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Editor's Choice

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Arsenic, antibiotics and interventions

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In December 1910, Wilhelm Johannsen (Box 1), a Danish plant physiologist, was invited to address the American Society of Naturalists. Illness prevented him from attending, but the paper he would have given was published in the *American Naturalist* in 1911.[1] It is reprinted in this issue of the *IJE*.[2] Raphael Falk in his commentary notes that the 100th anniversary of the paper seemed to pass with little fanfare,[1] although due tribute was paid to Johannsen in this journal in 2012.[3] Nonetheless, there may be many outside the field who are unaware of Johannsen's significant contributions to the young discipline of genetics. In 'The genotype conception of heredity' he introduces new concepts and terms: 'pure line', 'phenotype', 'genotype' and 'gene'; and provides evidence for the diffentiation of the genotype and phenotype.[1,4] Although Johannsen coined the term gene, he described it as 'nothing but a very applicable little word'.[2] Despite his high regard for the work of Thomas Hunt Morgan, he saw Morgan's theory, that genes carried on chromosomes provide the mechanism for heredity, as limited. To the end of his life Johannsen held to the view that the genotype was more than the sum of its genes: a non-reductionist approach that has regained currency.[5]

Due to his family's modest means, Johannsen was unable to take up a place at the Unversity of Copenhagen and was apprenticed to an apothecary. However, two years after completing his training as a pharmacist, he went to work in the Carlesberg Laboratory in 1881.[1] True to the contemporary understanding of Carlesberg as synomymous with lager, the laboratory was set up in 1875 by the owner of the Carlesberg brewery with the principal aim of developing 'as complete a scientific basis as possible for malting, brewing and fermenting operations'.[6] Johannsen resigned from his post at the Laboratory in 1887, but continued some of his research there between 1890 and 1894. In 1892 he was appointed lecturer in botany and plant phsiology at the Royal Veterinary and Agricultural College, and in 1905 professor of plant physiology at the University of Copenhagen. The appointment of someone without a university education to the position of professor caused some reaction in the press, but in 1917 he went on to become rector of the university. Although perceived as a misfortune in his youth, Johannsen in later life felt that being mostly self-taught had enabled him to approach problems unbound by orthodoxy.[7] Today his contribution is commemorated by the University of Copenhagen in the Wilhelm Johannsen Centre for Functional Genome Research, part of the Department of Medical Genetics.[8]

Arsenic—king of poisons

In 1909, the year in which Johannsen published his greatest work, *Elemente der exakten Erblichkeitslehre* [*Elements of the Exact Theory of Inheritance*],[11] Paul Ehrlich, who coined the term 'magic bullet', synthesized one organoarsenic compound. Initially known as 606, simply because it was the 606th compound synthesized by Ehrlich, it was marketed a year later under the brand name Salvarsan. Salvarsan was the first safe and effective drug for the treatment of syphilis and rapidly became the most widely prescribed drug in the world. Following its discovery, other organoarsenic compounds were introduced for use against various bacterial or parasitic infections, but few survived the introduction of penicillin in the early 1940s. Recent efforts to determine Salvarsan's mode of biological activity have been driven partly by historical interest and partly with an eye to new uses for organoarsenic drugs in an era of increasing antibiotic resistance.[12]

Therapeutic treatment is not usually the first association that comes to mind at mention of the word arsenic. Arsenic was listed as a poison by Dioscorides in the first century AD. The ancient Greeks and Romans, both

Box 1. Wilhelm Johannsen

Most of Johannsen's publications are in Danish and German and most commentators refer only to two papers in English: that reprinted in this issue of the *IJE* and a paper published in *Hereditas* in 1923.[9] However, Johannsen was invited to speak at the Third International Conference on Genetics, hosted by the Royal Horticultural Society in London 30 July– August 1906. His talk 'Does hybridisation increase fluctuating variability' (pages 98–112) was included in the report of the conference published by the Royal Horticultural Society in 1907.[10] The report covers every aspect of the conference, from lunch menus to scientific papers, and includes the photograph of Johannsen above. Courtesy of the Wellcome Library, London.

masters of the art of poisoning, preferred different agents. Whereas the drug of choice among the Greeks was hemlock, in the rest of Europe from the time of the Roman Empire onwards, arsenic was the king of poisons. Colourless, tasteless, odourless, readily available and, administered in a single large dose in food or drink, it is highly effective. Adding to its attraction, the symptoms of arsenic poisoning are difficult to detect. However, the discovery of a chemical test for arsenic by James Marsh in 1836 brought the heyday of this king of poisons to an end.[13]

It was once believed that tolerance to arsenic and thus immunity from poisoning could be developed by regular ingestion. Sadly, chronic daily exposure to low levels of arsenic, for the millions of people who currently imbibe it with their drinking water, confers higher rates of morbidity and mortality rather than tolerance.

Water supplies in much of Bangladesh used to consist of shallow wells. As these were often polluted by animal and human waste, international efforts were mounted to improve the water supply by digging tube wells into aquifers. Unfortunately many of these aquifers occur in geological formations naturally high in arsenic, and concentrations of arsenic in the water supplied by the wells can reach up to 1000 μg/l: two orders of magnitude above the 10 μg/l limit recommended by the World Health Organization (WHO).[14] The highly productive Health Effects of Arsenic Longitudinal Study (HEALS) was set up to evaluate the morbidity and mortality associated with this chronic exposure to arsenic in Bangladesh.[15] However, as the authors point out, as a population-based cohort study, HEALS also provides for the investigation of other potential disease risk factors. This issue of the *IJE* includes two such studies.[16,17]

Tyler McClintock and colleagues examine associations between betel quid chewing and carotid intima-media thickness (IMT) measured in a sub-cohort of approximately 1200 HEALS participants. Strong associations were seen in men for long duration and high cumulative exposure to betel quid, in analyses adjusted for age, body mass index (BMI), sex, education, systolic blood pressure and ever smoking. There was no evidence of associations in women, despite high cumulative exposure to betel quid being slightly more prevalent in women. However, only a small proportion of the women had ever smoked cigarettes and there was evidence of an interaction between high cumulative exposure to betel quid and ever smoking on IMT levels in men.[16]

In the body, arsenic is methylated to monomethylarsonic acid (incomplete methylation) and dimethylarsinic acid, of which the former is believed to be the more toxic metabolite. Arsenic methylation capacity, also known as arsenic metabolism efficiency, refers to the distribution of these arsenic metabolites in urine. There is some indication that betel quid may increase exposure to arsenic,[18] and smoking has been associated with less efficient arsenic metabolism.[19,20] Arsenic and arsenic metabolism efficiency have also been shown to be associated with higher risks of incident cardiovascular disease and higher levels of IMT in the HEALS cohort.[21,22]

Yu Chen and colleagues examined associations between mid-upper arm circumference (MUAC), measured in 20 000 participants at baseline in the HEALS cohort, and mortality over an 8-year follow-up. They identified MUAC

as an independent risk marker for all-cause and cardiovascular and mortality, but not for death from cancer. Associations with all-cause CVD deaths were strongest in men and among those in the lowest category for BMI.[17] One of the limitations identified by the authors is that the study lacks data on other anthropometric measures, so is not able to assess whether the high risk associated with a low MUAC and low BMI could be explained by these. Baseline analyses of HEALS data found that men, older, and/or thinner participants were more likely to be affected by arsenic exposure in terms of developing skin lesions;[23] possibly as a result of reduced arsenic metabolism efficiency, which has been shown to have a causal role in arsenic toxicity.[24] Although evidence within HEALS for a positive association between BMI and arsenic metabolism efficiency is equivocal,[25,26] data from elsewhere suggest an association is possible.[27]

Antibiotic resistance

Trachoma is an infectious disease of the eye caused by the bacterium *Chlamydia trachomatis*. About 110 million people live in endemic areas and need treatment, and an additional 210 million live where trachoma is suspected to be endemic. The greatest burden is found in sub-Saharan Africa, particularly in countries along the Sahel belt and in East Africa. In advanced stages of the disease the eyelashes turn inward and scrape the cornea, a painful condition called trichiasis, which can result in visual impairment or blindness.[28] The public health approach to treatment and prevention of trachoma is the WHO-endorsed SAFE strategy, the components of which are: **S**urgery for inturned eyelids, **A**ntibiotics to treat and prevent active infection, **F**acial cleanliness to prevent transmission and **E**nvironmental change, in particular increased access to clean water. One of the antibiotics widely used for mass administration in SAFE-eligible communities is azithromycin (AZM). AZM is a broad-spectrum macrolide antibiotic used against a variety of infections. However, based mostly on observations from cross-sectional studies, concerns have been raised about the emergence of macrolide antibiotic resistance in non-target bacteria. In this issue of the *IJE*, Jessica Seidman and colleagues show that one month after mass treatment with a single dose of AZM, the proportion of young children in rural Tanzania with macrolide-resistant *Escherichia coli* (*E. coli*) had increased from 16 to 61% in the intervention communities but remained unchanged in control communities. Although the proportion of young children with macrolide-resistant *E. coli* had dropped to 31% by six months, the authors caution that the cost of AZM resistance should be weighed against the risk of trachoma, especially in low prevalence communities.[29]

One of the cohorts profiled in this issue of the *IJE* is 'The study of respiratory pathogens in Andean children', located in the northern highlands of Peru. Via weekly household visits, the study is gathering data on viral respiratory infections in young children and interactions between causative respiratory viruses and common respiratory bacteria. Given the high levels of deaths each year from childhood pneumonia, almost all of which occur in lower-income countries, the study is focusing in particular on the potential interaction between influenza viruses and bacterial infection with *Streptococcus pneumoniae*.[30] Peru is mercifully free of trachoma infection.[28] However, AZM is one of the antibiotics of choice for the treatment of pneumonia.[31] Recently researchers from the study already mentioned in rural Tanzania reported the effects of mass treatment with AZM on acute lower respiratory tract infection. On the plus side, a single dose of AZM was associated with a 38% decreased risk of acute lower respiratory tract infection in the first month after treatment.[32] However, this beneficial effect was short-lived and countered by an increased prevalence of macrolide-resistant *Streptococcus pneumoniae*: 82% in the treatment group compared with 47% in the control group.[33]

In the era of HIV/AIDS, resistance to multiple antibiotics has contributed to the re-emergence of tuberculosis (TB) in higher-income countries as well as the ongoing pandemics in lower-income countries. Keren Middelkoop and colleagues investigated TB strain diversity over a ten-year period in a peri-urban South African township with high TB and HIV prevalence. The authors examined social, host and pathogen factors associated with success of the TB strains based on persistence over time and average number of cases per year. Neither social factors nor host factors exhibited strong associations with TB strain success, leaving the authors to conclude that pathogen characteristics appear to play the greatest role. Of the 267 strains analysed, only 4% were persistently successful and success was negatively associated with antibiotic resistance. Possibly, the authors suggest, the increased host mortality associated with multiple drug-resistant TB may negatively affect transmission, to the cost of the strain.[34]

Population-based interventions and socioeconomic inequalities in health

This issue of the *IJE* includes two studies of childhood outcomes from the Promotion of Breastfeeding Intervention Trial (PROBIT), the largest randomized trial of breastfeeding promotion undertaken to date. The trial itself in 1996–97 involved the implementation of a breastfeeding

promotion programme in 31 maternity hospitals in Belarus, randomized to receive the intervention or to continue usual practice. Compared with the control arm, the breastfeeding promotion programme substantially increased exclusive breastfeeding to three months and duration of any breastfeeding to twelve months. In a follow-up of the children at age 11.5 years, Oleg Skugarevsky and colleagues show that children in the intervention arm of the trial were less likely to have problematic eating attitudes than children in the control arm.[35]

Earlier work on PROBIT had demonstrated better cognitive function at age 6.5 years among children in the intervention arm of the trial.[36] Sengumi Yang and colleagues used these cognitive function data and data on the original breastfeeding outcomes to examine the question: 'Do population-based interventions widen or narrow socioeconomic inequalities?' Although the intervention had no effect on socioeconomic differences in child cognitive ability, the upward shift in exclusive breastfeeding to three months and duration of any breastfeeding to twelve months in the intervention group was accompanied by the emergence of socioeconomic differences that were absent prior to the intervention. Post-intervention, mothers higher up the educational hierarchy were more likely to continue exclusive breastfeeding to three months and less likely to wean before twelve months than mothers in the lowest education category.[37] In a commentary on the paper, Katherine Frolich takes issue with the idea that a cluster-randomized controlled trial, like PROBIT, despite the advantages of the study design, can be described as a population-based intervention. She argues that only interventions that change the context by targeting upstream factors, such as fluoridation of drinking water, rather than targeting behaviour changes in groups of individuals, can truly be described as population-based interventions in the sense intended by Geoffrey Rose.[38]

In a mega meta-analysis including 133 million people, nearly 4 million deaths from any cause and nearly 170 000 alcohol-attributable deaths, Charlotte Probst and colleagues compare socioeconomic inequalities in alcohol-attributable deaths with death from all causes. Pooling findings from studies of inequalities by education, occupation, employment status and income, they show the relative risk of dying from alcohol-attributable causes in the low socioeconomic group is roughly 1.7 times higher than for all-cause mortality.[39] In their Discussion, the authors cite evidence from Finland[40] that a reduction in alcohol taxes was associated with a greater increase in alcohol-attributable deaths in low socioeconomic groups, to illustrate the possibility that society level interventions may widen rather than diminish existing socioeconomic inequalities. Similar concerns drive the contribution of Caryn Bredenkamp and colleagues who use data from 80 countries over the last two decades to examine whether population-level improvements in undernutrition mask widening socioeconomic inequalities. Although they find considerable variation, with increases and decreases in inequality in countries where the prevalence of undernutrition has risen as well as in countries where it has fallen, the overall pattern they observe is not of increase, but the entrenchment of existing inequalities.[41]

The question of whether increases in health inequalities are inevitable as population health improves is examined in detail in a paper in this issue by Nancy Krieger and colleagues. Using data for United States (US)-born Black and White Americans from the National Health Examination Surveys (NHES) and National Health and Nutrition Examination Surveys (NHANES), the authors examine trends in inequalities in health status indicators over half a century from 1959, by income and education. As implied in their Discussion, the improved health of the US population over the past 50 years has been largely the result of interventions which have changed the context and so fall within Geoffrey Rose's definition of a population-health intervention. For both absolute and relative inequalities, the authors observe changes which range from increases in inequality, through stagnation and reversal, to decreases in inequality, depending on health status indicator, skin colour and socioeconomic measure. Although they warn against simplistic analyses that ignore such differences, the authors conclude overall that inequalities 'need not rise as population health improves'.[42]

The educational distribution of the participants in the NHES for 1959–62 and NHANES 2005–08 illustrate the large increase in educational opportunities that took place in the US over that nearly 50-year period. For example, 93% of US-born Blacks had less than a high school education in 1959–62, a proportion which had dropped to 26% by 2005–08; corresponding figures for US-born Whites were 80% and 12%, respectively.[42] Had the data also been stratified by sex, these differences might have been even more extreme. In their Editorial, Jennifer Dowd and Amar Hamoudi discuss the problems associated with using such data in analyses where, unlike those of Krieger and

Box 2.

'For generations of Americans, it was a given that children would live longer than their parents. But now there is mounting evidence that this enduring trend has reversed itself for the country's least-educated whites, an increasingly troubled group whose life expectancy has fallen by four years since 1990'. *New York Times*, September 20, 2012.

colleagues, the outcome is not ascertained at the same time as the exposure. The authors argue that proper account must be taken of such exposure group changes over the intervening period, a phenomenon they call lagged selection bias and which relates, in particular, to exposures fixed relatively early in the life course, like education. They illustrate their argument with examples in which failure to take account of lagged selection bias has resulted in differences between non-comparable populations over time being misinterpreted as 'trends'. Popular with the US press (Box 2), the authors caution that the translation of such misinterpretations into policy could have adverse effects on public health.[43]

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