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NUTRITION AND INFECTIOUS DISEASE

CONTENT

Cover: Young woman in Vietnam
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NUTRITION AND INFECTIOUS DISEASE

That nutritional status influences infection is well-known. Infectious diseases and nutrition have always been intricately linked to each other. However, some recently acquired insights in this field are not yet commonly known. This edition of MT*b* therefore highlights key points on the interaction between nutrition and infectious disease as we wish to raise awareness of how this affects millions of people worldwide. There is especially a need for more attention to nutrition in infection disease research.

This theme was inspired by the course given at VU University under the same name Nutrition and Infectious Disease originally taught by parasitologist Maiza Campos Ponce and Colleen Doak, nutritional epidemiologist and guest editor of this MT*b*. The course integrates two lines of research and exposes students to the complex inter-relationships between nutrition and infectious disease. Other relationships are rather straightforward, for example that good nutrition is important to a healthy immune system and that infections can increase nutritional requirements and contribute to undernutrition. In the past decades, we have gained a better understanding of the complexities through research, in particular into the biological interactions between nutrition and infectious disease.

The articles that we present here reflect current issues and emerging patterns in nutrition and infectious disease. They cover a range of topics related to the complex biological interactions between nutrition and immune function, including vitamin A supplementation, iron metabolism and breast milk. Two articles describe and analyse global patterns, including the emergence of HIV/AIDS and how it interacts with nutritional deficiencies, and the ongoing global epidemic of overweight and obesity. These two patterns have contributed to changes in population health that have also changed the dynamics of the relationship between nutrition and infectious disease. Many countries are experiencing a double or triple burden of disease, in which infectious disease and undernutrition – including micronutrient deficiency – co-exist with overweight and obesity. The phenomenon of undernourished children living in the same household as overweight or obese adults has been well documented as a global pattern that reflects the convergence of infectious disease, undernutrition and overweight/obesity in conditions of poverty. The paper on maternal vaccination and breast milk antibodies shows that there are ways to enhance the immunity of newborns, providing an extra reason to promote breastfeeding.

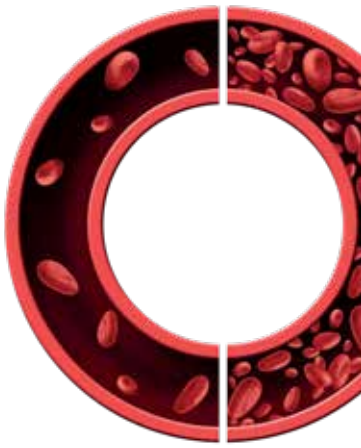
Enjoy your reading!

COLLEEN DOAK (GUEST EDITOR)
ANNEFLEUR LANGEDIJK

THERE IS A NEED FOR MORE ATTENTION TO NUTRITION IN INFECTION DISEASE RESEARCH

Peru Machu Picchu

The history of anaemia and infectious disease: *Past and present*



The shift from hunter gatherer to agricultural societies brought two fundamental changes in human diet and social structures. First, by producing surplus grains, agriculture stimulated population growth and greater population density, contributing to infectious disease.[1] Secondly, because early agricultural societies were largely reliant on a limited number of staple grains, the diet became less diverse and of poor nutritional quality as compared to previous hunter gatherer societies.[1] Figure 1 is a simplified schematic explaining why, historically, the shift from hunter gatherer to agricultural societies contributed to an increase in nutritional deficiency and infectious disease. These patterns are verified in the archaeological record, in which the emergence of agricultural societies coincides with evidence for nutritional deficiencies and infectious disease.

In addition to their historical convergence, poor nutrition and infectious disease are also intertwined due to additional complex biological interactions. This article focuses on the history of one of the seminal topics in the field of nutrition and infectious disease, specifically the relationship between infections and anaemia. In this overview, I begin with the archaeological evidence linking anaemia with infectious disease and then shift to the modern public health context of iron-deficiency anaemia caused by infectious disease. Finally, I discuss anaemia in relation to obesity, triggered by the inflammation stimulated by adipocytes, contributing to a pattern of obesity & micronutrient deficiency co-existing in many countries where infectious disease is highly prevalent.

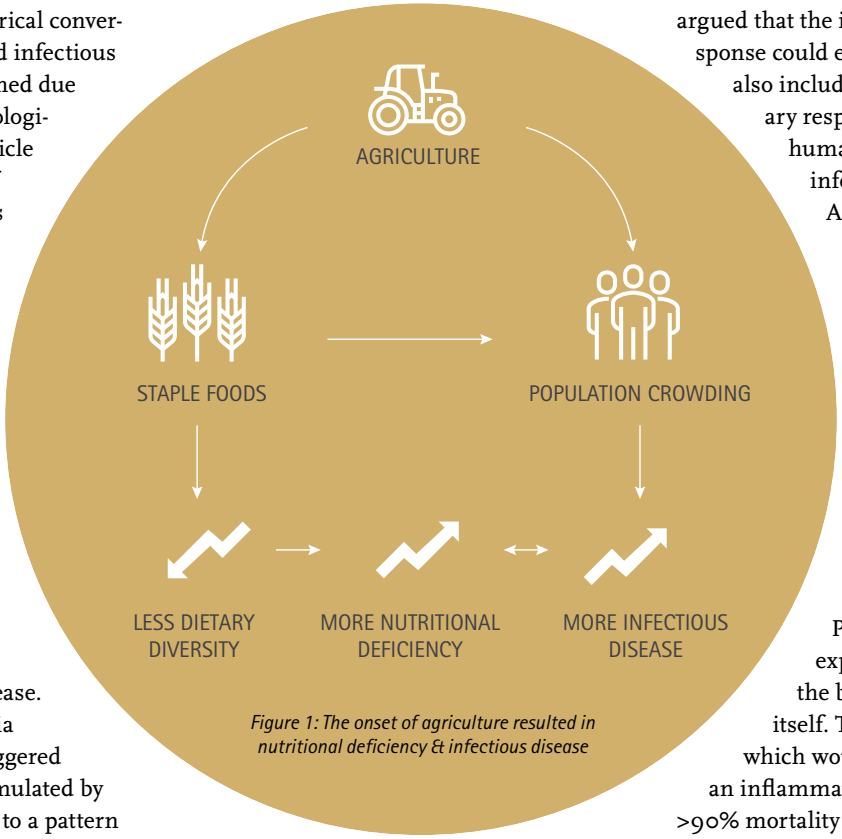


Figure 1: The onset of agriculture resulted in nutritional deficiency & infectious disease

ANAEMIA IN ANCIENT PERU

Until the last decade, archaeologists identified anaemia through malformations of the skull, known as porotic hyperostosis and cribra orbitalia. Porotic hyperostosis is an expansion of the bone marrow (hyperostosis) combined with bone pitting (porotic bones) on the sides of the parietal and temporal bone of the skull. Cribra orbitalia is a similar porous expansion, as seen with porotic hyperostosis, but located at the orbits (eye socket). These changes in skeletal remains were identified more than five decades ago as being consistent with the cranial bossing that is seen in genetic anaemias such as beta thalassemia. [2] More recent studies have also shown patterns in the occurrence of cribra orbitalia, corresponding to anaemia related to malaria.[3,4] Given the similarities in the physiological response and the co-occurrence in the archaeological record, porotic hyperostosis and cribra orbitalia were both seen as indicative of anaemia . In South America, bio-archaeologists have wondered why these skeletal malformations occurred so frequently in pre-Columbian populations. What was the cause? In answering this question, archaeologists focused first on dietary causes, especially iron deficiency.[1] Specifically, the cause was assumed to be related to the dependency on plant-based diets. Along with the onset of agriculture, early populations became reliant on a diet rich in the plant fibres (e.g. phytates) that inhibit the absorption of non-haeme sources of iron (i.e. iron from plants).

In the early 1990s, Stuart-Macadam [5] added to the debate by calling attention to the known relationship between inflammation and anaemia, drawing the attention of bio-archaeology to the anaemia of inflammation. She argued that the porotic hyperostosis and cribra orbitalia found in past populations were likely to have been caused by infection through biological mechanisms stimulated by inflammation. This process, known as the iron withholding mechanism, is part of the immune response, stimulated by interleukin 6 (IL-6). This mechanism maintains iron stores while withholding iron from parasites such as Plasmodium, which thrive in an iron-rich environment. Stuart-Macadam argued that the iron withholding response could explain the anaemia, but also included it as a vital evolutionary response protecting early humans against parasitic infections such as malaria.

As a Master's student, I explored whether porotic hyperostisis and cribra orbitalia could be explained by infection. I considered whether a specific malaria-like endemic disease caused by *B. bacciliformis* could be an explanation for the anaemia found in pre-Columbian Peru. Ultimately, the explanation did not fit the biology of the disease itself. The phase of the disease which would have triggered an inflammatory response has a >90% mortality rate. Few survivors would have displayed the bone changes that are found in the archaeological record, as these are most likely to occur during the recovery phase.

However, in delving into the early history of anaemia and the thinking about anaemia amongst bio-archaeologists, I became aware of and interested in the complex biological relationships between nutrition and infectious disease. Since my days as a Master's student in anthropology, the thinking in archaeology has changed. Now, porotic hyperostosis and cribra orbitalia are thought to be distinct conditions, reflecting nutritional deficiency and infectious disease respectively. Walker et al [6] proposed the theory that porotic hyperostosis is largely caused by a deficiency of one or more of the water soluble vitamins, such as folate, B-12 or vitamin C, but is not related to iron deficiency. They argue that the bone changes of porotic hyperostosis are more in line with megaloblastic forms of anaemia, such as pernicious anaemia from B-12 or folate deficiencies. Cribra orbitalia, on the other hand, occurs in patterns more closely related to infectious disease. In spite of the change in the thinking about the aetiology, archaeologists

agree that both conditions co-existed largely because infection and undernutrition also coincided historically.

LOWER-INCOME POPULATIONS IN LOW AND MIDDLE INCOME COUNTRIES ARE ALSO INCREASINGLY AT RISK OF OBESITY

IRON DEFICIENCY AND MALARIA: COMPLEX PUBLIC HEALTH ISSUES

The connection between anaemia and infectious disease continues to be an important concern. While some parasites directly contribute to anaemia by parasitizing and rupturing the blood cells, parasites that trigger the IL-6 response contribute to iron deficiency anaemia through the anaemia of inflammation described above. Furthermore, some parasitic infections that cause intestinal bleeding, such as hookworm, contribute to iron deficiency anaemia through blood loss. In addition, infections that cause diarrheal symptoms limit the absorption of nutrients while also increasing nutritional losses. Together, these relationships explain multiple pathways through which infections contribute to both anaemia and iron deficiency. In malaria endemic areas, these relationships lead to complex public health questions related to where and when iron supplements are appropriate. Although iron is important to immune functions [7], studies have shown that high iron (serum ferritin) at baseline was associated with an increased risk of malaria (*Plasmodium falciparum*) at follow-up.[8] Supplements can increase the risk associated with some parasites by providing an iron-rich environment. In a review of the evidence, the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria endemic areas advised against wide-scale iron supplementation in malaria endemic areas.[9]

OBESITY CONTRIBUTING TO ANAEMIA

The anaemia of chronic inflammation is also referred to as the anaemia of chronic disease due to the prolonged inflammatory responses related to overweight or obesity. In the past, the anaemia of chronic disease was a concern of wealthy countries or of higher-income populations within low and middle income countries. However, due to changes in the economy and the food supply, known as the nutrition transition [10], lower-income populations in low and middle income countries are also increasingly at risk of obesity.[11] Thus, the populations that are most at risk for the anaemia of chronic disease are most likely to be consuming foods that are energy dense but of poor nutritional quality, also resulting in a diet poor in iron. Due to these patterns, iron deficiency anaemia is exacerbated by a combination of inflammatory responses related to increases in body fat, changes in the global food supply and, in countries where parasites remain endemic, infectious disease.

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Nutrition, food security and HIV/AIDS

Most medical professionals will correctly answer the question 'Is HIV the cause of AIDS?' by stating that an infection with Human Immunodeficiency Virus (HIV) will cause Acquired Immunodeficiency Syndrome (AIDS) by impairing the human immune system. However, the answer to this question and thereby the prevention of an HIV infection is more complex than this.

EPIDEMIOLOGY OF HIV/AIDS

In 2016, 1.8 million people became newly infected with HIV, adding to the current total of 36.7 million people living with HIV.[1] Since the identification of HIV in 1981, 35 million lives have been lost to HIV/AIDS. One million people died from HIV-related causes globally in 2016.[2] The global scale-up of antiretroviral therapy, including higher treatment coverage and increased adherence to this treatment, has been instrumental in a 48% decline in deaths from AIDS-related causes in the last decade[1]. This therapy plays an important role in controlling the virus, slowing down the progression of AIDS and preventing HIV transmission, thereby ensuring that people living with HIV as well as those at risk can enjoy healthy and productive lives.[2,3] Although there is currently no cure for HIV, one of the Sustainable Development Goals is to end the AIDS epidemic by 2030. The UNAIDS 90-90-90 targets form an important part of this goal: 90% of HIV infected people will be diagnosed, 90% of the diagnosed people will receive antiretroviral treatment, and 90% of the people receiving treatment will be virally suppressed, all by 2020.[4] Currently an estimated 70% of people infected with HIV are aware of their status and 77% of these receive treatment.[1] This translates into 54% of adults living with HIV worldwide having access to lifelong highly active antiretroviral therapy (HAART).[2] Of the people receiving treatment, 82% are virally suppressed.[1] Although this is a remarkable achievement, there is still much more to do. In order to maintain a healthy and good quality life and to improve survival for individuals infected with HIV, nutrition and food security play an important role. The bi-directional relationships and interactions between HIV/AIDS, nutrition and food security are complex.[5] As is shown in Figures 1, 2 and 3, the HIV epidemic largely overlaps with populations who are malnourished and do not have or are at risk of not having access to sufficient quantities of good-quality food.

NUTRITION AND HIV/AIDS

Nutritional status affects the maintenance and optimal functioning of the immune system and therefore the health status and progression of HIV/AIDS. Early in the HIV epidemic, slim disease, as a result of protein-calorie malnutrition (wasting) with depletion of lean mass, fat, and micronutrients, was a condition associated with chronic diarrhoea and/or prolonged fever. Malnutrition and hunger increase vulnerability to HIV by weakening the body and the immune system and may lead to shortened survival and diminished quality of life. For those who have already been infected with HIV, malnutrition enhances the risk of opportunistic infections and a further and faster progression of AIDS. An HIV infection may cause decreased food intake (caused by pain during eating and vomiting for example), nutrient malabsorption, metabolic alterations, and increased energy and protein requirements. This leads to several complications, among which wasting has been established as a strong predictor of mortality in HIV-infected people, as already recognized early in the epidemic.[6] In addition, malnutrition can reduce the effectiveness and acceptance of HAART and other therapies.[7] Good nutritional status can strengthen the immune system and increase resistance to (opportunistic) infections related to HIV/AIDS, whereas malnutrition has the opposite effect.[8]

FOOD SECURITY AND HIV/AIDS

Poverty-induced malnutrition and HIV are related to food insecurity, as it is more difficult to obtain nutritious food that keeps HIV infected people healthy for longer periods in resource-poor settings. Food security is an important concept that extends beyond the individual and relates not only to good-quality food intake but also links it to health, (sustainable) economic development, environment and trade.[9] In relation to the different aspects contributing to the concept of food security, different definitions for food security exist. The one most used is a refined version of the one developed at the World Food Summit in 1996: 'Food security [is] a situation that exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life'. [10] In 2016, 687 million people were affected by severe food insecurity, and an estimated 815 million people were undernourished globally.[9] HIV infection reinforces pre-existing food insecurity while food insecurity may increase vulnerability to HIV. Hunger and poverty are determinants of risky 'survival activities', such as prostitution, migration and dropping out of school at an early age, increasing the risk of acquiring HIV.[11] Most HIV infections occur in people between the ages of 20 years and 29 years, also the peak childbearing years. This has a systemic impact on the social and economic systems in countries affected by AIDS, and these effects extend to children and their wider families. In addition, people infected with HIV and their families also face stigma and discrimination. Being infected with HIV can result in not being able to work leading to a decrease in food production or income for the household. In addition, the costs of health care utilisation, lost income due to care for people infected with HIV, funeral costs, and the care for orphans lead to more poverty and hunger and eventually to more food insecurity.[9,12]

Understanding the context of the cause of a disease can be the difference between life and death, especially in the case of AIDS. HIV does not necessarily

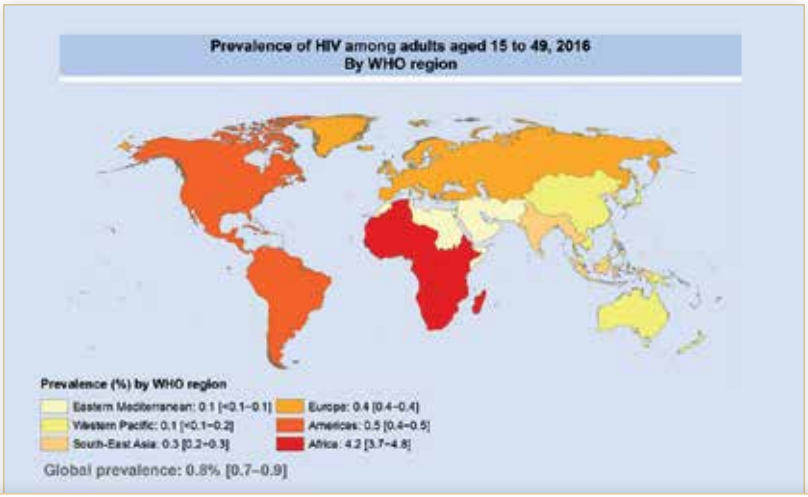

Figure 1: Prevalence of HIV among adults aged 15 to 49, 2016 by WHO region.

Source: World Health Organisation/ Information Evidence and Research (IER).[13]

Maps showing overlap in prevalence of HIV, food insecurity and undernutrition.

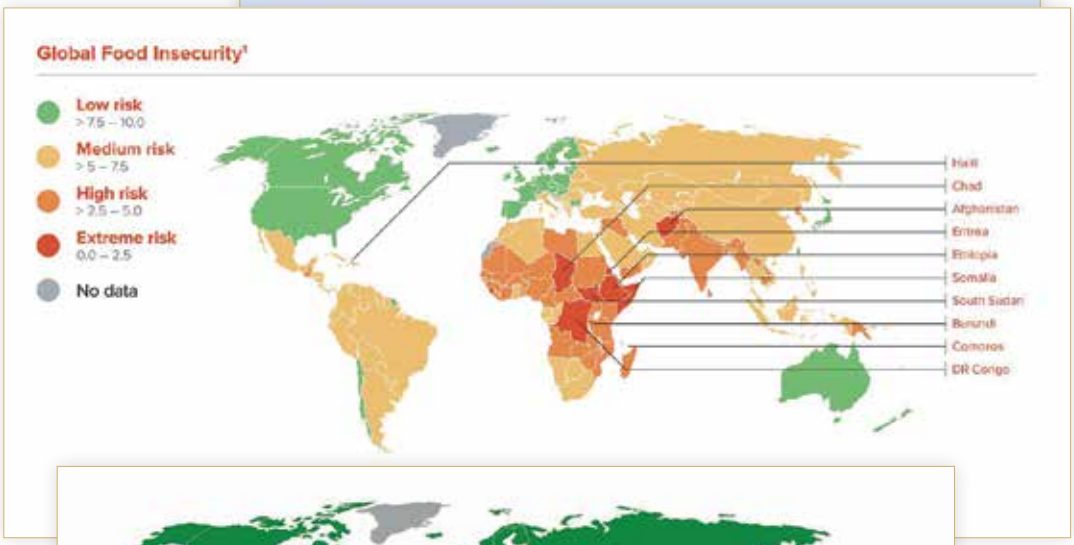

Figure 2: Maplecroft's Food Security Risk Index 2013.[14]

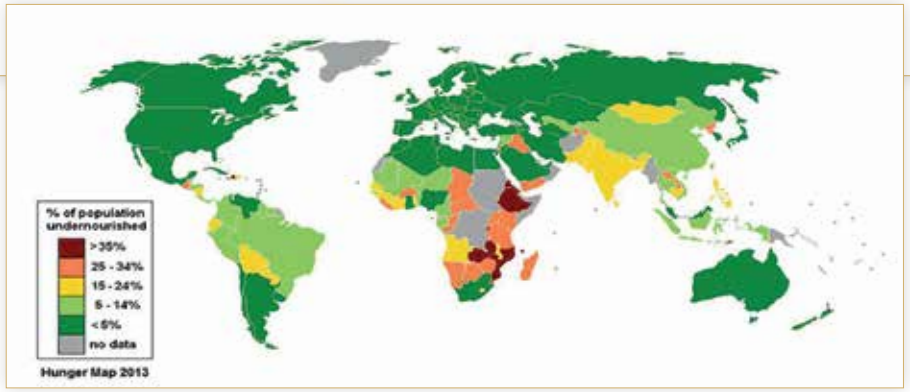

Figure 3: Estimated proportion of population that is undernourished.

Source: United Nations World Food Programme.[15]

lead to AIDS if the infected person is well-nourished and in a good physical condition. Hence, addressing malnutrition and food insecurity is crucial in mitigating the impact of HIV and the households and communities affected 5 and must be tailored to specific settings.[11] One individual HIV infection, especially in combination with malnutrition and food insecurity, causes a ripple effect with enormous consequences for that particular person, the household, the wider community and the country as a whole.

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Coexistence of obesity, micronutrient deficiencies and intestinal parasites in rural communities of Mexico: Preliminary study findings

The rapid growth of childhood obesity rates is one of the most challenging public health problems in Mexico and other middle-income countries. Low-income groups living in rural communities of Mexico often consume processed, energy-dense foods of poor nutritional quality at relatively low prices.[1] Children from these communities are more likely to become overweight or obese and to develop micronutrient deficiencies as well. In addition, they are at risk of intestinal parasitic infection due to their poor sanitation and education.[3] Hence, children from these communities may have co-existing obesity, micronutrient deficiencies and intestinal parasitic infections.

Obesity, micronutrient deficiencies and intestinal parasitic infections are 'insults' or stress factors that are associated with impaired development, systemic inflammation and metabolic changes in the short and long term.[3-5] The prevalence of each of these conditions was investigated in the global burden of disease study, which found that obesity (3.9%), micronutrient deficiencies (6.1%) and intestinal protozoa infection (5.7%) accounted for more than 10% of the global burden of disease.[3-5] Given the high rates in Mexico of overweight and obesity (more than 30% in children), micronutrient deficiencies (13% iron and 26% zinc deficiency) and parasitic infection (more than 50% of the population) [6-9], the large proportion of the Mexican population living in poverty (46% or 58 million) or in rural communities (20% or 25 million), and the possibility of a summative adverse effect on health of co-existing conditions, it is highly relevant to assess how many children have two or three of these conditions simultaneously. Thus, the objective of our study is to establish the proportion of children in rural Mexico living with co-existing micronutrient deficiency, high body fat and parasitic infection.

34% OF THE CHILDREN HAD AT LEAST ONE MICRONUTRIENT DEFICIENCY

MATERIALS AND METHODS

SUBJECTS AND STUDY DESIGN

A cross-sectional study was conducted involving a total of 301 primary school children (6-10 years of age), recruited from primary schools in two rural communities of El Marques in the State of Queretaro. The main ethnicity of the population is mestizo, and their main economic activity is agriculture. Caregivers received oral and written information about the study and provided informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Human Research Committee of the School of Natural Sciences at the Universidad Autónoma de Querétaro (UAQ). Children's parents or legal guardians (i.e. caregivers) were asked to attend their local health clinic to complete a medical history and a socioeconomic status questionnaire. Children who had received any deworming treatment in the previous four months or who had any physical or mental disability were excluded from the study.

ANTHROPOMETRY AND BODY COMPOSITION

Weight and height were measured in duplicate in line with World Health Organization (WHO) guidelines. Weight was determined using a calibrated digital scale (SECA Mod. 813, Hamburg, Germany) and height was measured with a portable stadiometer (SECA Mod 206, Hamburg, Germany). Whole body composition was measured to determine body fat percent, using dual-energy X-ray absorptiometry (DXA) (Hologic Mod Explorer, Bedford, MA, USA). The cut-off point for high body fat (HBF) was 30% for girls and 25% for boys.

INTESTINAL PARASITIC INFECTION

A direct copro-parasitological test consisting of a wet mount with iodine staining of slides was performed to screen and identify intestinal protozoa parasites, as described by WHO. A Kato-Katz smear (2 x 25 mg = 50 mg) was performed according to standard procedures to determine the presence of eggs of intestinal helminths. Children with helminth or protozoa infection were sent to the local clinic to receive treatment.

MICRONUTRIENT DEFICIENCY

Vitamin A, E and C blood levels were measured by reverse phase high pressure liquid chromatography (HPLC). Children with retinol concentrations <10 µg/dL were considered Vitamin A deficient, those with concentration of alpha-tocopherol <3 µg/mL were considered Vitamin E deficient, and children with concentrations of ascorbic acid <2 µg/mL were considered Vitamin C deficient. Furthermore, serum vitamin D was determined by a commercial 25 (OH)-Vitamin D direct ELISA kit (Immundiagnostik AG, Bensheim, Germany). Children with Vitamin D concentrations <50 nmol/L were considered Vitamin D deficient. Total iron concentration in serum was measured using a commercial kit (Iron Ferrozine, Elitech, Sées, France) and a spectrophotometer (Perkin Elmer, Mod Zeeman 5100). Children with iron concentrations <45 µg/dL were considered deficient. Zinc concentrations were measured in serum by atomic absorption spectrometry (AAnalyst 7000, Perkin Elmer Instruments, Norwalk, CT, USA). Zinc deficiency was defined as zinc plasma concentrations <65 mg/L. Children with any of the above micronutrient deficiencies (Vitamin A, E, C, D, total iron or zinc) were considered micronutrient deficient.

RESULTS

Most of the children (88%) examined were from low or middle-low socioeconomic status households. We did not find differences in crowding, socioeconomic status or caregiver's educational level among the children with none, one, two or three co-existing conditions. 34% of the children had at least one micronutrient deficiency; the most prevalent deficiencies were vitamin D (19%) and zinc (12%). 12% had more than one micronutrient deficiency. 53% of the children had at least one intestinal parasitic infection, the most prevalent being Entamoeba coli (22%), Endolimax nana (19%) and Ascaris lumbricoides (16%). 54% had high body fat. 12% had co-existing parasitic infection and micronutrient deficiencies, 20% had co-existing high body fat and parasitic infection, and 5.6% had co-existing micronutrient deficiency and high body fat. Most importantly, almost 14% of the children had all three conditions co-existing, i.e. micronutrient deficiency, parasitic infection, and high body fat (Figure 1).

DISCUSSION

The percentages of children with two or three co-existing conditions are alarming. These children are at risk of systemic inflammation, impaired growth, poor intellectual development, chronic diseases and a summative negative effect on quality of life.[10,11] A clear example of this are micronutrient deficiencies, which not only cause

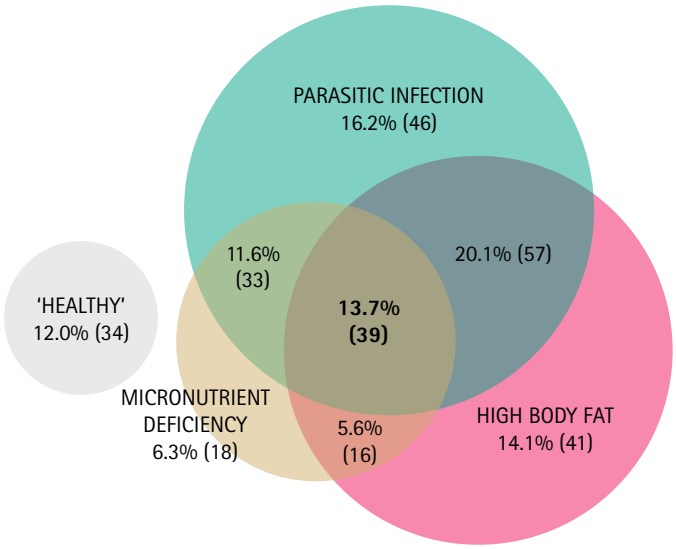

Figure 1. Combined prevalence of high body fat, micronutrient deficiency and protozoa infection in children (N=284).

specific diseases but also exacerbate infectious and chronic diseases, thereby increasing morbidity and mortality.[11]

The high prevalence of malnutrition and intestinal parasitic infection is likely to be related to poverty. The poorest people have a high risk of parasitic infection due to their lower level of education, poor sanitation and less access to health services.[2] Low-income groups living in rural communities in Mexico consume processed foods with heavy caloric content but poor nutritional quality. In our study region, they usually obtain their food from family-owned convenience stores that offer a wide range of calorie-dense foods and fried 'junk' food at relatively low prices. Children in particular are highly exposed to and influenced by visual cues present in these convenience stores - not only outside the store, where manufacturers of the main brands of 'junk food' advertise their products, but also on the shelf, where these 'junk food' brands advertise their products with promotions, plastic cartoon characters, and colourful labels (Figure 2). Other studies have associated the intake of these kinds of products (energy-dense and of low nutritional quality) with both obesity and micronutrient deficiencies.[12,13]

Given the high prevalence of co-existing malnutrition (i.e. high body fat and micronutrient deficiency) and parasitic infection, and the frequent co-existence of these conditions in the study population, there is a case to make for examining how widespread this problem is elsewhere in Mexico. Authorities and policy makers should be aware of these important public health problems. Strategies that have proven to prevent these problems in other settings and might be helpful for Mexico are decentralized public health policies including education, better living conditions including sanitation, programmes that promote healthy diets, and better access to healthy food.[2,14]

CONCLUSION

We found high prevalences of high body fat, micronutrient deficiencies, and intestinal parasitic infections as well as a frequent occurrence of these conditions simultaneously. Studies in other communities and municipalities in Mexico are needed to assess how widespread this problem is. Since the three conditions predispose to various diseases and disabilities, they need to be taken into consideration in future health and community programmes in Mexico.

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Inclusion of vitamin A supplementation in routine vaccination programmes not straightforward

There are many aspects one should scrutinize when new health interventions are implemented in low-income settings; especially since health interventions are usually developed in high-income countries, where circumstances are different. The combination of vitamin A supplementation and immunization, two existing interventions that are usually implemented separately, is in fact a novelty. So far, there are contradictory findings on vaccination and subsequent non-specific morbidity, and whether the simultaneous administration of vaccination and vitamin A could amplify any of these non-specific effects.

Immunization reduces childhood disease by preventing a certain infectious disease. Vaccines stimulate, we may even say trigger, the adaptive immune response to ensure a fierce reaction on a second encounter with a pathogen. Edward Jenner, the pioneer of the small pox vaccine in the late 18th century, discovered that this strategy, back then quite controversial, could save many lives. Vaccination is a powerful early life intervention, especially in countries where the burden of infectious disease is high. But since vaccines are mostly developed in high-income countries, the question arises whether they are equally suitable in low-income countries, in particular since in low-income settings the burden of disease is conditioned by infectious diseases, poverty and malnutrition.

The vaccines widely used in routine vaccination programmes include: Bacillus Calmette-Guérin (BCG; for protection against progression of tuberculosis), measles vaccines (MV), and whole-cell diphtheria-tetanus-pertussis vaccines (DTP). Since the early 90s, several studies have reported so-called non-specific effects (NSEs) associated with these vaccinations among children in high mortality areas.[1-3] The hypothesis on NSEs is that certain vaccines alter the susceptibility to unrelated infectious disease besides protecting against the targeted disease.

NSEs vary for different vaccines. Beneficial NSEs have been reported for live attenuated vaccines such as BCG and MV. 'Attenuated' simply means that the harmful (virulent) part of the pathogen is altered or taken away. Children who received these vaccines are reported to have reduced illness from unrelated infectious diseases.[4,5] However, several studies have reported that DTP vaccines may have harmful NSEs.[2,6] DTP is an inactivated vaccine, meaning the pathogen has been killed. The inactivated vaccine is still recognized by the immune system, thereby provoking an adaptive immune response. A recent study has linked DTP vaccination, if administered as the most recent vaccination, to increased susceptibility to other infectious diseases,[2] especially among girls.

TRAINED AND HETEROLOGOUS IMMUNITY

The specific mechanisms behind NSEs are not known although there are several theories. It is postulated that vaccines could induce 'trained immunity' and 'heterologous immunity', thereby increasing resistance or susceptibility to other pathogens.[7,8] Live vaccines are believed to induce trained immunity. This concept roughly means that the innate immune system helps fight against unrelated infectious diseases by a somewhat adaptive characteristic, or 'epigenetic reprogramming of innate immune cells'.[8] The hypothesis regarding heterologous immunity is that 'mediated cross-reactivity of T-lymphocytes' could affect the immune response of an unrelated infection. This can be either beneficial or, as hypothesized with DTP, could impair the desired immune response.

VITAMIN A SUPPLEMENTATION

Vitamin A deficiency is widespread in low-income countries where NSEs are reported. It can be a severe problem leading to blindness and a deprived immune system.[1] Therefore, vitamin A supplementation is recommended by the World Health Organization in children from six months onwards in areas with high levels of deficiency.[9] It is often provided simultaneously with routine vaccinations. The efficacy of vitamin A supplementation varies depending on the age at which the supplements are given.[1] Since vitamin A is immunomodulatory, which means that it modulates the immune system, it is suggested that supplementation could amplify the child's ongoing immune response.[1] For live vaccines this would indicate that the aforementioned beneficial NSEs are amplified, while harmful effects would be amplified in the case of inactivated vaccines.[10]

CLARITY IS NEEDED

Regarding vitamin A supplementation, there is a need to distinguish between the effects on vitamin A status and the effects of its interaction with vaccination on the amplification of NSEs. Currently, we are investigating such interactions by using data sets from several Southeast Asian countries. Preliminary results of our analysis of data from Cambodia indicate divergent directions of the associations between vaccination and morbidity for several vaccines. Children with BCG had less morbidity as compared to children who did not receive the BCG vaccine. On the other hand, girls who received DTP vaccination had a slightly higher prevalence of acute respiratory infections than girls

who did not. Among girls who received DTP vaccination, vitamin A supplementation was associated with slightly higher rates of acute respiratory infections compared to non-supplemented girls, although this association was not statistically significant. Recipients of measles vaccines had slightly less morbidity than unvaccinated children, especially when combined with vitamin A supplementation.

CONCLUSION

Careful scrutiny of the possible combination of vitamin A supplementation and vaccination programmes, which takes into account the beneficial and harmful NSEs of various vaccines, could have a major impact on child survival in low-income countries. More evidence on this topic is emerging, but the exact mechanisms need to be further unravelled.

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Maternal vaccination and breast milk antibodies for enhancing immunity against respiratory diseases in the newborn

BREASTFEEDING AND PNEUMONIA

Pneumonia is one of the major causes of childhood mortality, accounting for 1.4 million deaths under the age of 5 years in 2010.[1] The majority of these deaths occur in developing countries.[2] However, an intervention as simple and low-cost as breastfeeding may substantially reduce this mortality burden. Feeding practices for young infants have an important impact on health outcomes. In particular, infants who are exclusively breastfed have fifteen times less chance of dying of pneumonia than infants who are not breastfed.[3] Besides protection from disease, breastfeeding is also associated with other positive outcomes, ranging from better cognitive development, educational performance, nutritional status and more.[4]

The beneficial effects of breast milk are well recognized by international health organizations and in the public health community. Evidence supporting the advantages of breastfeeding has increased over the past years. The World Health Organization (WHO) recommends starting exclusive breastfeeding within one hour after birth and throughout the first six months of life. Furthermore, WHO recommends continuation of breastfeeding with complementary food up to two years of age and beyond.[5] An increase of breastfeeding practices worldwide would significantly reduce childhood morbidity and mortality.

ANTIBODIES IN BREAST MILK

We had the chance to study breast milk samples from a unique cohort of postpartum women from a maternal vaccine trial conducted in the rural Sarlahi region in Nepal. More than 3,500 pregnant women were enrolled in a maternal influenza vaccine trial between 2011 and 2013.[6] Both mothers and their infants were tested for respiratory syncytial virus (RSV) throughout the first six months postpartum by taking nasal swabs at any moment of respiratory illness. We developed a tool to measure antibodies in breast milk. The research question was whether mothers of infants who become sick in the first months of life have lower levels of antibodies in breast milk than mothers of infants who stay healthy. If this is the case, then antibodies in breast milk may be a mechanism via which maternal vaccines could protect young infants, in addition to well characterized antibody transfer across the placenta.

> AN INTERVENTION AS SIMPLE AND LOW-COST AS BREASTFEEDING MAY SUBSTANTIALLY REDUCE THE MORTALITY BURDEN IN DEVELOPING COUNTRIES

RSV infection is the second biggest cause of death in the infant period, second only to malaria. More than 99% of the mortality occurs in the developing world.[7] Currently, a maternal RSV vaccine is being tested in phase III clinical trials, and other promising candidates are also in clinical development. The transfer of antibodies against RSV via the placenta has been studied in different populations. However, it is essential to understand whether antibodies against RSV also protect the neonate via breast milk after birth.

MATERNAL VACCINATION

Maternal vaccination has emerged as a promising health intervention to combat infant morbidity and mortality among children too young to be vaccinated.[8] Several maternal vaccines are already being implemented for different diseases. For example, since 1999 maternal tetanus toxoid vaccination has been a very effective intervention to eliminate maternal and neonatal tetanus.[9] In 2012, WHO proclaimed that pregnant women are the highest-priority group for receiving influenza vaccination.[10] Maternal pertussis vaccination is implemented in several countries including the United States, the United Kingdom and Belgium. In addition, several vaccines are in development for implementation in pregnant mothers including maternal vaccines for Group B Streptococcus (GBS), respiratory syncytial virus (RSV), herpes simplex virus (HSV), congenital cytomegalovirus (CMV), and hepatitis E virus. Whereas maternal vaccines against GBS and RSV primarily aim to protect the infant from infection after birth, vaccines against HSV and CMV target women before conception, as primary infection during pregnancy is associated with poor foetal outcomes. Maternal vaccination boosts the levels of naturally occurring antibodies in the mother, allowing for greater transfer of protective immunity to the infant.

PROTECTING THE NEWBORN AND THE INFANT

In conclusion, current immunization schedules around the world are saddled with an immunity gap in the first months of life, a period

when infants are also vulnerable to infectious diseases. Maternal immunization may be a key tool in allowing vaccination schedules to bridge this gap by passively immunizing the newborn via the mother. Breast milk plays a key role in protecting young infants from infectious diseases and may also play a role in the protection conferred from maternal vaccination.

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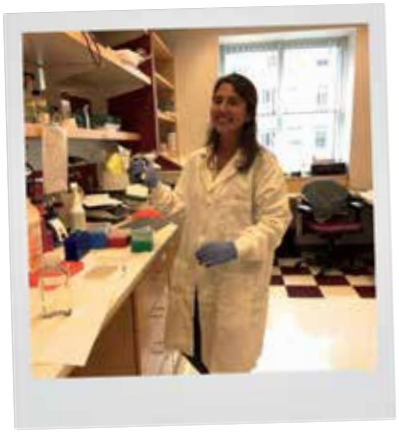

Natalie Mazur working in the University of Washington Harborview Medical Center laboratory after receiving a KNAW (Dutch Academy for Medical Sciences) ter Meulen scholarship.

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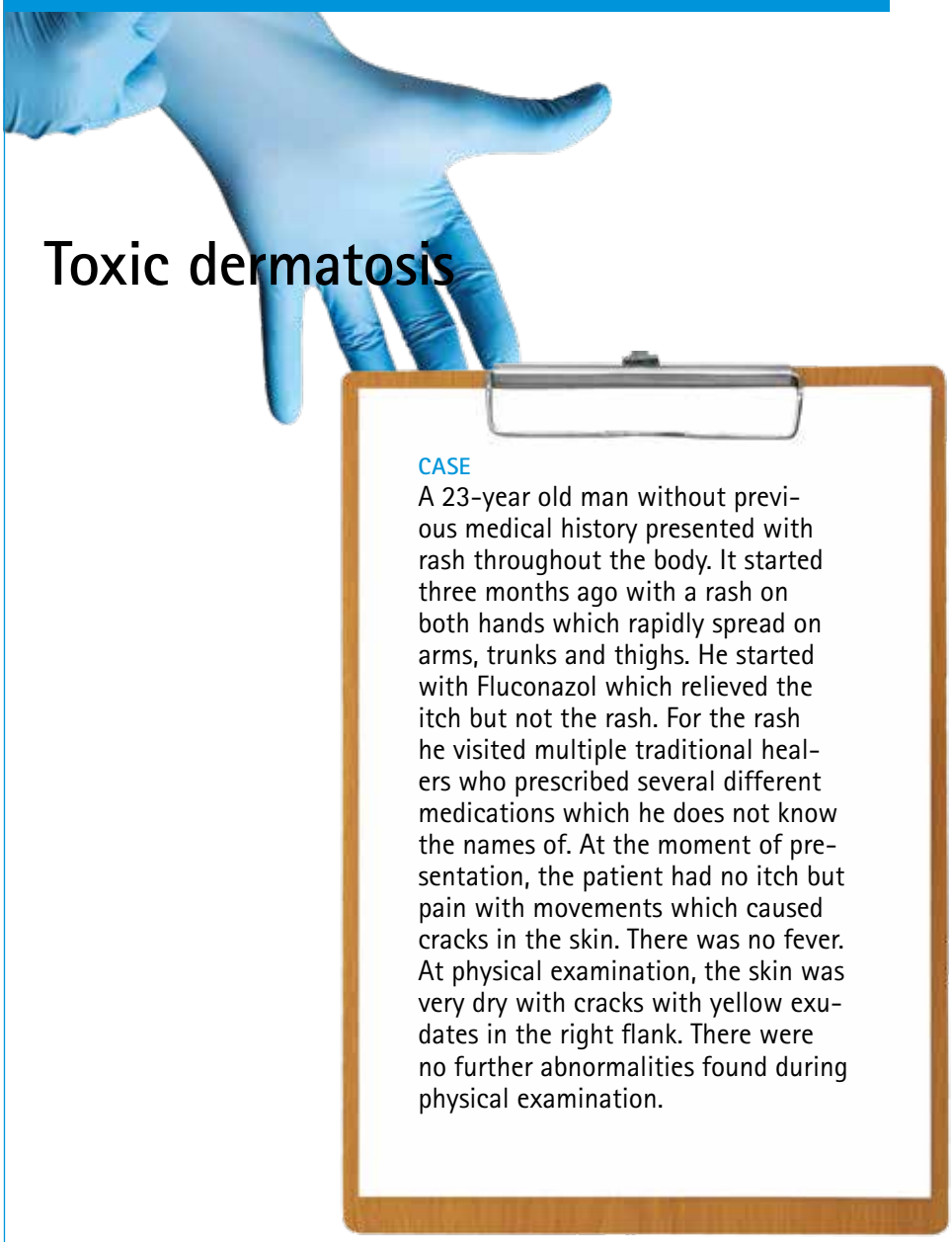


Toxic dermatosis

CASE

A 23-year old man without previous medical history presented with rash throughout the body. It started three months ago with a rash on both hands which rapidly spread on arms, trunks and thighs. He started with Fluconazol which relieved the itch but not the rash. For the rash he visited multiple traditional healers who prescribed several different medications which he does not know the names of. At the moment of presentation, the patient had no itch but pain with movements which caused cracks in the skin. There was no fever. At physical examination, the skin was very dry with cracks with yellow exudates in the right flank. There were no further abnormalities found during physical examination.

SETTING

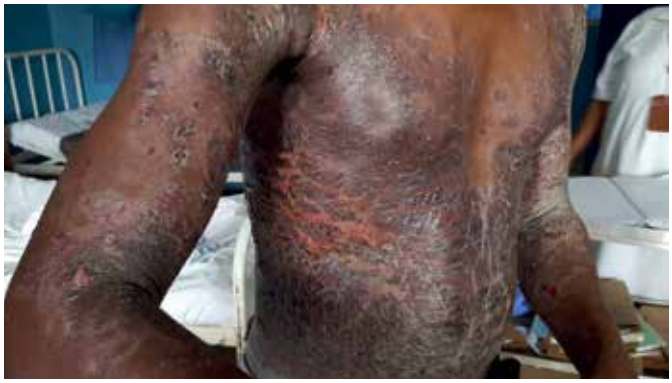
This case is from Biharamulo District Hospital, Kagera region, Tanzania. The hospital has 250 beds, and the medical staff consists of two medical officers and four assistant medical officers. They can carry out X-rays, ultrasounds and basic laboratory tests. The nearest referral hospital, in Mwanza, is 260 kilometres away.

SPECIALIST ADVICE

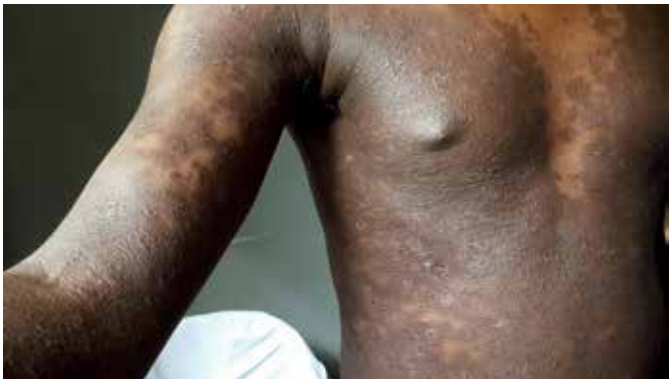
Dermatologists were consulted for advice on the differentials. They thought of toxic asteatotic eczema with infected cracks, probably caused by application of creams, and soap. They advised starting on antibiotics and topical therapy with strong paraffin or emulsifying ointment. Furthermore, they advised starting on prednisone 30 mg, assuming topical steroid ointment is very expensive in Tanzania and may not be available or affordable.

FOLLOW-UP

After five days of treatment and stopping with cleaning the skin with water, the skin looked much better and the pain was gone. After two weeks using prednisone, new itching skin lesions arose, consisting of annular lesions with an edge consisting of papules strung together. Again specialist advice was requested and the dermatologist thought of drug-induced lichen planus and advised taking a biopsy to differentiate between annular lichen planus, linear IgA dermatosis, and granuloma annulare. Unfortunately there was no possibility of taking a biopsy due to the costs and the patient was eventually started on a strong topical steroid ointment (clobetasol) combined with



Toxic asteatotic eczema with infected cracks.



Annular lesions with an edge consisting of papules strung together.

an antihistamine. After starting treatment, the patient did not show up for follow up. A cause of the lichen planus was therefore not identified, but it was known that he used diclofenac for pain relief and, due to the high incidence of malaria, it was conceivable that he had used antimalarial agents previously.

BACKGROUND OF LICHEN PLANUS

Lichen planus is an inflammatory skin condition that affects 0.5-1% of the population in all age groups with no specific gender predominance. Lichen planus has a higher incidence in certain populations. In the U.S.: more African Americans were seen with lichen planus (72%) in comparison to the general clinic population (21%). In the UK, most children presenting with lichen planus originated from India (80.8%) in comparison to 28% of the city's general child population. Furthermore, there is a predominance of lichen planus in children of Arab and Afro-Caribbean background.

The cause of lichen planus is unknown. Histologically, there is an autoimmune-mediated lysis and lymphocytic infiltrate in which cytotoxic T-lymphocytes act on the epidermis. There is an association with certain autoimmune diseases (thyroid diseases, rheumatoid arthritis, vitiligo, celiac disease, inflammatory bowel disease (IBD), primary biliary cirrhosis, alopecia areata and SLE), chronic liver diseases, particularly hepatitis C, and other viruses and bacteria, allergens and certain medications as discussed below.[1]

CLINICAL FEATURES

Classic lichen planus presents with the four Ps: purple, pruritus, polygon shaped and papules/plaques and are typically symmetric in distribution and affect any area on the body but rarely the face. There are many variants in morphology and location on the classic presentation which makes accurate diagnosis difficult. However, histopathological findings are largely consistent.[1]

ANNULAR LICHEN PLANUS

Approximately 3% to 7% of patients with lichen planus have the annular variant, with a predominance of male patients. It clinically presents as circular macules or plaques with raised borders with or without central atrophy with a diameter of 2-8 cm. Typically the lesions are localized but can be generalized.[1]

DRUG INDUCED LICHEN PLANUS

Drug induced lichen planus is an uncommon cutaneous adverse effect. A wide range of medications have been associated with lichen planus and the list is growing as new agents are discovered and prescribed. Inducers include treatment with gold, antimalarial agents, ACE inhibitors, nonsteroidal anti-inflammatory agents, thiazide diuretics, penicillamine, dental amalgams, sulfasalazine, beta blockers, Viagra and proton-pump inhibitors. Compared to lesions of classic lichen planus, these are often larger in size, less monomorphic and more eczematous and associated with desquamation and crust. Typically it spares the classic sites of lichen planus such as the flexor surfaces, mucous membranes, nails and genitalia.[2] The time lag between the taking of the drug and the first cutaneous manifestations can be as long as three years, especially with penicillamine therapy, and depends on whether the patient has had previous exposure to the agent, dosages, host reaction and concurrent medication. Pruritus is frequent, although some patients are completely asymptomatic.[3]

TREATMENT

Treatment of drug induced lichen planus consists of removal of the offending agent. The eruptions resolve generally in a few weeks but can take as long as a year, and occasionally the eruptions recur intermittently despite discontinuation of the agent.[4] In case of prolonged disease, extensive disease or severe symptoms, treatment with topical or systemic corticosteroids may be warranted, although the efficacy has not been evaluated in randomized trials but is based on clinical experience and a few clinical studies.[5] After treatment the skin may become hyperpigmented skin which can take several years to disappear.[2]

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The Arc of the Swallow by Sissel-Jo Gazan

translated from Danish by Charlotte Barslund

Eminent immunologist Professor Kristian Storm is found hanging in his office at the University of Copenhagen in an apparent suicide. But the young PhD student Marie Skov doesn't believe the professor killed himself. Already from Chapter 1 it is clear The Arc of the Swallow is no ordinary crime novel. The mystery revolves around the controversial research findings of an immunologist working in Africa and to understand the motivations of the murder the reader must follow the explanations of non-specific effects of vaccines and a description of the results of the fictitious Belem Health Project in Guinea-Bissau. Eventually Marie Skov and Deputy Chief Superintendent Soren Marhauge team up, delving deep into the world of immunology in order to get at the truth.

What makes the novel unique is that it both follows and deviates from the usual murder-mystery genre. The plot begins with what is assumed to be a suicide until the intrepid detective, aided by an amateur sleuth, uncovers a more sinister plot. As the detective duo dig deeper, they find themselves risking their jobs and their lives until they find the truth. In keeping with the genre, the book ends with a dramatic plot-reveal moment. Instead of the usual gathering of suspects in the living room – organized by a Miss Marple or a Hercule Poirot – the setting this time is the 2010 International Immunology Congress in the Netherlands. The murderer is unmasked with the help of the Dutch police, the World Health Organization and conference organisers.

You might wonder why this book was chosen in an issue focusing on nutrition and infectious disease. Although nutrition is not the focus of the book, it does play a role in the description of the biological relationships and in the climax of the murderer scene. A member of the audience is angry that the investigators are delaying an anticipated lecture about the link between nutrition and infant mortality. This remark fits within the context of the immunology conference pointing to the relationships between nutrition and immune function. Although not mentioned in this novel, vitamin A supplements may play a role in non-specific effects.

The murder is a fictional twist of course, though isn't life sometimes stranger than fiction? At the end of the book, the author describes the real Bandim Health Project in Guinea Bissau. The murder mystery is based on the controversial findings of this project regarding non-specific effects of vaccines. The novel however is more than an account of these remarkable findings – wrapped in a detective novel. It is an interesting and enjoyable read about the real Bandim Health Project, intertwined with family matters involving the 'detectives' Marie and Soren.

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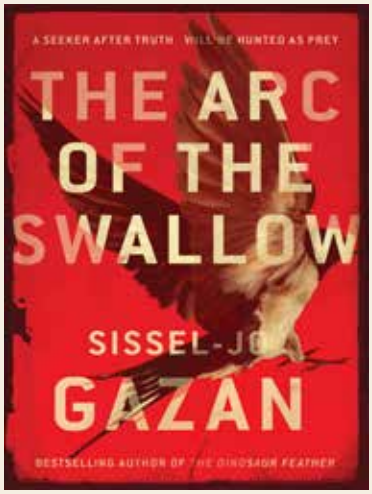

NVTG

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