explorers looked upon the indigenous peoples with disdain and ignored their interests. Nile water was essential for growing cotton in Egypt, which became part of the British empire in 1882. Hydro-politics was born. Nilometers were built at various places to monitor the water level (Figure 4). Control of the water flow from upstream was essential for agriculture. Dams were built to regulate the flow of water in the region and, later on, to provide hydroelectric power. After other European powers recognized that the course of the Nile was under British influence, Egypt and London signed the Nile Treaty in 1929, in which the use of water from the Nile was regulated to ensure that Egypt would have the right of vetoing all projects in the British colonies in the region that could decrease the flow of water to the country. As more countries became independent, the validity of this treaty was questioned, and the issue was renegotiated several times. The newly independent countries such as Kenya, Tanzania, Uganda, Rwanda, Burundi, and Congo all would have their say in managing the flow of water in the Nile.

Tvedt describes the history of all the countries subsequently and begins in Egypt. The developments in the past two to three centuries include the building of the first dam by Mohamed Ali,

Figure 3. The origin of the Nile at Jinja, Uganda (© Archives Rotterdam Center for Tropical Medicine)

Figure 6. Tsetse fly (© Archives Rotterdam Center for Tropical Medicine)

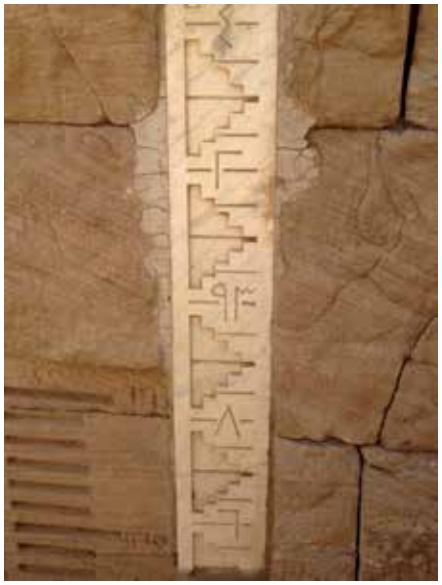

Figure 4. Nilometer at Aswan (Source Wikipedia)

Figure 5. Murchison Falls, Uganda (© Archives Rotterdam Center for Tropical Medicine)

the Mameluke ruler of Egypt, in the 18th century to ensure water flow in his country. British colonial rule in the region was unsuccessfully challenged by Napoleon. Later, the huge Aswan dam was completed when Egypt became independent under Gamal Abdel Nasser.

Tvedt continues to describe important milestones in the history of all the countries involved, during colonial rule or after independence, such as Sudan (the rise and fall of the Mahdi), South Sudan (the unfinished Jonglei canal that would channel the flow of water to prevent evaporation in the Sudd swamp), Uganda (dictatorship of Idi Amin, with floating bodies of killed adversaries feeding the crocodiles), Rwanda (the genocide) and Ethiopia (the fall of Emperor Haile Selassie and his replacement by communist rule, and the recent building of the controversial Grand Ethiopian Renaissance dam in the Blue Nile).

This book is well worth reading for all those interested in the region. While it is well referenced and authoritative, it is rather lengthy as the author elaborates extensively on virtually all topics, which makes it difficult for the reader to remain focused on the main issues. A more concise account would have improved readability. It is also surprising that, despite the extensive geographical and historical descriptions, there are no maps and no detailed index. While the importance of the Nile for people's health in terms of water and food is clearly presented, other health related issues are hardly addressed at all, such as the widespread risk of malaria, Dengue and other vector-borne diseases such as: bilharzia (hyperendemic in irrigation schemes e.g. in Sudan), animal and Human African Trypanosomiasis (HAT) (as evidenced by the presence of tsetse flies at Murchison's falls [Figure 5,6]), and onchocerciasis (Sudan – the former Abu Hamed focus). In addition, crocodiles and hippopotamus attacks are a common threat.

The book ends with an anecdote on changing times; in 2019 (90 years after London, Egypt and Sudan discussed the flow of the Blue Nile, at the height of the British empire), President Trump invited the leaders of the former British colonies to the White House to discuss the controversial Renaissance dam in Ethiopia. Trump suggested that he would be happy to perform the opening of the dam. A better example of the changing political situation would be difficult to find.

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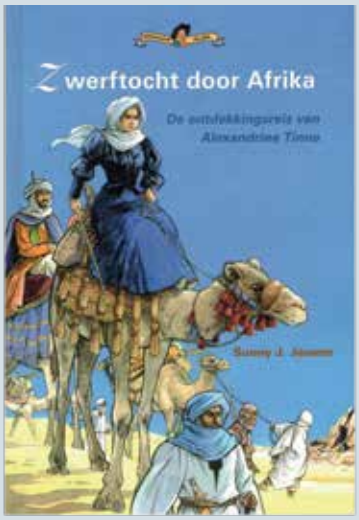
The remarkable story of Alexandrine Tinne – the unlikely explorer

Alexandrine (Alexine) Tinne was born in 1835 in The Hague, the Netherlands. Her family was very wealthy and well connected in circles that included the Royal Family. This was the Victorian age and, unlike what was expected of her, she refused to be married as this would have prevented her from doing what she liked most: travel!
After having explored Europe, she and her mother Henriette travelled through the Middle East, later joined

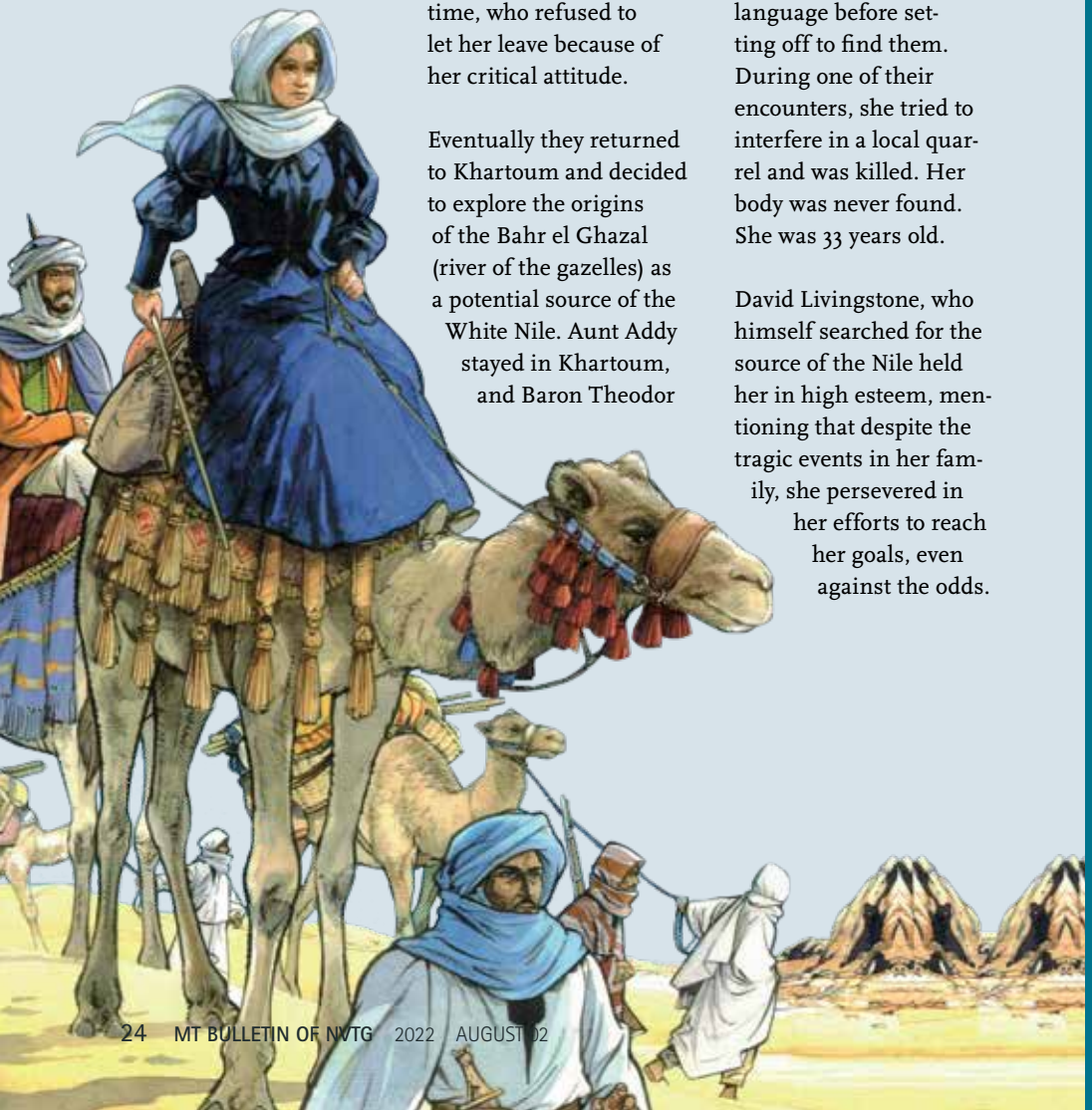


Alexandrine Tinne's journey to explore Africa

→

by her aunt Addy. She developed a passion for photography, exploring the influence of light and shadow. Their adventures were captured in letters that Henriette wrote on a regular basis to her increasingly worried family, relatives and friends, including King Willem I.

She travelled in grandeur; up to 30-40 boxes accompanied her party, including a desk and her iron-bed. Their travels on the Nile from Cairo to Khartoum were fraught with difficulties, including negotiating the Nile cataracts and sandstorms; part of the journey had to be completed by camel.



Nevertheless, the three ladies were always well-dressed and made a lasting impression on everybody they met, and their adventures were covered extensively in international newspapers.

Thereafter, Alexine became obsessed with finding the origin of the White Nile, similar to professional explorers such as Speke and Grant. They left Khartoum by boat and made it to the Sudd in South Sudan. She was shocked to see the horror of the slave trade in what is now South Sudan. Her encounter with slave traders filled her with disgust, and she was held by the slave driver headman for some time, who refused to let her leave because of her critical attitude.

Eventually they returned to Khartoum and decided to explore the origins of the Bahr el Ghazal (river of the gazelles) as a potential source of the White Nile. Aunt Addy stayed in Khartoum, and Baron Theodor von Heuglin and Hermann Steudner joined them as scientists. Then fate turned against her and her party. Her mother Henriette died of fever, as did von Heuglin. Alexine was also ill for weeks and increasingly weak, probably caused by cerebral malaria. She was saved by a rescue expedition sent by her aunt Addy from Khartoum. While preparing to travel back to Cairo, aunt Addy suddenly passed away. She met with her brother John in Cairo and passed to him the dead bodies of her mother, her aunt and 2 female servants. She refused to go back to Europe, and developed an interest in the mysterious Tuareg tribe. She learned their language before setting off to find them. During one of their encounters, she tried to interfere in a local quarrel and was killed. Her body was never found. She was 33 years old.

David Livingstone, who himself searched for the source of the Nile held her in high esteem, mentioning that despite the tragic events in her family, she persevered in her efforts to reach her goals, even against the odds.

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