

Advances in Experimental Medicine and Biology 719

Nigel Curtis
Adam Finn
Andrew J. Pollard *Editors*

Hot Topics
in Infection
and Immunity
in Children VIII

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 719

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Editors

Hot Topics in Infection and Immunity in Children VIII

 Springer

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Preface

Each of the chapters in this book is based on a lecture given at the eighth 'Infection and Immunity in Children' (IIC) course held at the end of June 2010 at Keble College, Oxford. Thus, it is the eighth book in a series, which collectively provide succinct and readable updates on just about every aspect of the discipline of Paediatric Infectious Diseases.

The ninth course in 2011 has another exciting programme delivered by renowned top-class speakers, and a further edition of this book will duly follow.

The clinical discipline of Paediatric Infectious Diseases continues to grow and flourish in Europe. The University of Oxford Diploma Course in Paediatric Infectious Diseases, started in 2008, is now well established with a large number of trainees enrolled from all parts of Europe. The Oxford IIC course, as well as other European Society for Paediatric Infectious Diseases (ESPID)-sponsored educational activities, is an integral part of this course.

We hope this book will provide a further useful contribution to the materials available to trainees and practitioners in this important and rapidly developing field.

Melbourne, Australia
Bristol, UK
Oxford, UK

Nigel Curtis
Adam Finn
Andrew J. Pollard

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We thank all the contributors who have written chapters for this book, which is based on lectures given at the 2010 Infection and Immunity in Children (IIC) course. We are grateful to the staff of Keble College, Oxford, UK where the course was held.

Sue Sheaf has administered and run the course for several years now. As course organisers we are extremely grateful for the work and effort that Sue puts into making the course such a success. We are constantly impressed by her ability to maintain a quiet, calm and efficient manner under pressure and her can-do approach. We are indebted to Sue and enormously appreciative of her contribution. We also thank Sue on behalf of all the speakers and delegates who have benefited from her behind the scenes administrative, organisational and diplomatic skills

Pamela Morison administered the production of this book. This involved painstaking checking, correcting and formatting of the chapters as well as liaising with authors and the publishers. Pam has mastered the art of persuading authors (and editors!) to meet deadlines, read formatting instructions and answer emails. Using a combination of gentle encouragement, persistent coaxing and cajoling, and high diplomacy, Pam has dealt admirably with the challenges this volume has presented. We thank Pam for her patient and cheerful approach to this difficult task, and we gratefully share with her the credit for this book's production.

We thank the European Society for Paediatric Infectious Diseases (ESPID) for consistent support and financial assistance for this and previous courses and for providing bursaries, which have paid the costs of many young ESPID members' attendance. We also acknowledge the recognition given to the course by the Royal College of Paediatrics and Child Health.

Finally, we are grateful to several pharmaceutical industry sponsors who generously offered unrestricted educational grants towards the budget for the meeting.

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Our Time of Pestilence: Purchasing Immunity and Ignoring the Misery of Others

Philip Alcabes

1 Prisoners of Life

In 1593, Thomas Nashe's poem "In Time of Pestilence" admonished the wealthy not to trust in their riches [1]:

Gold cannot buy you health;
Physic himself must fade;
All things to end are made;
The plague full swift goes by;
I am sick, I must die.

The Royal College of Physicians had already been in place for 75 years at that point. Physicians were making strides in identifying and differentiating plague from poxes and other maladies. But it was true that doctors—"physics," Nashe called them—were of little help, even for the wealthy.

How different today. The physic no longer fades. Residents of so-called developed countries believe that, as much as each of us must die, we must not die too soon. Gold *can* buy health, at least here in the wealthy world.

Median life expectancy is long in the affluent world today: over 82 years in Japan and Singapore, 81 in France and Canada, 80 in New Zealand and Spain (79 in the European Union generally) [2]. Even amid the capitalist muddle of American healthcare, half of U.S. residents live past age 78. Twenty percent or more of the babies born in the developed world in 2010 will still be alive at the start of the twenty-first century. We have used our wealth well, it could be said, using it for wellness.

But we pay a moral price. We remain "prisoners of life," as the eastern European writer Joseph Roth once put it: the implacable unpredictability of the universe is everyone's lot. The affluent are prisoners no less so than are the poor.

We who can buy our health and longevity easily imagine we can escape all harms. Striving to preserve the increasingly protracted future to which the public feels entitled, health authorities in affluent countries are expected to foresee the coming plague, the pandemic in waiting. The U.S. government awarded a contract to a private firm in 2006 for USD 363 million for development of multi-type botulinum antitoxin, for instance (there are only about 100 botulism cases per year in the

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U.S., almost all of them caused by just two of the seven possible botulinum neurotoxin types [3], but the need for antitoxin against all seven types was rationalized on the basis of future risk of bioterror events). The botulism contract of 2006 was dwarfed by the USD 5.6 billion spent that year for “pandemic influenza preparedness”—this was at the time of fears about H5N1 avian flu, which had killed about 200 people worldwide although none in the U.S. [4]. One American health official estimated that between 7% and 8% of U.S. health expenditures went for emergency preparedness that year [5]—even though the vast majority of fatalities are caused by non-emergent conditions like smoking, common infections, and so forth. And the expenditure has increased since then.

Emergency preparedness isn’t the only preoccupation. The affluent also seek to stem the forecast tide of dire consequences of the epidemics of modernity. Obesity keeps increasing, threatening to “reduce quality of life and increase the risk for many serious chronic diseases and premature death,” according to the U.S. Centers for Disease Control and Prevention [6]. The World Health Organization, lumping overweight with obesity and pointing out that two-thirds of adult men in the U.K. and other parts of northern Europe fall into this category, emphasizes that obesity is a malaise of modernity [7]:

Obesity and overweight pose a major risk for serious diet-related chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and certain forms of cancer... The rising epidemic reflects the profound changes in society and in behavioural patterns of communities over recent decades.

Note the recurrent appeal to *risk*. Preventing the ever-more-distant and ever-less-predictable future calamity means that risk becomes the grammar for our conversation about health. Meanwhile, our sense that freedom from epidemic threats is our due deafens us to others’ misery.

2 Purchasing Health

In Thomas Nashe’s day, English life expectancy was between 35 and 39 years [8]. Rates of infant and childhood mortality were well over 10%, and a man who reached age 30 had only even odds of living to 60. Many died of plague in plague years, so affecting to Nashe. But they died of consumption, spotted fevers, poxes great and small, purples, apoplexy, consumption, or a host of other conditions—some no longer part of our lexicon—in non-plague years. Horribly often, women died in childbirth.

Even in the early 1800s, even in the world’s wealthiest places, death in childhood or by child-bearing was common. One out of every four infants born in New York City died before its first birthday then, and only half of those Americans who survived childhood and adolescence lived past the age of 50 in 1810 [9].

Changes in social structure and expanded choices for women and laborers made life in the wealthy world longer and healthier by the twentieth century. Sanitarianism, primarily in the form of urban sewerage systems and clean-water supplies, had put paid to cholera outbreaks. Housing reform, along with improved nutrition, had begun to limit the spread of contagion. The workplace safety movement was reducing injury rates. Perhaps most important of all, affording women better control over their reproductive cycles was leading to reduced family size, lowering both infant and maternal mortality rates, and providing fewer opportunities for infectious foci to extend into severe outbreaks. Death began to seem escapable to the middle classes.

It was social reform that generated the healthful transformation of modern life, but consumerism was given credit for it. From roughly 1900 onward, buying the ingredients of the more salubrious life and the delayed death seemed increasingly possible. Products were available for this: disinfectants and deodorants, foods that had been inspected for purity, sanitary facilities, pasteurized milk [10]. In 1905, the director of New York City’s Bureau of Laboratories, Herman Biggs, asserted that health could be purchased. “Within natural limitations, a community can determine its own death rate,” Biggs said [11].

Today, we are followers of Biggs. Our credo is that we can purchase our immunity. We can buy longevity, and we do. Advanced life expectancy is the hallmark of the wealthy country today.

Everywhere else, the poor die in droves. They die of the chronic effects of malaria, schistosomiasis, onchocerciasis, filariasis, trypanosomiasis, or AIDS. They die during war or of hunger. They die in disasters. In the poorest parts of the world, half the population is dead by the age of 40—just as in England in Nashe’s day.

Today’s health conversation in the affluent world is wrapped up self-indulgently in the protracted future. The talk is of soda taxes, secondhand smoke, and obesity, of vaccines and autism, of diet and databases to track diabetes control, of *preparedness*. While everywhere else, people die badly. Focused on threats to the longevity to which we are now entitled, we manage to avoid, as Susan Sontag put it, “reflect[ing] on how our privileges . . . may . . . be linked to their suffering, as the wealth of some may imply the destitution of others” [12]. By speaking of the contemporary world only in the language of risk to our health, we allow ourselves to live with, and generally ignore, this fact: We of the affluent nations are party to depriving the rest of the world, the dollar-a-day world, of health and longevity.

3 The Deceptive Language of Risk

When we talk about epidemics, we are talking the language of risk, not of health. Specifically, not of *humane* health—the health of humankind. Those who do not have the gold for the risk-free life do *not* die in epidemics: the term “epidemic” is not accorded to the agents that kill the poor *en masse*. As the textbooks on public health or tropical medicine adumbrate, the diseases that scourge the have-nots (malaria, et cetera) are considered to be *endemic* problems in the so-called developing world. “Epidemic” means “meaningful to us”; “endemic” means “sorry, not our problem.”

For us in the affluent world, and especially our kids, today’s epidemics are of obesity, autism, attention-deficit/hyperactivity disorder, eating disorders, and binge drinking. We have, famously and controversially, experienced a pandemic of H1N1 flu. These are not cut of the same cloth as the pestilence of Nashe’s day. No, we call these “epidemics” because they capture meaning and reflect it back—to a society always eager to see a glimpse of what, we hope, is our true self.

3.1 The Obesity Epidemic

Obesity seems meaningful. To some people, it bespeaks hypertrophy, overindulgence, and a loss of a sense of proportion—the defects of excess allegedly inevitable in a consumer society. It seems to others to point up a putative toxicity to modern life—a noxious, or at least unhealthy, “food environment” that is supposedly of a piece with oil spills and coal-fired smogs in the natural environment.

To still others obesity has a moral tone: it represents bad parenting. To attend to epidemic obesity is to utter the contemporary version of the timeless complaint that this generation’s moms and dads just don’t enforce moral codes the way earlier ones did. It’s as if fat children were evidence of individual parents’ moral turpitude. A great proportion of children are now born to unmarried mothers: 44% of all births in the U.K. in 2006 [13], about half of all births in France, 55% in Sweden [14], for instance. It’s as if that were evidence of a deep moral failure in our civilization, of which rampant obesity were the inescapable resultant and catastrophe the impending final outcome.

The terms the health profession uses to speak of the epidemic of childhood obesity implicate our own childrearing. The language of risk raises a warning finger at how we moderns create, conduct, and end our marriages. It laments the decline of home cooking, the rise of restaurant meals, snack meals, solitary meals, or on-the-go meals. Anxieties about the culture are shaped into epidemic fears.

For instance, a Stanford University researcher told the *Washington Post* a couple of years ago that “we have taught our children how to kill themselves” [15]. In 2002, Dr. Howard Stoate, then chair of the All-Parliamentary Group on Primary Care and Public Health, referred to childhood obesity as a “time bomb” [16]. The American Public Health Association calls obesity “the biggest problem facing children today” [17]—as if American kids’ fat future were more dire than the mere misfortune of children in the world’s poor nations. Those children in the teeming slums of Lagos or Lahore might be filthy, hungry, disease-ridden, orphaned, or all of those—but they aren’t fat.

It is true that obesity *can* lead to medical problems [18–20], and is said to be responsible for both early death [21–25] and, not incidentally, low self-esteem and poor school performance [26].

But the chances of dying from the effects of obesity are slim enough that the great majority of people who are considered obese by current standards—BMI above 30, that is—will suffer no shortening of life because of it.

In the U.S., famous now for fatness, 112,000 deaths in the year 2000 could be attributed to obesity (BMI ≥ 30) [25], amounting to roughly 5% of all U.S. deaths. A large-population epidemiologic study cannot rule out contributing causes of death of all sorts, so the true number of obesity-provoked deaths might be smaller. But accept the 5% figure for the sake of argument. According to the CDC, obesity prevalence among U.S. adults is far higher now even than in the 1990s [6], stood at 26.6% overall in 2007 [27], and is now above 20% in every U.S. state except Colorado [28]. Some prevalence-incidence bias must be considered, since deaths in year 2000 were incident events among a virtual cohort of earlier years’ obese. Therefore, compare the proportionate mortality of 5% to earlier estimates of obesity prevalence, roughly 20%. Even with this correction, three quarters of obese people died of disorders unrelated to their fatness. With increasing obesity prevalence, the proportion of obese people whose death is not attributable to obesity is certainly even greater now. Almost all excess deaths attributed to obesity in the U.S. occur among people in their 60s (after age 69 obesity has no impact on mortality rates) [25] and American obesity mortality is accounted for largely by incomplete management of diabetes and/or hypertension [29, 30], two of the main adverse accompaniments of high BMI. Some, and possibly a great many, of the deaths blamed on excess body mass might equally plausibly be attributed to America’s porous health-care net.

With obesity, in other words, it is risk itself that is epidemic. Some health professionals have begun to talk about obesity as a kind of contagion. In 2005 the CDC sent one of its epidemic intelligence teams to study an “outbreak” of obesity in West Virginia, as if it were cryptosporidiosis or dengue fever [31]. A 2007 article in the *New England Journal of Medicine* reported research findings showing that obesity can “spread through social networks” [32]. Fat people, in other words, make their friends fat. As Freud observed, when spirits and demons are believed to animate all living things, “these souls which live in human beings can leave their habitations and migrate into other human beings” [33]. Freud was referring to the beliefs of primitive peoples; evidently, contemporary health researchers’ thinking is not as far removed from that of the ancients as we are prone to think.

Obesity would not be epidemic were it not for the availability of things you can purchase to fight it. The responsible citizen is supposed to buy the low-fat foods, the fitness-center membership, and the diet books, send her kids to fat camp, take tennis lessons. The anti-obesity crusade is a sales campaign for a multi-billion dollar industry [34]. Both mirroring our anxieties and affording a rationale for increasing corporate profits is a combination that defines an epidemic in the wealthy world today.

3.2 *Influenza and Pandemic Risk*

Unlike obesity—or autism, ADHD, eating disorders, or any of the other popular epidemics of the affluent—influenza really does spread from person to person and can be directly responsible for substantial mortality. But is that what makes a flu pandemic worthy of so vigorous a response as in

2009, and why governments of rich countries spent so much money on it? No. The reason for that was the same combination as for other so-called epidemic threats: the mirroring of contemporary anxieties in tandem with expanding markets for products.

The U.S. Centers for Disease Control and Prevention lumps all sorts of respiratory infections together, along with pneumonitides and other influenza sequelae, so as to claim that 36,000 Americans die from “flu” each year—probably several times higher than the true number of deaths directly caused by influenza [35, 36]. Would anyone claim that this overemphasis on flu as a cause of death has *nothing* to do with the availability of vaccines and antivirals against flu—in contrast to the paucity of products for responding to other respiratory viruses, respiratory syncytial virus, and so forth?

Officials have issued dire forecasts about the possibilities for widespread human mortality in a flu pandemic—even though flu outbreaks with pandemic strains, apart from the outlier of 1918, have all been relatively mild. Flu seems to bring out the Cassandra in public health professionals, whereas the far higher tolls taken by malaria, TB, diarrhea, or AIDS don’t. In part, that contrast has something to do with the sense that flu seems like a problem of the developed world—one can catch flu in the office, riding the commuter train, or at the shopping mall, whereas the diseases that are the misfortunes of villagers in Bangladesh, Burundi, or Bolivia, however much more baleful their toll, seem to speak not of modernity but of dirty water, mosquitoes, and shanty towns.

But much of the contrast between the flu response on the one side and the relative nonresponse to diarrhea and TB on the other has to do with the urgency with which officials press for product-heavy responses. Officials overstate problems for which the corporate world has solutions, and understate the ones that don’t expand markets.

Thus health authorities responded with alacrity to their own allegations that there would be an onslaught of flu in 2009—while giving short shrift to worse threats. In the U.S., federal funds to combat methicillin-resistant *S. aureus* (MRSA) and other hospital-acquired infections, which kill roughly 100,000 Americans each year [37], amounted to USD 17 million in 2009 (the amount was increased to USD 34 million in 2010) [38]. By contrast, the U.S. government allocated USD 6.1 billion from 2006 to 2009—prior to the outbreak of H1N1 flu, that is—for influenza pandemic “preparedness”; an additional USD 4.86 billion was allocated during the 2009 H1N1 outbreak [39]. Even though the 2009 H1N1 flu, even in the worst-case scenario, would have led to fewer deaths than the normal, year-in-and-year-out, hospital-acquired infection mortality. In fact, even by the CDC’s inflated flu calculations, H1N1 flu killed half as many Americans as did MRSA alone.

Among the funds moved in the context of the H1N1 flu outbreak, the U.S. government transferred USD 2 billion from public coffers directly to private vaccine manufacturers, in recompense for 250 doses of vaccine, sufficient for almost all Americans [40]. It is a reminder of the intimacy with which the “not our problem” sensibility colludes with bolstering markets, to discover that the funding donated by U.S. agencies to the millions of citizens of Haiti in response to the January 2010 earthquake, about USD 800 million [41], amounted to half the sum that America donated to seven pharmaceutical companies for flu vaccine.

Perhaps everyone expects the corporate-friendly U.S. to seize on rumors of epidemic threat as an excuse to shift public monies into private hands. But it is not an American phenomenon alone. France appropriated 869 million euros to buy vaccine, Germany transferred 500 million euros for the same purpose, Canada paid 400 million Canadian dollars, and the U.K. spent hundreds of millions of pounds (exactly how much has been strictly secret) [42–44]. Collectively, taxpayers in wealthy countries subsidized a major part of a global vaccine market now estimated at well over USD 20 billion [45]. Ratepayers’ tax monies become pharmaceutical company profits.

I have no argument with private companies manufacturing pharmaceutical products. Nor do I allege that Pharma twists official arms.

My point is that no arm twisting is needed. The officials are already on board, have already forsworn any skepticism about the role of for-profit corporations in public health efforts to contain

alleged epidemic threats. As World Health Organization Director-General Margaret Chan said, in response to recent accusations that pharmaceutical companies had too much influence in WHO policy making around flu, “At no time, not for one second, did commercial interests enter my decision-making” [46]. Of course not. There was no need for “commercial interests” to intercede in decision making about flu. There never is. Officials look out for corporate interests without being asked.

Rather than split hairs about whether WHO’s influenza advisors revealed so-called conflicts of interest, as the Council of Europe has asked, members of the medical and public health professions should ask a more challenging question: What did national health officials in powerful countries like the U.S., Canada, the U.K., Germany, and others decide *not* to pay attention to. Professionals should ask why, in the U.S., national health agencies collect data on firearm violence, an epidemic that verifiably kills as many Americans as AIDS and more than flu [47], but they finance not a single gun-violence-control initiative. Professionals should ask about hospital-acquired infections, mentioned earlier, and about roadway accidents, which kill more people worldwide than flu does [48, 49].

With respect to flu, health professionals must be more exacting of officials. Why, during the 2009 flu outbreak, did no official or official advisor say, “in the worst-case scenario, H1N1 flu is going to hospitalize or kill far fewer people in Europe and the U.S. in the coming year than malaria does *in one month* among African children, fewer than diarrhea does, fewer than AIDS.” Expert science advisors, the people who, it is commonly said, cannot be expected *not* to have ties to pharmaceutical companies should be confronted, asked why none said to his or her country’s health authority, “whatever you do, *don’t* recommend shifting millions of euros into private hands for the purchase of an imperfect vaccine that most people don’t want to get anyway.” Or why so few said, “whatever you do, don’t recommend spending lots of public money to increase the stockpiles of oseltamivir.” Few of the masters of science managed to tell the truth. They were swept up in managing the imagined epidemic.

Without disrespect to the Parliamentary Assembly of the Council of Europe or the *BMJ* [50], I assert that the problem is *not* merely that pharmaceutical companies or vaccine manufacturers influenced WHO officials’ decision to raise a pandemic alert about flu. Nor is the problem that the words “epidemic” and “pandemic” have lost some imagined denotative meaning from the good old days of plague and poxes.

The problem is that people in rich countries demand long life and expect public officials to spend money to ensure it. The health sector is complicit. Health professionals define epidemic threats not on the basis of real harm, let alone real suffering, but on the basis of what will serve as a rationale for the sale and purchase of products that allay people’s anxieties about the culture we live in. When Pakistani or Congolese or Peruvian kids die of diarrhea it’s a *shame*, but when American or European kids get fat it’s an epidemic.

4 Beware the Forecast Epidemic

The warding off of infection, the resistance to environmental toxins, the lifesaving medical interventions, the consequent opportunity to live to the limit of our capabilities—those are our society’s achievements. But long life is not an entitlement. We of the affluent world do not *merit* long life more than do the poor.

Medical and other health professionals must beware the power of epidemics, particularly the epidemic that is forecast, envisioned, or merely imagined, to promote the concentration of wealth and power in the hands of the privileged. We should be loath to embrace the assertion of Herman Biggs. It is not an unalterable fact that the wealthy will and should buy their way into health. It is not an unassailable law of nature that the poor will die young.

Just over a half-century ago, in the Rede Lecture at Cambridge University, C.P. Snow adumbrated that science held the promise to fix the world's problems [51]. I do not see two distinct cultures, nor an abyss gaping between them, as Snow perceived. I question Snow's assertion that, even in the 1950s, nonscientists, particularly the educated humanists from among whom the governing classes sprang, were always too ignorant of science to fulfill science's promise. But I do think Snow was right in outlining a mission that scientists should take up, most certainly medical scientists, who are surely the humanists of the scientific sphere. Scientific knowledge gives its possessors an opportunity to make the world a bit less odious for our fellow prisoners of life. But if scientists are beguiled by the prospect of a long life free of risk, science and society will miss this chance.

Private, corporate interests have discovered how to turn the scientific project of improving everyone's life chances into corporate profits. Policy makers have intuited how to turn science's project into legitimizing the continuance of their political power. The question for the health profession is, How will we pursue the scientific project not for profit or legitimation, but to make the world a bit less unjust, to make more people less miserable?

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