

## CELEBRATION

# Zena Stein, Mervyn Susser and epidemiology: observation, causation and action

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In this issue of the *International Journal of Epidemiology* we highlight the contributions of two pioneering self-taught epidemiologists, Zena Stein and Mervyn Susser. Their joint paper 'Civilization and Peptic Ulcer', originally published in the *Lancet* in 1962, appears as one of our series of reprints of important epidemiological papers, along with several commentaries. These include a reflection, 40 years on, by the original authors. A companion series of papers originated in an international symposium held by the Mailman School of Public Health of Columbia University, New York, to mark the 80th years of both Zena and Mervyn. The event ended in a manner perhaps unusual for such an occasion: it was closed by Ahmed Kathrada, a friend of Zena and Mervyn, who was incarcerated with Nelson Mandela on Robben Island during the struggle against apartheid in South Africa. He read out a letter from Nelson Mandela to mark the occasion (Box 1).

The interlocked careers of Zena and Mervyn have been described elsewhere,<sup>1</sup> as well as in the present collection.<sup>2</sup> The range of their work in epidemiology and public health can be appreciated from the bibliographies which we have made available on the web (<http://www.ije.oupjournals.org>). Therefore here we will just give a brief account of their continuing contributions to epidemiology and public health.

For both Zena and Mervyn their work in epidemiology and public health started in South Africa and has continued to have a strong attachment to that country. Their initial driving motivation was to contribute to the health and medical care of 'non-whites' in apartheid South Africa in the early 1950s. This majority population was virtually ignored in medical curricula at the time, so the task meant striking out with a small group of colleagues to direct a 'township' clinic, in Alexandra, Johannesburg. Although they began with no knowledge of epidemiology, the effort naturally led them to carry out one of the first studies of community health in the developing world, published in the *Lancet* in 1955 as 'Medical Care in an African Township'.<sup>3</sup> It was during this period that they developed ties with Ahmed Kathrada, Walter Sisulu, Joe Slovo and Nelson Mandela, among many others, in the anti-apartheid movement. The efforts made by them and others such as Sidney Kark<sup>4</sup> (a mentor) to address the health of the community as a whole is of more than historic importance; if anything, it may be even more germane today than it was then. Even as the AIDS epidemic brings catastrophe to South Africa—as outlined in the



Photograph of Mervyn Susser and Zena Stein by Paul Weinberg, reproduced by kind permission of the photographer

present collection<sup>5</sup>—medical training in that country still fails to give any centrality to the care and prevention of HIV/AIDS. Zena and Mervyn are once again in the centre of the melee, supporting those in South Africa who want to bring about change.

Due to political difficulties in South Africa in 1955, they settled in England for the next decade. Taking positions at Manchester University, they took up research on what are now called developmental disabilities. Their many early contributions to this field are exemplified by studies showing the influence

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**Box 1** Letter from Nelson Mandela

Dear Zena and Mervyn

As someone who became an octogenarian three years ago, I have great pleasure in saying 'Welcome to the Club'.

Over the years, especially when we were in prison, we managed to get trickles of information about you. It was always heartening to know that, albeit under different circumstances and many miles from home, your commitments and active contribution to struggle for democracy remained undiminished.

Although we are divided by a great distance today, please know that our thoughts and best wishes are with you, and with all the friends who are joining you in the celebration.

Hearty congratulations!

Nelson Mandela

of the social environment on the subsequent development of children with marginally low IQ.<sup>6</sup> But this was only one of many directions established. The peptic ulcer paper was written during this period.<sup>7</sup> In his related post as Medical Officer for Mental Health in Salford, Mervyn established a psychiatric registry and used it for the first study of the incidence of specific mental disorders in a large urban population.<sup>8</sup> Both Zena and Mervyn were interested in issues related to social class, with Zena working with Fraser Brockington on educational attainment and social background,<sup>9</sup> and Mervyn producing his first detailed review of social class differences in health.<sup>10</sup> Then, at Zena's urging, Mervyn joined with William Watson, an anthropologist, to write the first edition of the influential textbook *Sociology in Medicine*,<sup>11</sup> demonstrating how society and health are interwoven across every stage of the lifecycle. With the current enthusiasm for 'lifecourse epidemiology'<sup>12</sup> it is salutary to read, in an earlier paper on peptic ulcer than the one we are reprinting in this issue, that the 'process of ageing is not only inherently determined; every organism incorporates its life experience from birth onwards'.<sup>13</sup> It was fitting that Mervyn wrote the forward to the first textbook of lifecourse epidemiology.<sup>12</sup>

When Zena and Mervyn moved to the US in 1965, they were recruited by the School of Public Health at Columbia University to lead the Division of Epidemiology. Mervyn, appointed chairman but with no formal training in the discipline, was faced with the challenge of articulating to a sceptical faculty the need to make a transition to the 'chronic disease' era of epidemiology, while at the same time, retaining the insights about society and health described in *Sociology in Medicine*. The result was a series of lectures later formalized in *Causal Thinking in the Health Sciences*.<sup>14</sup> The book was widely read; the *Annual Review of Public Health* included a critique and commemoration of the book 25 years later.<sup>15</sup> At the time, the book was mainly recognized for its clean distillation of the concepts needed for understanding and investigating risk factors. A contemporary reader will see several particular features which distinguish it (together with another pioneering text, Jerry Morris' *Uses of Epidemiology*<sup>16,17</sup>). First, the distinction between distant and immediate causes was made, with the determining role of the former rendering them the appropriate target for interventions that could have major public health significance. Second, an ecological view of epidemiology was advanced and the importance of considering different levels of determination of disease—later developed with Ezra Susser and others<sup>18,19</sup>—was already apparent. Finally

—and perhaps most unusually—the need to consider and critique why we, as epidemiologists, think the way we do, was advocated. Our frames of reference, it is suggested, can constrain our imaginations and lead us astray. This insight has relevance for the peptic ulcer paper and commentaries we are printing in this issue (Box 2).

Zena and Mervyn's subsequent contributions to epidemiology and public health are numerous and wide-ranging; so much so that we cannot do them justice in a short commentary. Among the areas they innovated were social epidemiology, discussed above, and genetic epidemiology,<sup>24</sup> exemplified by their investigations of genetic causes of spontaneous abortions.<sup>25,26</sup> We will discuss only their series of studies on prenatal nutrition and cognitive development, and their ongoing research on HIV/AIDS in Africa. These two are chosen because they illustrate well how Zena and Mervyn combined scientific rigor and social commitment in the way they practised epidemiology.

Their interest in prenatal nutrition and cognitive development spans many decades, dating back to the 1960s, and continuing with current research. Undoubtedly, however, one study stands out above the others: the investigation of the consequences of the Dutch Hunger Winter of 1944–1945.<sup>27</sup> Many observational studies<sup>28,29</sup> and reviews of the literature suggested that low birthweight was associated with impaired cognitive function and intelligence. They recognized that the problems of attributing causation in this area are immense, however, and therefore subjected it to a much more rigorous test within a quasi-experiment, made possible by a historic tragedy, the acute but severe famine in Holland precipitated by a Nazi blockade. The design compared cognitive outcomes in birth cohorts exposed and unexposed to the famine at various stages of prenatal life. The investigation found that in a developed society there was no evidence of an effect of prenatal famine on IQ at age 18. This result refuted the favoured hypothesis of the time (which they had also held), supported by prior observational data,<sup>28,29</sup> and it drew heavy fire, but the result was confirmed as well as elaborated by a randomized trial of prenatal nutritional supplementation which they carried out with David Rush in Harlem.<sup>30</sup> The trial found prenatal protein supplementation to have only modest beneficial effects on cognition (e.g. on infants' habituation), and these were counterbalanced by an unexpected adverse effect on preterm birth. The original controversy and disappointment about the main finding of the Dutch famine study are an important part of the history of this field, though perhaps unfortunately they

**Box 2** Frames of reference

In *Causal Thinking in the Health Sciences*<sup>14</sup> the importance of frames of reference in the organization of causal models in epidemiology was emphasized. To illustrate this, two in-depth examples were given, one of schistosomiasis as illustrative of transmissible disease, and one of duodenal ulcer as illustrative of a non-transmissible disease. In their innovative work on peptic ulcer—an example of which is reprinted in this issue of the *International Journal of Epidemiology*<sup>7</sup>—Mervyn and Zena had developed a counterpoint to the prevailing view of peptic ulcer as a prototypical ‘disease of civilization’. They interpreted the intriguing birth cohort patterns of peptic ulcer as compatible with exposure of the older age groups to poor environmental conditions in their childhood or young adulthood; peptic ulcer ‘could be a disease of an early phase of urbanization’. The British birth cohort with the highest risk of peptic ulcer had lived at different stages of their lives through the stressful periods of the First World War, the depression and high unemployment in the 1930s and then the Second World War. Nonetheless, Mervyn and Zena adhered to the almost universally held view that peptic ulcer was a non-infectious disease—and thus within the non-transmissible disease ‘frame of reference’ Mervyn developed for duodenal ulcer in his book.<sup>14</sup> Similarly, Jerry Morris—who had also carried out innovative work on peptic ulcer<sup>20</sup> (and whose textbook *Uses of Epidemiology*<sup>16</sup> was much concerned with the increasing burden of peptic ulcer, along with coronary heart disease and lung cancer)—applied chronic disease models to considerations of the aetiology of peptic ulcer. Indeed, in the preface to *Uses of Epidemiology* he stated that ‘a more accurate title would be “Some Uses of Epidemiology in the Study of Non-communicable Diseases”’.<sup>16</sup> As several of the commentaries in this issue make clear,<sup>21–23</sup> over the past 20 years we have learned that a major determinant of peptic ulcer is *Helicobacter pylori* infection; this is an infection generally acquired in childhood which would be related to the poor environmental conditions accompanying early industrialization, which Mervyn and Zena discussed in their 1962 paper.<sup>7</sup> For epidemiologists—including Mervyn, Zena and Jerry Morris—working with a non-communicable disease frame of reference, the search for this determining—and treatable—cause of peptic ulcer was perhaps constrained by infectious agents being ruled out of consideration. The importance of critically evaluating frames of reference—as, innovatively advocated in *Causal Thinking in the Health Sciences*<sup>14</sup>—is well illustrated by this example, and is surely as relevant today as it was in previous periods.

have now been overshadowed by important results that later emerged, among which are the early clues that prenatal nutrition is related to neural tube defects,<sup>27</sup> and the sharp association of prenatal famine with schizophrenia.<sup>31</sup> It is salutary to remember the original finding from the Dutch Hunger Winter study, particularly when there has been considerable enthusiasm generated by largely observational findings that maternal nutrition, birthweight and exposures during infancy and childhood are related to chronic diseases in adulthood.<sup>12,32</sup>

By contrast, Zena and Mervyn’s work on HIV/AIDS is a relatively recent development. But for that very reason, it is exemplary for young epidemiologists, in a different way. New York was an epicentre of the epidemic in its early phase in the 1980s, and they were among a small number of well-established ‘chronic disease’ epidemiologists ready to join the effort to combat it, relearning and retooling as required by the evolving public health crisis. A few years thereafter, the pattern of the epidemic shifted, and it became clear that HIV/AIDS was poised to bring catastrophe to South Africa within a decade. Zena and Mervyn did all they could to alert the African National Congress and others of the impending disaster, organizing a conference in Maputo with health activists of the region, including some of the nascent shadow government. In the context of this dramatic and dangerous period of transition to democracy, however, all warnings of a future health event tended to be drowned out. Not to be deterred, they continued the effort, and Zena initiated a (still flourishing) training programme in the epidemiology of HIV/AIDS, which brought many South Africans to New York City to obtain epidemiology degrees at Columbia University, School of Public Health; virtually all of them returning to South Africa. Zena was one of the first and most effective advocates for promoting women’s condoms, and for developing and testing new microbicides and

other methods that women control to reduce heterosexual transmission risk of HIV.<sup>33</sup> Mervyn as editor of the *American Journal of Public Health* brought these issues to the fore. Their work continues, with many offshoots, now evident in a developing partnership between the Nelson Mandela School of Medicine in Durban and the Mailman School of Public Health in New York.

Epidemiology is ultimately a science that provides the basis for public health action, and that is no less the case in the era of molecular and genetic epidemiology.<sup>34</sup> Zena and Mervyn’s contribution has been in showing that only the strongest possible evidence—combined with the strongest possible commitment to the necessary social and environmental changes that the evidence indicates are required—provides the basis for effective public health policy and practice. We look forward to their continued contributions in this regard.

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## The evolving HIV epidemic in South Africa

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In this paper we trace the evolution of the HIV epidemic in South Africa, placing it in historical context, and including an insider's view of the national response to it. The paper is written as a tribute to our mentors Zena Stein and Mervyn Susser, for whom the eighth decade of their lives—the 1990s—was the most challenging of all. Immersed in the struggle against the

AIDS epidemic in their native South Africa, they had to bring to bear all of their past experience, and then some. While working with the opposition to the old Apartheid regime, Zena and Mervyn had already anticipated a need for general training and remodelling in public health after the transition to a democratic society. It soon became clear, however, that history was overturning these plans. As South Africa came under the threat of a catastrophic AIDS epidemic, Zena and Mervyn found their lives largely taken over by a new struggle, the control of HIV/AIDS. By the time of Nelson Mandela's release from prison, it was clear that in the absence of a sustained courageous national intervention, HIV/AIDS was going to have a devastating impact, especially among Black Africans, due to the migrant labour

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system. Zena and Mervyn were among the first to try to alert the government-in-waiting to the pattern of the epidemic. Their key roles and contributions in the Maputo conference of 1990 remain a testimony to their commitment to the problem of AIDS in South Africa (see below; also see companion paper by Ida Susser focusing on women and HIV/AIDS). Since then, and continuing into the present, the largest part of their time has been dedicated to this foremost public health problem of our times, especially training of HIV epidemiologists in South Africa (including the authors).

## Historical Context

In what follows, we describe the circumstances governing the evolution of the epidemic. We note first that, as expected, the particularity of the epidemic is a matter of the history of the country and of the evolution of its economic and social structure.

After the Cape of Good Hope was first colonized in 1652, political domination of the indigenous peoples grew steadily and their social segregation became more complete. The discovery of underground wealth, of diamonds in 1866 and gold 10 years later, led to the region developing a strategic value. The ensuing flood of immigrants and capital transformed the whole pastoral society of both Afrikaner farmers and those black tribes still unsubdued by the colonists. Around these riches, the new mining tycoons, perhaps best represented by Cecil Rhodes, had to build a workforce. To do this, in addition to enticing a rush of European immigrants to the area, they needed to convert black tribesmen, who were subsistence farmers, into labourers. Hut taxes and poll taxes and the desire for manufactured products coerced tribal warriors into the necessities of a monetary economy. New enticements and needs induced them to live in male-only 'compounds' (essentially single-sex barracks) during almost year-long stints as underground workers in the mines—creating the migrant labour system, an essential element of the apartheid design.

## Patterns of Work and Migration

Black workers were only allowed to visit, but not stay with, their families in the cities, and to work under the terms of the pass laws. The relatively few black women in this new urban environment found work serving the households of white families; and a few survived by providing the sexual needs of the men in the mine compounds. This back-and-forth form of migration led to widespread prostitution or, in some cases, 'town-wives' at the mines, with black men returning to their tribal wives only during their periods of leave.<sup>1,2</sup>

Such conditions were fertile ground for the rampant spread of sexually transmitted diseases. In a classic paper of 1949 on the social pathology of syphilis, Sidney Kark<sup>3</sup> first spelled out the mode of transmission of epidemic sexual disease and provided the dismaying data to demonstrate it. The route of migratory labour from city to tribal reserve created the trellis for transmission of syphilis.

The social conditions of migratory labour described by Kark were one of the foundations for the later spread of HIV in southern Africa. To this, for HIV, one must add a secondary route of increasing importance across all sub-Saharan Africa—transportation routes. In Uganda and Tanzania, for instance, the epidemic

followed the tracks of the main truck routes. In South Africa, one illustrative study that enlisted sex workers at truck stops in the KwaZulu-Natal province of South Africa clearly demonstrates the multi-country distribution of the drivers across the whole region to the north of South Africa.<sup>4</sup> Hence, when in 1985 a survey of workers in the gold mines (drawn from the whole Southern African region) showed HIV to be rare in South African miners but already at 3% prevalence in Malawians, it was a warning that South Africa was yet to see the worst given the inter-linked nature of southern African economies.<sup>5</sup>

## The Anti-Apartheid Movement and HIV

The Apartheid regime saw the HIV epidemic as a problem in blacks or gays and saw neither as a priority deserving of serious attention. Hence, during its embattled last days, it remained indifferent. At the same time, it was not uncommon for black communities to attribute the epidemic scare to the evildoing of a hated government. Any effort to take up the challenge of the immense task of changing patterns of sexual liaison was doomed as it would have to overcome the stigma of the Apartheid government's unpopular population control programme, which targeted the black communities.

As late as 1989, the progressive anti-Apartheid movement was more concerned with dealing with the immediacy of liberating the country than the possibility of a future AIDS threat. Some shift in sentiment followed the first formal meeting of anti-Apartheid health activists inside the country with those in exile and their international allies. This meeting, organized by the Committee for Health in Southern Africa (CHISA), which was chaired by Mervyn, took place in April 1990 in Maputo, Mozambique.<sup>6</sup> By chance, this was weeks after Nelson Mandela's release from imprisonment—after 27 years on Robben Island—which heralded the opening moves in the transition from Apartheid. A short while later, the National AIDS Convention of South Africa (NACOSA) was established and their work gave the impetus to the new government of 1994 to undertake the first serious endeavours to stem the epidemic.

## Overview of the HIV/AIDS Epidemic

The first case of HIV infection in South Africa was reported in 1982 and this heralded the start of the first wave of the HIV epidemic, which was limited to the gay community, blood transfusion recipients and haemophiliacs. At least until 1987, levels of HIV infection in the general heterosexual population remained relatively low, as shown in mineworkers,<sup>7</sup> voluntary blood donors,<sup>8</sup> and stored specimens from community-based surveys.<sup>9</sup> In 1990, prevalence in women attending public antenatal clinics hovered close to 1% with an estimated doubling time, based on mathematical models, of 14 months.<sup>10</sup> The heterosexual HIV epidemic is distinct in that it was due to subtype C HIV while the preceding epidemic among gay men was almost entirely due to a different subtype of HIV, subtype B.

Since establishing a foothold in South Africa, the heterosexual HIV epidemic has had a distinctive character—'explosive' spread with no sign of a 'saturation' plateau and predominance in women at younger age. The spread of HIV in South Africa is best described as explosive because of the rapid rise in HIV prevalence. National HIV prevalence rates, based on annual

anonymous antenatal surveys,<sup>11</sup> rose from 0.76% in 1990 to 10.44% in 1995 and 22.4% in 2000. The sharp epidemic curve shows no sign as yet of a plateau suggesting saturation and possible decline. Incidence and prevalence rates at the epicentre of the epidemic in KwaZulu were soon found, in an unremitting pattern, to be highest in young women in late adolescence and in men a decade older (Figure 1).

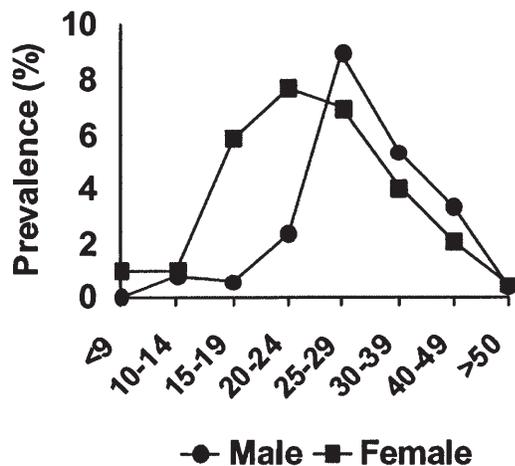
In later years, while imputed incidence remains exceptionally high in young women, the expected rise in prevalence among survivors of both sexes to older ages naturally followed.

Temporal trends in Hlabisa, a rural district in South Africa of KwaZulu-Natal, and across all the similar rural districts of KwaZulu-Natal also point to an explosive epidemic. Since 1992, anonymous HIV serosurveys in Hlabisa,<sup>12</sup> conducted among prenatal clinic attenders, showed a rise in prevalence from 4.2% in 1992 to 34.0% in 1999. Incidence rose from 2.3 per 100 person-years in 1993 to 15.0 per 100 person-years in 1999, as estimated from age-prevalence by statistical methods<sup>13</sup> and, more recently, from the use of the detuned assay (Table 1). Both prevalence and incidence rates for 1999 show 20–29-year-old women to be the most affected age group.

The assembly of various sources of data has enabled actuarial estimates and forecasts to be made of the longer-term trajectory of the epidemic. These macro-level models, although inevitably built on a number of assumptions, are as robust as careful

analysis can ensure.<sup>14</sup> In the year 2000, it is estimated that 40% of all adult deaths in South Africa were due to AIDS. The ratios of deaths at ages 15 to 49 years to deaths at ages 50 years and over in 1990 versus 1999/2000 in males were 0.66 and 1.00, respectively, and in females were 0.31 versus 0.78. The projections for 2010 are even more devastating. In 1990, 38% of 15-year-olds died before age 60 while in the year 2010 it is expected that 80% of 15-year-olds will die before age 60.

Some illustrative data from a large tertiary referral hospital in Durban, KwaZulu-Natal demonstrate the burden on health care services of AIDS morbidity within the HIV epidemic.<sup>15</sup> In 1998, a cross-sectional survey of the in-patient population in the medical wards found that patients with HIV occupied 54% of the beds, and 84% of these met WHO AIDS case criteria. In keeping with HIV seroprevalence data, HIV infected patients were significantly younger than the uninfected (34.9 versus 47.1 years). Case fatality in HIV infected patients was 22%, and 9% in the uninfected. At this referral hospital 56% of HIV positive patients presented with pulmonary tuberculosis. In rural Hlabisa, ongoing HIV testing of newly diagnosed tuberculosis patients<sup>16,17</sup> shows that HIV prevalence rose from 36% in 1993, to 59% in 1995 and 65% in 1997. New tuberculosis cases have a similar age and gender profile to that seen in the HIV epidemic, a preponderance of women and the women are on average about 10 years younger than the men.



**Figure 1** Age and gender differences in HIV infection in rural KwaZulu-Natal 1992

Source: Ref. 19.

**Table 1** Prevalence and incidence of HIV infection among prenatal clinic attenders, aged 15–49 in Hlabisa: 1992–1999

Year	N	Prevalence of HIV (95% CI)	Incidence per 100 person-years
1992	884	4.2% (3.0–5.7)	
1993	709	7.9% (6.0–10.1)	2.3
1995	314	14.0% (10.4–18.4)	7.2
1997	4731	27.2% (25.9–28.5)	8.2
1998	3166	29.9% (28.4–31.6)	9.9
1999	3014	34.0% (32.3–35.7)	15.0

Source: Ref. 13.

## Conclusion

In 1990, Chris Hani, chief of the ANC guerilla force (known as ‘Spear of the Nation’) said, ‘Those of us in exile are in the unfortunate situation of being in the areas where the prevalence is high. We cannot afford to allow the AIDS epidemic to ruin the realization of our dreams. Existing statistics indicate that we are still at the beginning of the AIDS epidemic in our country. Unattended, however, this will result in untold damage and suffering by the end of the century.’ Chris Hani was tragically assassinated shortly before democracy was achieved.

Since political liberation in 1994 many have commented on ‘what went wrong’.<sup>18</sup> What could have been done and was not? We see four possibilities of ‘what might have been’. First, the government might have given strong moral leadership, calling on citizens, community-based organizations, and non-governmental organizations to join forces and on those working in health, social and educational institutions to initiate and oversee the critical steps of education, facilitation and prevention. A concerted social movement, which created new norms in sexual behaviour, was needed. Without strong political leadership this movement could not be realized and prevention efforts remained fragmented and their effects dissipated. Second, government needed to take concerted action, using its extensive resources to focus especially on the main source of spread, after the successful 100% condom use in sex workers model of Thailand. This type of intervention, promoting 100% condom use among South African youth early in the epidemic, could have had a dramatic impact on the epidemic curve. Third, those in charge of economic policy should have targeted the migrant labour system for change, appreciating that it was a major factor. Finally, a sustained effort could have been made to introduce effective treatments that became available at low cost, at the very least nevirapine for prevention of maternal to child

transmission. Probably a combination of all these steps would have been required to bring the epidemic under control.

In practice none of these steps were approached with the foresight, vigour and urgency that were called for. The historic change achieved by liberation forces was not harnessed to confront the epidemic, and the prophetic words of Hani went unheeded. We must continue to campaign for the goal he put forward, for until we achieve it, the untold suffering of HIV/AIDS will continue in southern Africa.

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# From Susser's causal paradigms to social justice in Australia?

Fiona Stanley

There are significant implications for epidemiology, public health and social justice from the recent critiques of modern risk factor epidemiology by Susser and others. The need to move away from a focus at the proximal end of causal pathways and from single risk factors in individuals to looking at populations and the social and environmental contexts in which risk factors arise, points us more towards the social antecedents of diseases and other poor outcomes. In this paper I argue that we must pursue this broader agenda if we are to address the increasing burden of social morbidity in our communities, particularly amongst children and youth.

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## Susser's Critique of Modern Epidemiology The need for a new era

'The present era of epidemiology is coming to a close. The focus on risk factors at the individual level—the hallmark of this era—will no longer serve. We need to be concerned equally with causal pathways at the societal level and with pathogenesis and causality at the molecular level.'<sup>1</sup>

The recent criticisms of modern epidemiology<sup>1–9</sup> stem from its focus on single risk factors in individuals and the tendency to ignore the social, behavioural and ecological contexts in which risk factors arise. Study after study describes the associations of many disease outcomes with social or economic factors and then proceeds to control for them in analyses that focus on more proximal risk factors in the causal pathway, some of which

could be thought of as early signs of the disease. 'We have a myopic over-emphasis on proximal causes of disease and a concomitant neglect of upstream or distal factors that culminate in the final causal chain.'<sup>3</sup> This approach encourages a public health response which targets the individual to change behaviour, rather than targeting the societal situations which provide the environments in which risks arise.

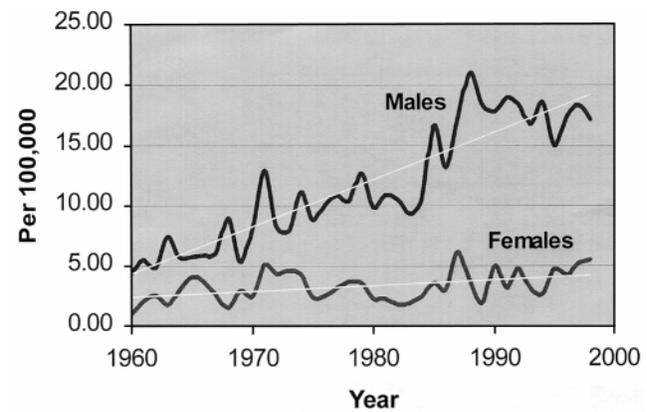
Modern epidemiology also assumes that both risk factors and disease outcomes are static and dichotomous rather than evolving and distributed throughout the whole population. Many social risks operate across a continuum of intensity ('dose') as well as varying throughout life. Population interventions that seek to modify mean population exposure may result in far greater reductions in poor outcomes than those which target individuals.<sup>10</sup> We use sophisticated mathematical modelling to seek the independent effect of single risk factors and control for confounding, which frequently results in the important distal factors, which may be important in the causal path, being rejected from the model.<sup>11</sup>

Only recently have we started to realize that molecular and genetic science could be used to advantage to help elucidate these pathways, rather than be rejected as 'basic science' and nothing to do with proper epidemiology or public health. In fact the elucidation of the code for the human genome and the explosion of genetic and biomedical research should actually encourage collaboration with epidemiologists.<sup>12</sup> Whilst promises relate mostly to new treatments, the most exciting research that should emerge from this new knowledge is to investigate how genetic risks are modified by the social and physical environments in which we live, which may open up many more roads to effective interventions to improve public health. If epidemiologists do not participate in this process, it may not deliver the benefits in terms of improving population health.

## Developmental Health and Well-being in Australia

These issues in epidemiology and public health are not just academic arguments.<sup>13–15</sup> They have enormous relevance to the response which we now urgently need to mount to counteract the effects of the rapidly changing social, biological and ecological environments in which we live. Over the last 30 years in Australia (and in many developed countries) we have observed increases in many major childhood disease categories and disabilities.<sup>16</sup> These include mental health disorders, asthma and allergy, type 1 diabetes, neurological and developmental problems such as cerebral palsy, autism, and behavioural problems. (See ref. 16 for detailed references for each of these trends.) These increases are so substantial that the levels of morbidity can only really be tackled by preventive strategies as the health care and welfare systems cannot afford to meet the demand for treatments and services, and for many of these diseases there are no effective treatments.

Figure 1 shows the dramatic increases in young, particularly male, suicide rates in Australia—the rate for males has quadrupled and that for females has doubled over the last 30 years.<sup>16</sup> The startling level of mental health morbidities in West Australian children is similar to that reported from Canada<sup>17–19</sup> (Table 1)—one in five teenagers has a mental health morbidity which interferes with their daily life. The increasing rate of



Source: Australian Institute of Health and Welfare Mortality Monitoring System

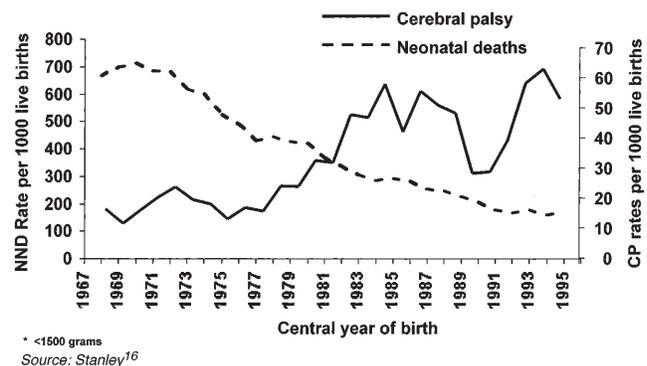
Figure 1 Suicides, 15–19-year-olds, 1960–1998

Table 1 The Western Australian Child Health Survey: children with mental health<sup>a</sup> problems

	Number ('000)	Per cent
Males	30.0	20.0
Females	23.5	15.4
4–11-year-olds	30.8	16.0
12–16-year-olds	22.7	20.6
All children	53.5	17.7

<sup>a</sup> As determined by caregiver and teacher using the Child Behavioural Checklist.

Source: Zubrick *et al.* 1995.<sup>17</sup>



\* <1500 grams  
Source: Stanley<sup>16</sup>

Figure 2 Very low birth weight\* cerebral palsy and neonatal death rates (3-year moving averages) in Western Australia, 1967–1996

cerebral palsy in very low birthweight infants (Figure 2) as more and more of these tiny babies survive epitomizes the 'perinatal paradox',<sup>20,21</sup> our obsession with keeping small babies alive and our dismal failure to prevent preterm births and disability in the wider community. Trends in preterm births are increasing<sup>16</sup> and much of low birthweight and preterm birth arises in social adversity.<sup>22–24</sup> The major (and increasing) cause of post-neonatal cerebral palsy in Western Australia is now child abuse.<sup>11</sup>

Those in social research disciplines are reporting similar increases in behavioural problems, child abuse and neglect, educational problems, drug and substance abuse and juvenile crime. Whilst the causal pathways to these problems are many and varied there are similar and common antecedents in many of them. If we can elucidate effective early interventions, we may influence a variety of outcomes not just health.

### Changes in Australian Society— 'The Great Disruption'<sup>25</sup>

Table 2 lists the indicators of social functioning in our society which have changed dramatically over the last 30 years in Australia; changes which have occurred in many countries. These profound changes in population risk add complexity and a sense of urgency to our work. Changes in these social patterns have the potential to impact adversely on developmental health and well-being and do so in complex and interacting ways.

### Implications of Susser's New Paradigms for Epidemiology and Public Health Response to the Challenges of Modern Society

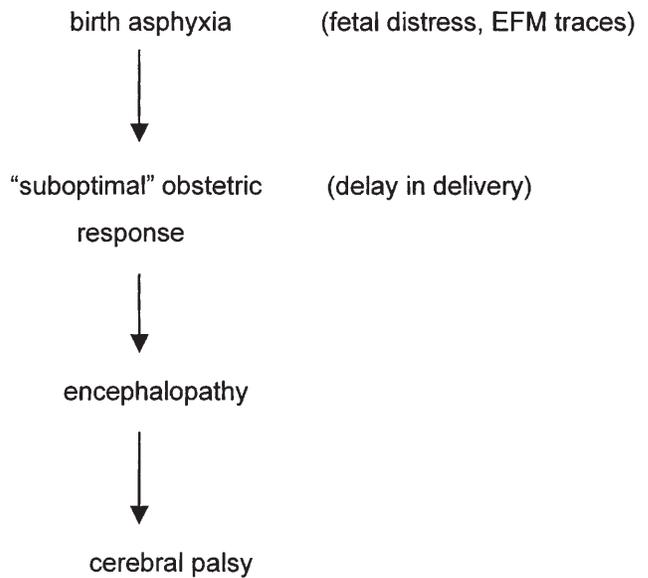
Susser's new epidemiological paradigms and these increasing social problems in our societies have profoundly important implications for our research and prevention agendas. Our own research in Western Australia, as well as that from elsewhere, has shown that the social, community, family, biological and economic influences identified for many complex disease pathways appear similarly important in a range of other educational, psycho-social, behavioural and criminal outcomes.<sup>26-28</sup> Causal pathways thinking opens up the concept of multiple outcomes from single pathways and multiple pathways to single outcomes. Of course it also opens up new and more numerous preventive strategies, some of which, if acting early enough in the pathway, are far more effective and perhaps cheaper than those targeting later risk factors or early disease.<sup>11</sup>

Figure 3 shows the traditional risk factor thinking in the cause of cerebral palsy. Focusing on this birth asphyxia pathway

**Table 2** Indicators of social disruption in Australia 1970s–2000s

<b>Families, neighbourhoods, wider society</b>
<b>Increases:</b>
Divorce, blended families, family conflict, violence, stress
Work (stress, women working)
Child care
Families in poverty
Children needing fostering
Unemployment
Extended adolescent dependency
Addictions, gambling
Inequalities (wealth, health, education, access, information)
Insecure neighbourhoods, social isolation
Environmental degradation
Racist sentiments
Individual greed, corporate wealth

Source: Stanley, Blair, Alberman 2000,<sup>11</sup> Stanley 2000.<sup>16</sup>



Source: Stanley, Blair, Alberman 2000<sup>11</sup>

**Figure 3** The 'Holy Grail' (single risk factor) cause of cerebral palsy

has damaged obstetric care, as obstetricians have been sued for not delivering the perfect baby following the availability of new tools supposedly able to detect 'birth asphyxia' and doing caesarean sections to reduce brain damage.<sup>11</sup> As many have now shown, the causal pathways to the cerebral palsies are many, most commencing antenatally.<sup>11</sup>

Modern epidemiologists would argue that there have been some successes with the individual risk factor approach to prevention. Whilst we have had considerable success in preventing cot deaths by changing infant care practices (particularly prone lying)<sup>29-31</sup> and neural tube defects by population strategies to increase folic acid intake,<sup>32</sup> Aboriginal rates for these are still high and overall birth defect rates are rising.<sup>33</sup> Pearce<sup>5</sup> and others suggest that the success of risk factor epidemiology has been of more temporary and more limited value than many claim. He suggests that the achievement of the public health movement on a global basis has been to shift the problems (such as smoking-related illnesses) from rich to poor within countries, or from rich to poor countries. This is a direct implication of an epidemiology based on individual factors (e.g. tobacco smoking) rather than on population factors (e.g. tobacco production, advertising and distribution, and socioeconomic influences on consumption).<sup>5</sup>

Simplistic causal paradigms which ignore the multi-level and complex nature of pathways, and policies and interventions which focus on a limited number of risk factors at some point along these pathways, are not going to serve us well.

Thus the implications for epidemiology are to acknowledge the complexity of causal pathways to a range of poor outcomes, investigate the social and ecological contexts in which causal pathways arise, develop better measures and analytical methodologies, create cross-disciplinary research collaborations with geneticists, psycho-social researchers, economists, sociologists

and others, expand and link large population data bases to better serve a causal pathways approach and plan longitudinal studies carefully to enable multiple and interacting pathways to be studied. Figure 4 shows the new scientific tools we now have to improve epidemiological methods to better serve public health in this new era.

The implications of this approach for public health include challenging the current focus of health promotion on single risk factors to change behaviour in individuals, and identifying effective ways of intervening early in causal pathways. We must also develop collaborations across governmental departments with those making policy in health, welfare, education and crime prevention.

Figure 5 shows the causal pathways to poor Indigenous health in Australia stemming originally from white colonization.<sup>34</sup> The current risk factor approach focusing on individuals would be to target disempowered, marginalized, poorly educated and poor groups of mothers, to stop them smoking, to prevent low birthweight, ear disease and infections in their children. Such programmes fail, whereas those which attempt to strengthen the communities and the conditions in which they live tend to succeed.<sup>35</sup> Success in preventing otitis media is extremely important in Indigenous communities as it is the beginning of

another set of pathways to poor hearing, poor language and educational skills, low self-esteem, delinquency, substance abuse, unemployment, teen pregnancy and crime and thus poor adult social and physical health.<sup>36</sup>

### A New Research and Policy Paradigm—Towards Social Justice?

Research is currently done in silos, yet much research (methods, exposures, causal pathways and analysis) in these different disciplines is of enormous relevance to the causal pathways affecting outcomes of interest to those in other disciplines. Similarly policy and practice is developed in silos—health, education, welfare, employment, justice, housing and family services—and yet decisions made in each of these areas will have profound effects on the outcomes in development, health and well-being. Too few policies are evidence based, cost effective and for many of them we do not have the capacity to truly evaluate the impact of what we do. Australia is a small country (20 million people) with excellent well-funded public services and outstanding population data bases. We have established a major innovative ‘Partnership for Development, Health and Well Being’ which will embrace the Bronfenbrenner ecological model of child development (Figure 6).<sup>36</sup> In this model, the important influences of the larger social structures and economic, political and cultural environments on health and other outcomes are recognized. The impact of the apartheid regime in South African on black children’s health, development and well-being is a powerful example of this.

The rationale for this Partnership include the rising rates of poor childhood outcomes which are so costly and overwhelm current services, the similarity of complex pathways to poor outcomes, most outcomes being associated with adverse social environments, effective solutions coming from elucidating the complex pathways and how to interrupt them, and multi-disciplinary collaborations suggesting important questions and

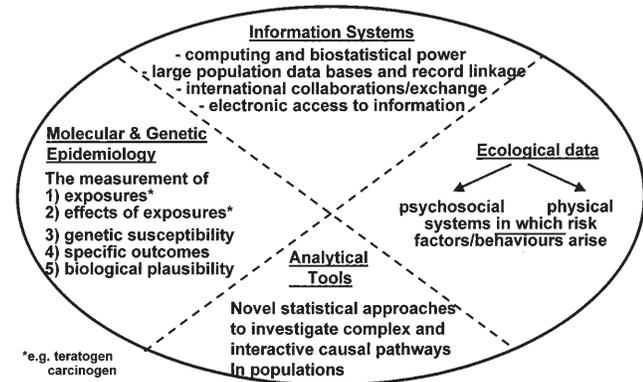
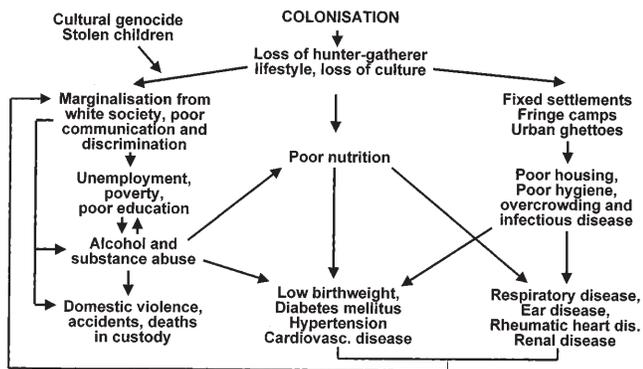


Figure 4 New scientific tools to underpin epidemiological methods to best serve public health



Source: Mathews 1997<sup>34</sup>

Figure 5 Impact of white colonisation on Aboriginal health today

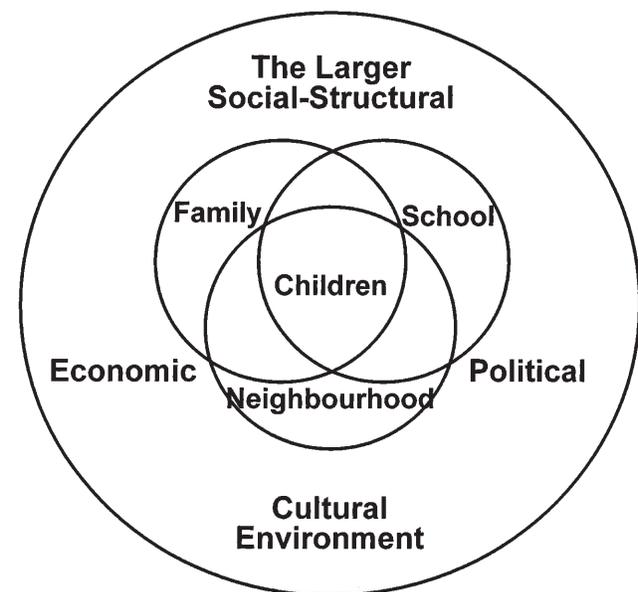


Figure 6 Ecological contexts shaping child development

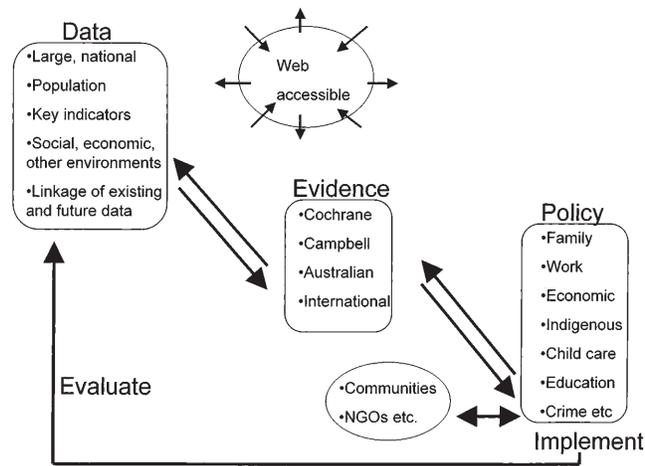


Figure 7 National partnership

the best methodologies to address them. As well, in Australia we have many underused data bases which are immediately available and could be linked together to provide a rich national resource to both aid research and start to evaluate the impact of interventions. Between-State comparisons could be undertaken. Collectively we believe we could increase the capacity for research and government funding for interventions, and the best minds nationally could underpin planning for studies of Australian children with broader and better research agendas than presently. The concept of the Partnership is shown in Figure 7.

As Nelson Mandela said in 1997, 'There can be no keener revelation of a society's soul than the way it treats its children'. If we follow the leadership of Mervyn Susser and Zena Stein, two outstanding public health people whose lives we are celebrating in this symposium, the bringing of rigorous science to improve public health and social justice is how we must proceed.

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# Health rights for women in the age of AIDS

Ida Susser

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Gender inequality continues to fuel the 20-year-old HIV/AIDS epidemic in many countries.<sup>1</sup> Although in the US and Western Europe HIV/AIDS predominantly affects men, in 1999, worldwide, UNAIDS reports approximately the same figures for men and for women—i.e. 1.1 million deaths among men and 1.2 million among women.<sup>2</sup> In sub-Saharan Africa, prevalence figures estimated by UNAIDS for the numbers of men and women infected with HIV are 10.1 million and 12.2 million, respectively.<sup>3</sup> In addition, women are becoming infected with HIV/AIDS and dying at younger ages than men.<sup>3</sup> Estimates for southern Africa suggest that 50% of children age 15 now will die of HIV/AIDS and that three times as many girls as boys in the age group 15–29 are already infected with the virus.<sup>4</sup> However, we are still not able to offer women effective strategies for prevention and governments and non-governmental organizations (NGO) are struggling to develop appropriate counselling and treatment options. Under these dire circumstances, it becomes essential to continually re-consider our approaches.

Let me begin by recognizing the specific influence of Zena Stein on women's health and women's rights. Long before the advent of HIV/AIDS, Zena, always in co-operation with and supported by Mervyn Susser, had embarked on her many decades of research on reproduction and spontaneous abortion. However, soon after the HIV virus was identified, she turned her concerted attention towards the particular problems of women and AIDS.

In the early 1980s when HIV/AIDS was first noticed and later diagnosed medically among gay men, the emphasis was on the men. Almost immediately, poor women with the disease were

also identified. However, they were swiftly classified according to other characteristics, as Haitians or as partners of drug users. They were not seen collectively as women. Some time later, transmission of the virus from HIV-positive mothers to one-third (in the US, and a greater proportion in sub-Saharan Africa) of their infants was discovered. However, these unfortunate mothers, seen in some contexts as guilty women producing innocent victims, often aroused scant concern for their own condition.<sup>6</sup>

It has been well-documented that in the US women were long neglected in research and medical care with respect to HIV/AIDS, a neglect exemplified in diagnosis, pathogenesis, treatment and benefits.<sup>1,5,6</sup> In Africa, neither men nor women benefited much from scientific advances in medical care and public health. The Multicenter AIDS Cohort Study, (MACS) a longitudinal cohort initiated in 1984 and funded by the National Institutes of Health, was confined to gay men in the US and provided much early knowledge of the pathogenesis and prognosis of the disease, and later of responses to treatment. This research provided the base for over 550 publications on HIV/AIDS. Although the knowledge gained from this work was crucial, it could not adequately document the way in which HIV/AIDS reflects the environment in which it is found: in the dominant modes of transmission and the social relations through which transmission is patterned; in the specificity of opportunistic diseases and the synergisms between them; and in the variable responses to treatment with respect to gender, nutrition and general health status.

As Zena and others pointed out, in line with its early spotlight on gay men in the US, research into sexuality and HIV/AIDS is much better developed among men than among women.<sup>7</sup> Despite this climate, and before women sex workers were targeted as an at-risk population, Zena Stein and Robin Flam, then her student, extrapolating from what was known to what was likely, began to develop research on women sex workers.

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In sub-Saharan Africa there was a need for more research into contemporary sexuality and HIV/AIDS among both men and women. Zena joined with Anke Ehrhardt to create one of the few US research centres where such issues have been researched and discussed, and with respect to southern Africa, Zena has been the centre's spearhead.

## Methods Women Can Use

Early on, Zena conceptualized the conflict between the use of the male condom and the limited ability of women to insist on its use in order to protect themselves from sexually transmitted infections and from mortal infection by HIV in particular.<sup>8</sup> She proposed a possible role for a protective substance, a vaginal microbicide (she termed it virucide) which a woman could apply clandestinely, if need be, and pressed for research to create and test such a product. She raised the possibility, especially relevant in Africa, for a microbicide to be formulated that would yet allow sperm to survive. She also recognized a role for the female condom, just then seeking FDA (US Food and Drug Administration) approval—a process that took 7 years!

These ideas, conceived in 1987, were put forward in a paper, in turn submitted to and turned down by the *New York Times* (as an Op-Ed), then the *New England Journal of Medicine*, then *The Lancet* and finally the *American Journal of Public Health* (AJPH). When several reviewers prominent in the AIDS field advised rejection, Alfred Yankauer, the then editor of the AJPH decided to publish it anyway.<sup>8</sup> In retrospect, the paper is seen by many as a classic and a breakthrough in thinking about women and the prevention of sexually transmitted diseases. She developed the idea further in her Plenary presentation to the Tenth HIV/AIDS International Conference in 1994 at Yokohama, Japan, the first time a major session was devoted to methods women can use.

## Women's Changing Experiences with HIV/AIDS in Southern Africa

Since the efforts of Zena and others in the late 1980s, women have clearly been the focus of much work on HIV/AIDS. Health educators and community activists have concentrated on women for education about prevention. However, early messages to them could not be narrower: 'ask the man to use a condom' and 'love faithfully', disregarding the fact that, unlike their men, many women who contract AIDS only have one partner, usually their husband.<sup>6</sup>

Nevertheless, in spite of this concentration on women's education, in southern Africa, the 1:1 prevalence sex ratio of women to men found at the outset has now risen, as noted above, as high as 3:1 in the 15–29 age groups.<sup>4</sup> In the face of such rising rates among women, many concerned health leaders are now calling for attention to men, as those generally wielding greater power in heterosexual relationships.

While tardy, this concern to reach men is constructive and important. However, my own fieldwork and my analysis of policy suggest that a further concern deserves attention. Women's diseases have now been counted and their immediate knowledge and perceptions of disease analysed; at the same time, in analysing the contexts in which prevention is to be introduced we

have under-used an essential resource—the women's own abilities to change and to develop new opinions and strategies. In order to build on this crucial resource, we need to facilitate women's control of their own sexuality and their freedom to actively make choices and determine strategies. Microbicides might be suggested here, but, so far, findings have not matched expectations in this research.<sup>9</sup> The only existing alternative that women can use, the female condom, widely accepted by many women in southern Africa and elsewhere, needs to be made more accessible.<sup>10–12</sup> Women need to hear over the radio and in their churches and clinics information about all forms of prevention and the care of people with AIDS. Both in KwaZulu/Natal, South Africa and in the Oshikati and Rundu areas of Namibia, we found women anxious to receive information and struggling to find community strategies to address the tragedy. We found women taking care of members of their families with HIV/AIDS but not having the necessary resources, such as plastic gloves, medication or transportation, knowledge of possible treatments and safety procedures for the providers.

Some enlightened NGO have tried to provide strategies and options for women. One outstanding example has been the long-standing support by the British NGO, Action Aid, of one of the first and most effective women's organizations in Africa, The AIDS Support Organization (TASO). TASO was first organized in Uganda in the 1980s by a few committed professional women, several of whom were AIDS widows, looking for a way to confront the epidemic. TASO became an international model for women's organizations in the struggle against AIDS and stigma and now, replicated in many other countries throughout Africa, provides care, counselling and support for people with AIDS and their families.<sup>13</sup>

The idea that women can change and learn new strategies to address the AIDS epidemic seems contradicted by reports that pregnant women may not go for testing even when they are informed that their babies could be saved by medical intervention, such as the administration of antiretroviral drugs during labour. In a recent interview, one Botswana woman asked a trenchant theoretical question: 'how will my baby live if I am not there to take care of her?'. This was neither ignorance nor superstition, but a thoughtful questioning of the reach of medical solutions. A Zambian woman, HIV positive and with two infected infants, represented a contrasting perspective when she said to a reporter: 'Of course I shall try to become pregnant again, because only then will I have another chance for a baby that will live'. In fact, the perspectives of each mother reflect clearly rational choices in different social contexts. Some studies of HIV/AIDS orphans document a life of stigma, deprivation and misery as was possibly envisaged by the Botswana mother. However, a recent follow-up of 18 HIV/AIDS orphans in Windhoek, Namibia, not published as yet, but conducted by Scholastika Iipinge and other researchers at the University of Namibia, offers some hope. This research, which suggests that the children in foster placements with relatives were not treated differentially from their children raised in the same households, would provide support for the Zambian mother's determination to try for a third time to give birth to a healthy baby.

Such contradictory perspectives and findings as these should give us pause when we advocate 'counselling' as a solution. The real question facing us is 'counselling for what?'. The ramifications of the epidemic are continually changing as the disease

moves across different groups and recasts the social situation as it ravages the population. In order to address this challenging and fast-changing disease, we have to assist local people with whatever resources and knowledge are currently available, but nevertheless, we have to enlist the women themselves in working out what is appropriate action. Perhaps, initially, HIV/AIDS orphans were particularly stigmatized in many places, perhaps now that HIV/AIDS has become a way of life in almost every extended family in southern Africa, orphans are no longer singled out in this way. Obviously parents that see possibilities for their children to live can also make different decisions with respect to the substitution of formula for breastfeeding, or in finding HIV-negative foster mothers to nurse the babies of HIV-positive women. Both men and women are beginning to confront and cope with the epidemic in new ways and 'counselling' or 'education' has to continually re-adjust both to the mutations of the virus and the creativity of the local people.

Our failures to protect women are not reason to abandon women for work among men. Ethnographic research in southern Africa since 1992, conducted by myself and colleagues, concerned strategies available to men and women to protect their communities from HIV/AIDS and to care for those affected by the disease, and offers some new approaches to the problems of gender inequality.<sup>11,12,14-18</sup> In South Africa and Namibia we found that both men and women said that given the woman's condom, they would not hesitate to use it.<sup>11,12</sup> In 2000, a Namibian NGO, Women's Action and Development, adopted the cause of the female condom and actually organized a demonstration to demand access for Namibian women. Some of the local researchers, in combination with active local representatives from WHO and UNAIDS, formed a Women's Health Initiative. The Namibian Ministry of Women's Affairs, with support from UNAIDS and UNICEF, conducted trials to see if women would use the female condom. The report documenting the success of these trials, combined with active support and petitions from local men and women, resulted in the public launching of the 'Femidon' (the woman's condom) as part of Namibian HIV/AIDS prevention options.<sup>19</sup> Although prices were subsidized, people still had to pay \$8 Namibian for three female condoms (approximately \$1 US) in contrast to approximately \$2.50 Namibian (approximately 25 cents US) for 10 male condoms. In the first 3 months after launch marketers expected to sell 3000 female condoms. In fact, 18 000 were sold! Such events dramatize the fact that, even at higher costs, men and women are willing to try new methods and strategies in order to confront the AIDS epidemic and that a method that may not have been imaginable before the epidemic can be culturally appropriate now.

Among the San of the Kalahari, where Richard Lee and I have been conducting fieldwork, women, as in other parts of southern Africa, were interested in the female condom. However, they contrasted significantly from other women in the region in their attitudes towards men. Where many women among the Ovambo and Kavango in Northern Namibia expressed some fear about directly discussing sexual issues with their male partners, San women were less intimidated. In 2001, in a San village, a woman said to me 'Give us the condoms and we will teach our men to use them'. In this short sentence she expressed a sense of entitlement. This, supported by a wide range of ethnographic data we collected among the San and rarely found

elsewhere, demonstrates the importance of understanding women's options as they vary among different groups.<sup>12</sup> In addition, among the San, the practice of women nursing the babies of other mothers has been long documented.<sup>20</sup> In 2001, we noted at least one instance of a San daughter breastfeeding the surviving baby of her recently deceased mother, along with her own newborn child. Such strategies, combined with an effort to inform women of their own HIV status, could be mobilized among kin who wished to protect babies from the HIV virus.

## Changing Gender Expectations

In every society values are contested and those contests and their partisans have to be understood in historical context. An appropriate address to the HIV/AIDS epidemic requires understanding evolving visions of gender and sexuality among women in southern Africa. These conjure up a range of ideas as cultural views and voices change: ideas of boundaries of the body; moments when conversation is allowed and when people may not speak out; when and at what ages among young girls' virginity can be insisted on and in what ways such insistence on virginity may be used counterproductively and repressively against the young girls themselves; under what circumstances can single or married women safely refuse sexual intercourse. In different situations around the world, men have begun to change their images of masculinity, helping with child care and limiting their sexual partners, in response both to changing social conditions and, specifically, to the demands of women. This evidence of men's flexibility also suggests hopeful directions for HIV/AIDS prevention.<sup>21</sup> Finally, but of considerable import, are responses to the threat of HIV/AIDS in which communities adapt collective strategies locally and social movements may grow in broader scale and thus transform the available options for prevention and treatment.

No less important than understanding the changing views of men and women in southern Africa, is to understand the perceptions among the cosmopolitan policy makers in the centres of power in the modern world, in cities like New York, Washington and Geneva. What options such influential groups regard as culturally appropriate for the women of southern Africa confronting the epidemic. Both international decision-makers and local health professionals, relying on earlier ethnographic descriptions of tradition, culture and modesty, can too easily fail to grasp the capacities of people to change and learn new methods, or for communities to respond constructively as they face the extreme circumstances of the epidemic. Only if global decision-makers have a clear understanding of the potential of women and men to respond to desperate circumstances in constructive ways can they direct the finances and the intellectual resources in effective ways.

Gay men in the US have fought to have their sexuality viewed with dignity and consideration and to take control of their own future, nevertheless, still, poor gay men have fared least well.<sup>22</sup> Since it has been poor women, women of colour and women of Africa who have been the most dramatically affected by HIV/AIDS, and since such women may have even less access to power than those stigmatized for sexual orientation, their sexuality has not been afforded the same consideration and dignity. Neither HIV international policy makers nor local public health workers have yet been fully effective in providing the resources for

women to define and expand their own strategies and options for protection, treatment and care with respect to HIV/AIDS.

The treatment of the female condom, in the US media and even among many women researchers on microbicides, is a contemporary and important example.<sup>10–12</sup> As long as the female condom is dismissed as a cumbersome and inelegant device in the US and judged by different standards than the male condom, its acceptance as a highly desirable alternative to the male condom in southern Africa can be conveniently ignored, a tragic loss to the urgently needed prevention agenda.

From the international to local level we need to re-examine the extent to which we have or have not understood and facilitated women's own concerns, choices and plans. In the light of the continuously changing biological and social context of HIV/AIDS we need to work towards an approach which gives women the tools they need, and enrols them as strategists. Only under such conditions can scientific perspectives reach their full potential in combating the HIV/AIDS epidemic.

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# Two lives, three legs, one journey: a retrospective appreciation of Zena Stein and Mervyn Susser

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In their first edition of *Sociology in Medicine*, Mervyn Susser and William Watson, his collaborator, noted:

The proponents of a genetic cause of the unequal distribution of intelligence in the social classes have long argued their case with the proponents of the environmental cause ... But whatever effects innate intelligence may have on the social mobility of individuals, current theories in genetics cannot by themselves account satisfactorily for the observed class distribution of low intelligence.<sup>1</sup>

This observation drew upon work Zena Stein and Mervyn Susser had published in 1960, barely four years after their arrival in Britain from South Africa and three years after receiving positions at the University of Manchester.<sup>2–5</sup> Using a grant awarded to Zena, they had conducted a follow-up study of a randomly selected sample of young adults drawn from a population who, as children, had been determined by their schools to be educationally subnormal (ESN). Without disputing the possibility of causal links between genes and subnormal intelligence, Susser and Stein sought to elucidate the social factors embedded in the designation of a child as mentally deficient. They found that almost all ESN children notified by the school authority of Lancashire County and of Salford City (adjoining Manchester) derived from the lower social classes. But they also saw evidence that the career of a working class ESN child varied by family organization and family culture, both of which signalled particular hazards.

On the one hand were 'demotic' families, those geographically rooted over several generations in which the men were manual workers without acquiring greater skills and education; families that remained separate from local middle class values. In this subculture, Stein and Susser contended, children were at risk of intellectual delays that teachers and physicians might diagnose as intellectual deficiency. Supporting that position was their finding that intelligence scores for these children at adulthood, following years of life experience, were significantly higher than their initial IQ scores. Stein and Susser also argued that, because of social bias, children of demotic families were at

greater risk of being labelled ESN. They found that the IQ threshold for ascertaining ESN was higher for these children; moreover, those who came from broken homes or families in trouble with the authorities were more frequently designated ineducable and, in adulthood, were more frequently institutionalized. On the other hand, children of 'aspirant' working class families diagnosed as ESN tended to have significantly lower IQs at initial testing and little change at follow-up. They came from families seeking upward mobility through educational attainment and non-manual employment. All children in the sample from aspirant families showed symptoms of neurological damage, severely defective hearing, and/or an IQ at the imbecile level. It was possible, according to Stein and Susser, that teachers and doctors offer children from this subculture a label that avoids a worse diagnosis of mental deficiency and allows them special educational treatment.

The study came to a number of conclusions. It raised questions about the validity of genetic surveys and clinical research, both possibly flawed by ascertainment bias. It made the point that IQ was not invariant; subsequently, it suggested that mild mental retardation in clinically normal children might be reduced or prevented through educational interventions. Finally, Stein and Susser asserted, 'It is evident from this investigation ... that culture, social class and family function profoundly influence the diagnosis and management of the educationally subnormal child'.<sup>5</sup>

This relatively early study contains important elements that would persist through much of Mervyn Susser's and Zena Stein's research. First is the belief that human health and disease are in large measure socially determined; they are deeply influenced by a community's social relations, culture, and its institutions of medical care. Second is the commitment to elucidating or addressing social inequities or injustice, often as they are manifested and experienced as disease and death by segments of a population. Third is a conviction that their research ought ultimately lead to clinical, institutional and social policy changes.

Finally, more difficult to discern, is a dynamic, dialectical sense of history. In this period this was most clearly stated by Mervyn Susser. In *Sociology in Medicine* he wrote: 'The individual organism ... [and] populations comprise survivors of a process of selection working through the interaction of constitution and environment over time, and they are best studied by methods which allow for the time dimension'.<sup>6</sup> This consciousness of life as a process continually affected by living in and overcoming one's environment was not simply an academic abstraction, but one derived from two lives already marked by perilous times.

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Mervyn and Zena were born in South Africa (26 September 1921 and 7 July 1922, respectively), the children of Latvian and Lithuanian immigrants fleeing the efflorescence of anti-Semitism in the Russian Empire. Zena grew up in a Jewish community in Durban. As a teenager, she was particularly well aware of the human costs of racism in Nazi Germany. Zena's mother led the effort to organize assistance to the German-Jewish refugees arriving in Durban, often accommodating them in her home while helping them find new residences, schools and employment.

Zena's parents, part of the progressive community in Durban, formed a Left Book Club with friends. Here they developed critical perspectives on such issues as labour, the Spanish Civil War and the internment camps in Germany. Zena's parents also invited Blacks and Indians to their home, highly unusual in South Africa of the 1930s. Mervyn, too, became aware of socialism, communism and fascism, but more on his own, through his wide reading during his high school years.

The experience of World War II proved critical in crystallizing Mervyn and Zena's opposition to racism and segregation in South Africa, while ultimately allowing them to see in medicine and later epidemiology a way to merge their developing political and social philosophy with their professional lives. It is not without interest that for South Africans, World War II was a European war, a war that only indirectly affected their country thousands of miles away from its colonial metropolitan centre. Although South Africa entered the war on the side of the Allies, military duty was neither mandatory nor especially popular. The South African army was a volunteer army, one that attracted the country's more politicized or socially conscious citizens.

In 1940, after completing his initial year at Witwatersrand University in Johannesburg, Mervyn joined the army as a private in the infantry and participated in the hard-fought Abyssinian and North African western desert campaigns. During those years, Mervyn was deeply influenced by his sergeant, who provided him with a range of political literature that he consumed during periods of inaction. After three years in the army, Mervyn transferred to the Air Force and active service in Italy, where he received additional political education from the left-leaning friends of his squadron. It was the closest one of these who convinced the skeptical Mervyn that he ought to study medicine, and that it could be wielded as an instrument of social and political reform.

For Zena, the early war years coincided with her university training in Cape Town. There she was immediately radicalized by her swift education into the racial and class inequities of South African society, and there she engaged in debates, discussions and demonstrations. Political action did not interfere with her brilliant academic career; in four years, Zena earned a Bachelor's and Master's degree in history and was awarded two gold medals for her work. In 1942, she was offered the Queen Victoria Scholarship to study history at Cambridge, but postponed that offer in order to join the army. In devoting herself to the war effort, Zena has said that she was making common cause with male friends and relatives who, to her anguish, were in danger of being killed.

During the last year of the war, Zena took advantage of special courses in the basic sciences to prepare herself for medical training, something she had previously declined, following her father's wishes. In these classes, she met Mervyn, recently

discharged from the Air Force. They had met as children, when Mervyn, a student in Durban, began his life-long friendship with Zena's older brother, Sylvester. The two of them, in fact, planned Mervyn's Bar Mitzvah for him, and Mervyn, who had lost his own mother to suicide, was taken under wing by Mrs Stein. Separated by university, then by the war, Mervyn and Zena now found in each other a political camaraderie that linked, then deepened, their renewed relationship. They were married during their fifth year in Witwatersrand Medical School. For the past half century, their personal, political, and professional lives have been conjoined.

Involved in the spectrum of post-war politics, Zena and Mervyn concentrated especially on student-related issues. In one of their actions they organized a mass student protest against the medical school's practice of barring Black students from its autopsy room whenever the corpse examined was to be that of a white person. This practice had mainly to do with maintaining political dominance over non-whites, since the school hired Black labourers to wash and carry the corpses, black and white, into the autopsy theatre.

The years following 1945 were heady with contradictions. The official propaganda line, that the country had fought for equality and against authoritarianism, made of the war an extraordinary moment in which the hypocrisy of South Africa became ever more apparent. However, the immediate post-war period appeared to be one of hope and even optimism as the relatively liberal government passed legislation aimed at expanding the rights of Africans and of providing needed services to Black townships. Even before the war ended, it had assigned Sidney Kark and his wife Emily to train personnel for a national system of community health centres focused upon primary care and preventive medicine. Pholela, the landmark health centre, initiated by the Karks in 1940 in rural Natal, was to be the model. The new centres, plus Pholela itself, formed the training grounds for a significant number of socially conscious young physicians, some of whom would help develop medicine as a social and communal enterprise throughout the world. In South Africa, sadly, such clinics proved a short-lived experiment, stifled after 1948 by a resurgent Nationalist Party promoting a policy of apartheid that rigidly separated the races and denied Blacks the most basic services. Forty centres, most in black areas, had been established.

Mervyn and Zena learned of Pholela and Sidney Kark's interest in social medicine during their second year of training. They were already committed to practising a medicine that would make a difference to the Black population. They sought to work in a community setting offering preventive or 'promotive' medicine that touched many aspects of life. Mervyn and Zena found in Kark an inspirational teacher and guide. Through him they could gain expertise in the treatment of the diseases of the African population, particularly those associated with malnutrition and infection; these had been barely touched on in their medical lectures or textbooks, which focused almost entirely on the diseases of whites. Most excitingly, Kark instructed Stein and Susser in epidemiology; his was a non-theoretical clinical epidemiology whose source of data was the patients and the community and whose purpose, *inter alia*, was to improve the services provided by the health centres.

Their epidemiological and medical careers began coevally in 1952. Immediately after internships, they joined with another

radical couple, Michael Hathorn and Margaret Cormack, to direct and staff the Alexandra Health Center and University Clinic in the black township of Alexandra in Johannesburg. Together they all held two-and-a-half jobs, which allowed them time for further training, research and, in Zena's case, to have two more children, Ezra and Ruth, in addition to Ida. (Ida was born in 1950, the year Stein and Susser graduated.) At Alexandra, the foursome struggled to develop a sound comprehensive health care service. They created an appointments system, added specialty clinics, developed multi-professional health care teams that included women from Alexandra Township, and created domiciliary obstetrics and tuberculosis programmes.

Zena and Mervyn's commitment to learning about and treating diseases in the Black population included, for all visits, the systematic recording of diagnoses. From these data derived their inaugural epidemiological articles, published after their exodus from South Africa. But in the year before their departure, Stein and Susser saw their first scientific paper in print.<sup>7</sup> In it they succeeded admirably in drawing a socioeconomic sketch of Alexandra Township, as evocative as it is concise, and of the morbidity that followed from the Township's pervasive poverty, population density and social disorganization. Alexandra contained the manual labourers, the majority of whom were male, who had been permitted to migrate to Johannesburg to work in its factories and businesses. Such places were central to the organization of a society moving from a rural to an industrial economy, like the slums of Manchester or Mulhouse in the early 19th century, but unique because of the rigors of apartheid legislation. In terms reminiscent of social critics of that earlier century, Stein and Susser described the patterns of disease and death peculiar to South African social change.

'Alexandra Township, with its 80 000 African and Coloured people living in an area of 1.5 sq. miles, lies on the outskirts of Johannesburg ... The population is changing from a rural to an industrial society; the old extended family, which provided its own social security, is breaking up ... The men are employed in ... the factories, in businesses, as domestic servants, at an average wage of about £3 a week. Many women work in the city ... sleeping in servants quarters in Johannesburg ... Budget studies ... have shown that it is theoretically impossible for an Alexandra family to subsist on the average income ... There are no sewers; refuse disposal is inadequate; the roads are ditches and the streets are unlit. Because of a lack of funds no fundamental measures for the control of communicable disease can be undertaken ... With both parents at work and no after-school activities girls and boys bring themselves up as best they can. Not infrequently the high-school girls have illegitimate babies or contract venereal disease, while boys join gangs and embark very early on a life of crime. Fear of the white man, his prisons and pass-laws; economic insecurity; fatigue from long hours of work and underfeeding—all give rise to emotional tensions.'<sup>8</sup>

Despite their meaningful work at Alexandra, Mervyn and Zena were well aware of the increasingly restrictive legislation and policies of the Afrikaner nationalist government. Politically engaged, already working with Nelson Mandela and Walter Sisulu and other radical opponents of the regime, they knew

their time at the clinic was limited. On a matter of principle—speaking at a rally for Helen Navid, a friend and colleague recently banned by government order as director of the Entokozweni Community Center because of political activism—Mervyn refused the request from his governing board that he either not appear on the platform or resign. He was swiftly fired; Zena of course left with him. The year was 1955. They returned to Durban, where they worked for six months as registrars at King Edward VIII Hospital while awaiting faculty appointments to the Durban Medical School of Natal University, positions that required government approval. At that time, they were founding members of the progressive, white National Congress of Democrats, allied to the African and the Indian National Congresses. They also joined an illicit underground cell, part of a network formed to generate resistance and offer money and safe housing to dissidents in flight. But they also feared for their eventual arrest, an agonizing prospect for parents of three young children.

In 1956, the year of the Suez crisis and the uprising in Hungary, Stein and Susser left for a brief stay abroad, which unexpectedly became a long journey out of South Africa to London, Manchester and New York City. Still awaiting word on their positions, increasingly convinced they would never come through, Zena had persuaded Mervyn to book passage for the whole family to London, where they could stay a year, long enough for Mervyn to earn the higher specialist qualification in the Royal College of Physicians. With the rapid arrest of many of their friends in South Africa that year and the flight of others abroad or underground—later to include Mandela, Sisulu, Oliver Tambo and Joe Slavo—Mervyn and Zena realized their sojourn had turned into exile. But with the strong recommendation of Jerry Morris, whom they had recently met, Mervyn was offered the position of Lecturer, Zena of Research Fellow, in the Department of Social and Preventive Medicine, at the University of Manchester. They were to remain there until 1965.

In Manchester, Zena and Mervyn drew on the clinical, social and epidemiological data they had brought from South Africa. They published their pioneering descriptive studies of childbirth-related morbidity and mortality rates in Alexandra and of the critical factors associated with those outcomes, based on the results of their domiciliary obstetrics practice there.<sup>9,10</sup> Given the lack of interest in the health problems of non-whites in South Africa, the Stein and Susser articles were almost alone in presenting well-measured obstetric morbidity and mortality rates of that population. (Exceptions include the work by Eva Salber and Evelyn Bradshaw, whom they cite.) With this research, Stein and Susser inaugurated their life-long interest in reproductive epidemiology, an area that would come to include research on low birthweight, mental retardation, and spontaneous abortion.

Shortly after these publications, Mervyn and Zena began studies of the epidemiology of enuresis. In their research, they were able to demonstrate that variations in enuresis rates were associated with many of the same social factors they had found in mildly retarded and backward children, namely social class, family structure, family culture and custodial institutions. Through this work they hoped to create a model that could elucidate the relation between social and clinical factors in an easily defined outcome. 'If we could unravel the association of a complex variable such as social class with one symptom, we

might hope to reduce broad relationships to more specific ones. By so doing, we wished to devise socio-medical methods ... for the study of the social relationships of disease and aberrant development.<sup>11</sup>

Characteristic of their work, Stein and Susser conceptualized children with enuresis as *survivors* of a group, all of whom began as bedwetters.<sup>12</sup> This application of the cohort model may have been influenced by their crucial application of cohort analysis to peptic ulcer shortly before. (The classic article that followed plus an account of its genesis, 'Civilization and Peptic Ulcers 40 Years On', is to be found elsewhere in this issue.) But an historical perspective, as already noted, is emblematic of their approach. It was to be present again in future cohort investigations, the Dutch Famine study<sup>13</sup> in particular, as well as in more theoretical writings like the austerely abstract *Causal Thinking*<sup>14</sup> and Mervyn's recent work with his son Ezra on the current crisis in epidemiology.<sup>15</sup>

The last major publication of the Manchester period was *Sociology in Medicine*, which Mervyn co-authored with William Watson, a collaboration which, by all accounts, was Zena's inspiration. The book was Susser's most comprehensive and theoretical attempt at combining the social and the medical in order to understand the multi-level relationships between social milieu, health and disease. Like their contemporaries in social medicine, Susser and Watson sought to elucidate the social context of disease by using concepts and techniques drawn from epidemiology, demography, anthropology, sociology and/or social psychology. Mervyn's understanding of social science and medicine was further deepened by exchanges with Herbert Hyman, Robert Merton, Paul Lazarsfeld, and others at Columbia University after Stein and Susser's arrival in the US in 1965. The relationship between social science and epidemiology has been the subject of a number of works, including the aforementioned *Causal Thinking*.

Stein and Susser came to the US for a year-long sabbatical. Mervyn had received a Belding Scholarship from the Association for the Aid of Crippled Children to learn what he could from American sociology and another from the Milbank Foundation to survey departments of community medicine in the country. Like their previous one-year sojourn to London, this trip became the next leg of their life's journey. Mervyn was offered and accepted the position of Professor and Head of the Division of Epidemiology in the School of Public Health of Columbia University. Zena accepted an Associate Professorship and became, shortly thereafter, head of the Epidemiology Research Unit of the New York State Psychiatric Institute. Their pioneering work in their new positions has already been described elsewhere.<sup>16</sup>

Their arrival in the US also marked a third shift in their epidemiological research. As previously described, their research in South Africa had been a clinical epidemiology closely linked to practice. At Manchester, where they did not see patients, theirs became an analytical approach to the distribution of disease states, with an eye towards policy change. In the US they turned to analytical epidemiology, with results that have made them justly well-known. Well before their departure from Manchester Stein and Susser had begun their thinking about cause in epidemiology, deeply influenced, after 1960, by MacMahon, Pugh and Ipsen's germinal textbook on modern epidemiology.<sup>17</sup>

If Stein and Susser had several times made the point that populations and individuals were the survivors of a long process

deeply modified by experience, they understood that individuals could draw upon their history to make sense of or shape the present and near future. What was true of conceptual work, as already indicated, held for political and moral concerns. In the UK Stein and Susser became public speakers and educators on conditions in South Africa, and, in addition to demonstrating and founding the Manchester Anti-Apartheid Committee, they provided support to those who, like themselves had been forced to flee the country. Once in the US they continued to aid refugees; after 1973, like Zena's mother years before, they made their home an asylum for émigrés, particularly those escaping Pinochet's Chile. They encouraged and advised other political activists, like Mary-Claire King, who, as she describes in this issue, used her profound knowledge of human genetics to identify the 'disappeared' in Argentina and the Balkans. During the 1980s, as the anti-apartheid movement intensified in South Africa, Mervyn and Zena organized CHISA, the Committee for Health in Southern Africa, once again to alert the public about the links between social organization (including the recognition of human rights) and disease in that country.

In post-apartheid South Africa, Mervyn and Zena continue to be politically and scientifically engaged, particularly against the AIDS epidemic that is ravaging the country's Black population. Their indirect and direct contribution to research is evident in the two articles in this journal by Quarraisha and Salim Abdool Karim and by Ida Susser.

In their scientific work, Stein and Susser have often enough made clear their political posture, their dedication to social change and human dignity, and the role of epidemiology in affecting both. Their lives have also been committed to developing and pursuing a scientifically rigorous, technically innovative epidemiology. When their investigation of the Dutch famine winter led them to conclude that they could find no association between their measures of mental competence and prenatal nutrition, they accepted the outcome despite the fact that it undercut strongly held beliefs and progressive politics in the field of nutrition and human development. Subsequently, Ezra Susser and colleagues, in re-analysing data from the Dutch Famine Study, were able to find associations between levels of prenatal nutrition and specific health outcomes as the cohort matured. As a consequence, the Study has led to a new body of research concerning prenatal determinants of adult health.

More recently, they publicly raised their voices against the policies of Thabo Mbeki, the president of South Africa, when they saw him abandoning the results of years of scientific research to embrace the hypothesis that the human immunodeficiency virus was not a cause of HIV/AIDS.<sup>18</sup> In their long lives, in which they have produced a formidable, important body of work, they have striven to maintain the integrity of both their political and scientific values. It is a lesson worth noting.

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# Genomic sequencing in the service of human rights

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## Dedication

Like everyone else who is a part of the celebration of the 80th year of Mervyn Susser and Zena Stein, the invitation to include my work in this collection has delighted, honoured and overwhelmed me. I have known Zena and Mervyn since I was 30, both my entire life as an independent scientist and my entire life as a mother. That I have been able to be both has been due to the example of Zena, more than anyone in the world. For 25 years, she has supported me intellectually and emotionally, with intercontinental collaborative projects or a cup of tea, whichever was more critical at the moment.

As my birthday present for Mervyn and Zena, I offer the story of genomic sequencing in the service of human rights, because

it grows from the way they do science. Not that this is literally a Susser-Stein project. I have been swept up in many of those, but this is not one of them. Rather, I was able to conceive of this project 17 years ago and carry it out since because of the principles I have learned from these two. In thinking about this celebration, I have tried to formulate those principles explicitly, which is a little difficult, because for me, learning from Zena and Mervyn is entirely deductive. But here are a few things I have learned from them that have been important to me:

The most righteous projects demand the most rigorous science.

No question is too big to ask.

The most important questions come from people on the frontlines.

Good and evil are both real, and the distinction is obvious.

Speaking a language poorly is better than not speaking it at all.

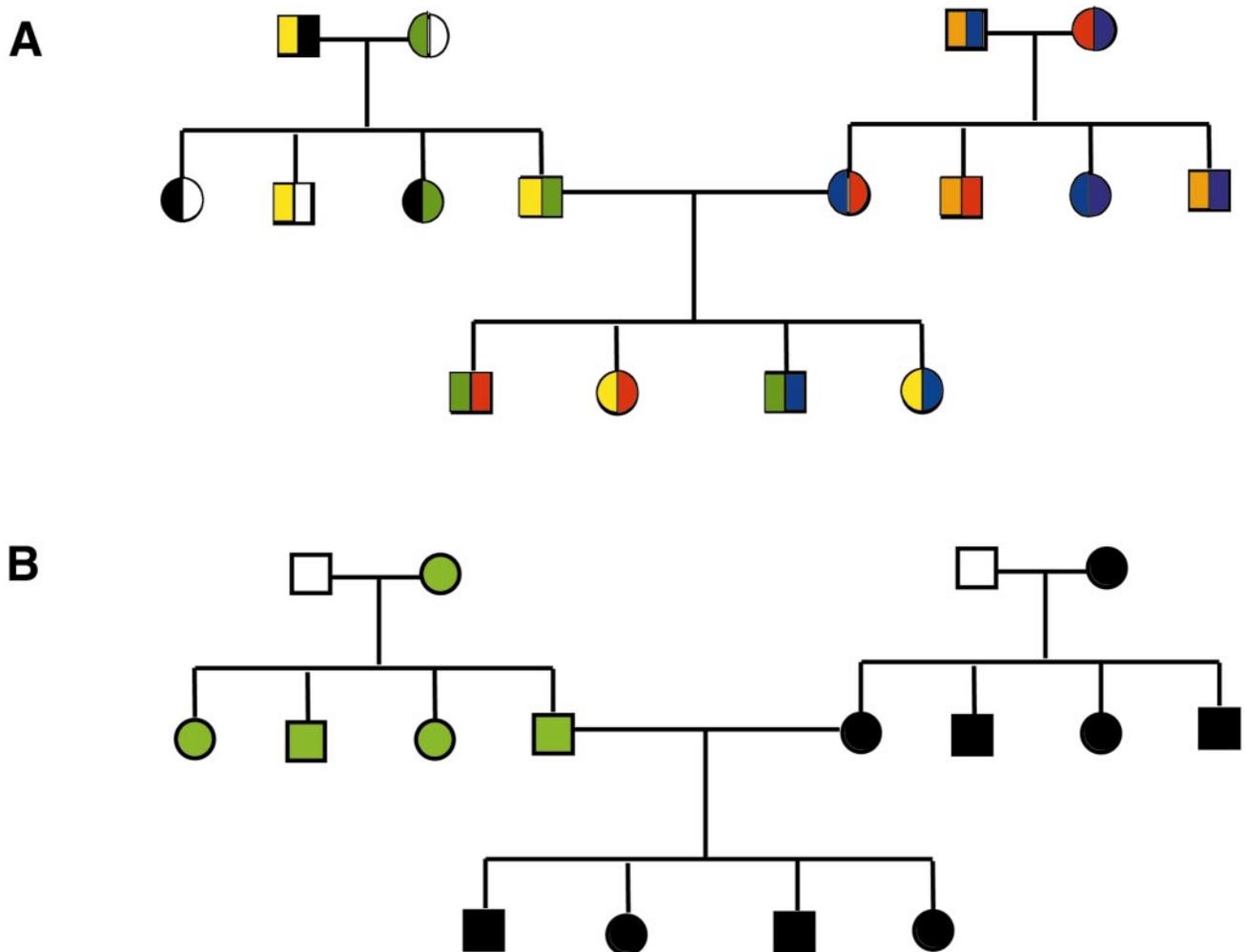
Progressive politics are perfectly compatible with good wine.

So many thanks, Mervyn and Zena, and happy birthday. I hope you will like this story.

Mary-Claire King

Tools of genomic analysis have been used to assist the identification of victims of human rights violations.<sup>1-4</sup> Here we describe two recent applications, the identification of a young adult Argentinian born in captivity 22 years ago when his mother was abducted and disappeared in Buenos Aires in 1978, and the identification of remains found in mass graves in the Balkans in the 1990s. In both these situations we used DNA sequences to identify one individual among many (one child among many children; one body among many bodies) by genetically matching the individual to family members whose relative had disappeared.

Identical genomic information is carried by all tissues of a person, and thus is an inseparable source of personal identity. There are two genomes: nuclear and mitochondrial. Nuclear genes are inherited from both parents (Figure 1A); mitochondrial genes are inherited only maternally (Figure 1B). For resolving questions of identity in human rights contexts, mitochondrial DNA (mtDNA) is especially powerful, for several reasons. First, one purely maternal relative can provide information about an entire lineage. This is possible because a mother transmits her mtDNA sequence to all her children, male and female. Therefore, each person shares their mtDNA sequence with their mother, sisters, brothers, maternal aunts and uncles, maternal grandmother and her brothers and sisters, and so on. In many human rights investigations, only a few relatives survive to provide a record of genetic information. If the missing person (male or female) has one surviving relative to whom he/she is purely maternally related (i.e. related entirely through mothers),



**Figure 1** Inheritance of nuclear genes (A) and mitochondrial genes (B). Males are indicated by squares and females by circles. Nuclear genes (A) are inherited from both parents; siblings may share zero, one, or both parental forms of any specific sequence. Mitochondrial sequences (B) are inherited entirely through mothers. All people with black symbols share the same mtDNA sequence; all those with green symbols share a different mtDNA sequence.

then mtDNA can be useful.<sup>3</sup> Second, mtDNA is powerful for identification because mtDNA is extremely variable from family to family. Throughout human evolution, and indeed earlier, mutations have accumulated in mtDNA.<sup>5,6</sup> Because one portion of the mtDNA genome does not encode any genes, a very large number of mutations could accumulate in this region without any deleterious effect.<sup>7</sup> In consequence, one portion of the mtDNA genome is the most variable region of the entire human genome.<sup>8</sup> Thus, mtDNA sequences are shared by purely maternal relatives, and each maternal lineage has an mtDNA sequence that is nearly, or even completely, unique. Third, there are many more copies of the mtDNA genome than of the nuclear genome in a cell, so mtDNA is easier to obtain from remains of victims.

We have used mtDNA sequencing to identify victims of human rights abuses in 11 countries and regions.<sup>4</sup> In this report, we explain its application to two historical situations, in Argentina and in Croatia.

## Methods

For all living individuals, small blood samples are obtained by venepuncture or finger prick and blood absorbed on sterile filter paper and sealed in a sterile plastic envelope. Samples are obtained from all participating family members of a missing person. For cases involving living, putatively kidnapped children, blood samples from these children are collected in the same manner at the request of the overseeing courts. For remains of deceased people, any tissue could in principle provide DNA for identification. For remains that are largely skeletonized, as are usually encountered in human rights investigations, teeth or bone are generally the only remaining sources of DNA. In our experience, teeth are the best source of DNA from skeletonized remains, because enamel protects the pulp of the tooth, where cells containing DNA are located, from both degradation and contamination.<sup>3</sup> For these projects, DNA was extracted and mtDNA sequenced as previously described.<sup>2,3</sup>

Although most mtDNA sequences are unique to one lineage, some are 'public sequences', in that they appear in multiple families who are not closely related to one another. Frequencies of these public mtDNA sequences vary between populations.<sup>9,10</sup> For this reason, for each of our projects, it was essential to establish a database of mtDNA sequences obtained from the local population. From the mtDNA sequences of these population controls, we estimate the frequency of each sequence we encounter in an identification case and thereby evaluate the likelihood of observing a match between a missing person and survivors by chance rather than due to biological relationship.

## Results

### Argentina

In March 1976, a military dictatorship overthrew the elected government of Argentina. Between 1976 and 1983, thousands of Argentinian citizens (and other nationals) disappeared. Among the disappeared were infants and young children, who

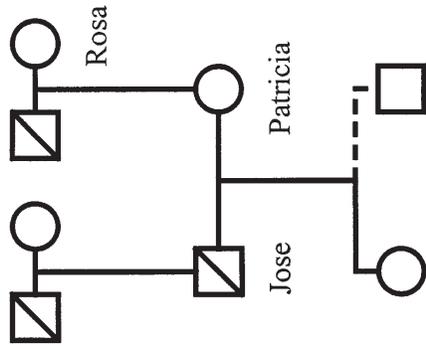
were kidnapped at the same time as their parents. Also among the disappeared were children born in captivity to young women who were pregnant at the time of their abduction. In 1977, the grandmothers of these children formed the Asociación de Abuelas de Plaza de Mayo to locate the missing grandchildren. The grandmothers collected reports of clandestinely 'adopted' children and undertook a variety of strategies to locate missing children.<sup>1,4,11</sup> After the military withdrew from power following defeat in the Falklands War, elections were held and a National Commission on the Disappearance of Persons (CONADEP) was established to determine the identity and circumstances of the disappearances. By September 1984 CONADEP had documented evidence of the kidnapping or killing of over 8800 people.<sup>12</sup> By 1986, *Nunca Mas*, the official report of CONADEP, indicated the actual number of disappeared might be as many as 30 000.<sup>13</sup> Included among these were 220 documented cases of disappeared infants and children.

Throughout this period, the grandmothers learned of children who might have been among the kidnap victims. But which children belonged to which biological family? Beginning in 1984, we used genetic testing to identify these children, establishing at the same time a databank of DNA and a database of mtDNA sequences of family members seeking a disappeared child.<sup>1,2,4</sup> The Argentinian National Genetic Databank includes one mtDNA sequence representing each participating maternal lineage. We found that mtDNA sequences are quite diverse in the Argentine population. In our database, the average number of nucleotide differences between mtDNA sequences of two randomly selected unrelated individuals is 11.2. This diversity has proven useful in identifying children located by the grandmothers or who have come forward themselves.

The case of Guillermo is a recent example. In 1999, the Abuelas de Plaza de Mayo were informed anonymously of a young man (Guillermo) who might have been an abducted child. Guillermo was interested in participating in the investigation and provided a blood sample to the laboratory. We sequenced mtDNA from Guillermo's sample and compared it to all sequences in our database of Argentinian families. Guillermo's mtDNA sequence was identical to that of one person in our database, namely Rosa, the mother of Patricia (Figure 2).

Rosa's DNA was in our database for the following reason. On 6 October 1978 security forces had kidnapped her daughter Patricia and Patricia's husband Jose. Patricia was 8 months pregnant. She and Jose were taken to the clandestine prison at the Navy Mechanics School. Fellow prisoners reported that Patricia gave birth to a son, whom she named Rodolfo, on 15 November 1978. Patricia and Jose remain disappeared. Rosa had been searching for Rodolfo for the past 21 years.

As an additional test of the sequence match of Guillermo and Rosa, we obtained a blood sample from an undisputed daughter of Patricia and Jose. This daughter, Mariana, was visiting a friend at the time of her parents' disappearance and hence survived. As anticipated, the mtDNA sequences of Guillermo, Rosa, and Mariana were identical and differed from all other mtDNA sequences in our database. Because our mtDNA database includes >2000 entries, an estimate of the frequency in the Argentinian population of Rosa's sequence is 1/2000. Therefore the likelihood



Mariana Guillermo/Rodolfo?

**mtDNA HVR1:**

**Rosa and Mariana Guillermo** CGCTATGTAATTTTCGTACATAATTACTGCCAGCCCATCATGAATATTGTACGGTACCATAAATACTTG CGCTATGTAATTTTCGTACATAATTACTGCCAGCCCATCATGAATATTGTACGGTACCATAAATACTTG

**Rosa and Mariana Guillermo** ACCACCTGTAGTACATAAAAAACCCAAATCCACATCAAAAAACCCCTCCCCCATGCTTACAAGCAAG ACCACCTGTAGTACATAAAAAACCCAAATCCACATCAAAAAACCCCTCCCCCATGCTTACAAGCAAG

**Rosa and Mariana Guillermo** TACAGCAAATCAACCCTCAACTATCACACATCAACTGCAACTCCAAAAGCCACCCCTCACCCACT TACAGCAAATCAACCCTCAACTATCACACATCAACTGCAACTCCAAAAGCCACCCCTCACCCACT

**Rosa and Mariana Guillermo** AGGATACCAACAAAACCTACCCACCCCTTAAACAGTACATAGTACATAAAGCCATTTACCGTACAT AGGATACCAACAAAACCTACCCACCCCTTAAACAGTACATAGTACATAAAGCCATTTACCGTACAT

**Rosa and Mariana Guillermo** AGCACATTATAGTCAAATCCCTTCTCGTCCCCATGGATGACCCCCCTCAGATAGGGGTCCCTT AGCACATTATAGTCAAATCCCTTCTCGTCCCCATGGATGACCCCCCTCAGATAGGGGTCCCTT

**mtDNA HVR2:**

**Rosa and Mariana Guillermo** GGTGCTGCACAGCCCACTTTCCACACAGACATCATAACAAAAAATTTCCACCAAACCCCCCTT GGTGCTGCACAGCCCACTTTCCACACAGACATCATAACAAAAAATTTCCACCAAACCCCCCTT

**Rosa and Mariana Guillermo** CCCCCTGCTTCTGGCCACAGCACTTAAACACATCTCTGCCAAACCCCAAAAACAAAGAACCCCTA CCCCCTGCTTCTGGCCACAGCACTTAAACACATCTCTGCCAAACCCCAAAAACAAAGAACCCCTA

**Figure 2** The mtDNA sequence of Rosa and her undisputed grandchild Mariana is shown above the mtDNA sequence of Guillermo, whose identity was not known. The sequences are identical to each other and different from all others in our database of more than 2000 people. Sites at which this sequence differs from the consensus mtDNA sequence<sup>8</sup> are underlined

that Guillermo shares this sequence with Rosa (and Mariana) by chance, rather than because they are maternally related) is 1/2000 or 0.0005.

As Guillermo's case indicates, mtDNA sequencing allows identification of a maternal lineage even when information from the family is incomplete. This is the case for the disappeared grandchildren, who are now young adults and whose parents remain missing. More than 60 have been identified and been reunited with their biological families. Guillermo, the most recent, now grapples with the news of his origins.

### Croatia

In mass graves remains from many people are co-mingled. Identifying remains present in a mass grave is important both for families and for prosecution of war crimes. Positive identification of individuals can be difficult using only classical forensic analysis. Individuals may swap or hide identifying documents in attempts to flee persecution. Genetic evidence can aid such identifications, adding a level of resolution not previously available.

On 19 November 1991 patients, staff and local refugees were awaiting evacuation from Vukovar hospital in Croatia when Serbian troops overran the hospital. Reports indicate that 300 people were transported from the hospital to the nearby countryside. A mass gravesite discovered shortly thereafter at a farm near Ovcara was thought to contain the bodies of those who had been in the hospital. In 1995, at the request of the International Criminal Tribunal for the former Yugoslavia (ICTY), an international team of forensic investigators excavated the gravesite. Remains of 200 people, 198 men and 2 women, were exhumed.<sup>14</sup> For each set of remains, morphometric traits were documented, as was location within the gravesite and proximity to any documents, clothing, or other belongings that might indicate identity.

Three sets of materials were sent to our laboratory for DNA sequencing: tooth and bone samples from remains, blood samples from surviving relatives of missing individuals, and blood samples from volunteers from the general population to serve as population controls. We received samples of tooth or bone from 62 individuals, 59 of which yielded adequate mtDNA for sequencing. The mtDNA sequences of 233 maternal relatives of missing family members and of population controls were determined using DNA extracted from blood. The mtDNA sequences of teeth and bone were compared to mtDNA sequences of maternal relatives. The frequency of each sequence was estimated from the population controls from the region and from our global database.

Of the 59 mtDNA sequences from remains, 46 matched the sequence of a relative searching for a missing person. In 21 cases the mtDNA sequence of the deceased individual matched only one family. In 26 cases the mtDNA of the deceased individual matched more than one family; that is, the sequence was 'public,' at least locally. Additional evidence from the mass grave could be brought to bear on all these identifications, with focus restricted by mtDNA sequencing only to the families potentially related to each individual. The mtDNA sequences of 13 other individuals matched no survivors. These cases most likely represent individuals without living family members available

to participate. Relatives of deceased were informed of results of the forensic analysis. Positive identification of the victims was included as evidence presented by the prosecutor of the International Criminal Tribunal of the former Yugoslavia at the Hague.<sup>14</sup>

The mtDNA sequences from the Vukovar project revealed interesting features of the genetics of maternal lineages of Bosnian, Croatian, and Serbian populations. The maternal lineages of these populations overlap. That is, individuals who self-identify as Croatian have mtDNA sequences found also within the Serbian and Bosnian populations. Similarly, individuals self-identifying as Serbian have mtDNA sequences found also in the Croatian and Bosnian populations, and so on. Despite their ethnic and religious divisions, there are no significant differences in frequencies of mtDNA variant sites among these groups.

### Conclusions

We have described how our approach has been applied in Argentina and in Croatia. We have applied the same approach to human rights cases in El Salvador, Guatemala, Haiti, Rwanda, Mexico, Chile, Honduras, Ethiopia, Philippines and elsewhere in the Balkans. Human rights violators have used increasing levels of technology to perpetrate their crimes. Genomic tools provide an opportunity to use advances in biotechnology to combat these crimes worldwide.

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