entrainment in night shift workers. At the same time, there will be emergencies when physicians must work across circadian nadirs and, for these times, we must identify optimal short sleep schedules and truly effective fatigue counter measures.

One important factor left out of the Australian Medical Association's risk assessment checklist is how rested physicians are at the start of duty. Sleep loss has cumulative effects on performance, and the intern or resident who is out late at night is far more likely to have lapses in judgment and performance than the well-rested intern or resident. It is essential that the interns/residents do their part to minimise fatigue-related error. This particular point cannot be regulated, and therefore requires a cultural change. As such, physician role models must reiterate this particular point frequently.

In conclusion, while we await improved science upon which to base work hour schedules for healthcare

providers, the Australian Medical Association's National Code of Practice for work hours, combined with the cultural change of delivering rested physicians to the bedside, is an excellent foundation on which to build evidence-based practice of safer work hours.

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Genetics

Genetics and occupational safety and health

Karl T Kelsey

Commentary on the editorial by Schulte (see page 717)

In occupational health much has been made of the potential impact of the "genetic revolution" on worker health.¹ Schulte² and OEM are right to ask the direct question—what hath this wrought? In the accompanying editorial Schulte acknowledges that although genetics has not yet had a major impact upon occupational health and safety, with continued research critical questions raised by this type of information will need to be addressed and answered.² Has what we posited 20 years ago to be a relatively straightforward march toward understanding genetics and integrating these data into exposure-related disease susceptibility become so very complex? Just how important is this issue and how far away are we from genetics having any palpable effect on worker health?

The general approach to the hazardous environment can be characterised by (1) problem recognition, (2) evaluation of the environment, and (3) application of controls (including prevention and hazard elimination). This simple guiding paradigm has stood the test of time. We apply

it today, intuitively and explicitly including the rapid changes in science and technology. Does the genetic revolution affect our paradigm? Indeed, it is probable that knowledge of genetic susceptibility to a toxicant or infectious agent could affect our recognition of potential harm as well as our parallel evaluation of the hazardous environment. In fact, it also might suggest novel control strategies or approaches to hazard elimination. Hence, keeping a watchful eye on the progress of this "revolution" is indicated.

Where are we to look for the signposts? As Schulte suggests, genetic variation in individual response to exposure to beryllium stands as a prominent example. Here the science is sound and there is active discussion of the appropriateness of worker genetic testing and screening.³ The practice of occupational medicine in this one area has incorporated the genetic data, although as yet there is no consensus on its potential utility. Although the science addressing genetic susceptibility to workplace toxicants is not similarly established for any

other case, it is conceivable that this may occur. In the case of infectious agents, we have the example of the *CCR5* polymorphism and its association with resistance to HIV.⁴ Here the science is sound, but this has had less prominent effects upon worker health. It is similarly likely that there will be genetic variation described that will have a significant impact on individual susceptibility to other important infectious agents, such as tuberculosis.⁵ This will resonate in the healthcare workplace, as well as in other workplaces where this disease is endemic.

Interestingly, what these cases have in common is that they are single agent exposures with a pathologic process involving pathways that are either known or under very close scrutiny. Thus, one is tempted to assert that it is far too early to look for scientifically useful biomarkers of susceptibility to complex mixtures and complex environments. As this really represents the majority of workplaces, it is completely possible that the genetic revolution will affect worker health only very moderately in the foreseeable future. That is not to say that genetics may not have profound influence; rather, the simple has become complex, and the utility of this technology must await a scientific consensus that is likely to remain elusive.

So, what of the contributions in the meantime? Where will this research have an impact? Assessing this landscape, it is likely that the study of genetics and genomics applied to exposure-related disease will point us in new directions and thereby reap enormous rewards in defining

disease mechanism. One profound example actually arises from the recognition of disease associations that are not genetic. Rather, our research is now pointing us to the companion study of *epigenetics*. This can be defined as the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.⁶ Epigenetic changes are almost certainly responsible for heritable adverse consequences of DES, and recent research points to likely epigenetic roles for the induction of the toxic consequences of herbicide exposure,^{7,8} and asthma and respiratory disease (which are obviously exposure-associated).⁹ Hence, perhaps one of the great contributions of genetics and genomics to occupational health is not in the elucidation of gene-environment interactions and disease associations. Rather, one of the real values of this research is its failure to become a part of practice and, thereby, has opened other complementary paths of research. So it is—the simple becomes complex.

As we move ahead we can be assured that new paradigms will emerge to supplant the old ones, pushing us further towards having the tools we require to more completely understand occupational disease. Genetics is a piece of the puzzle, but only a piece. We have begun to realise this and, importantly, we may soon be ready to incorporate what we have learned and move forward once again to new frontiers. The practice of occupational medicine is ready to incorporate novel approaches and information, but only when it is rigorously tested, medically reliable and ultimately adaptable into our time-tested framework for protecting worker health.

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Genetics

Genetics and occupational health and safety

Harri Vainio

Commentary on the editorial by Schulte (see page 717)

A recent study in China concluded that the incidences of neurasthenia and of ultrasonographic abnormalities in the livers of vinyl chloride-exposed workers increased with increasing cumulative exposure dose.¹ This is an important finding, especially as the exposure to vinyl chloride studied was below the current Chinese permissible occupational limit. The same study also reported that the *CYP2E1 c1c2/c2c2* genotype was significantly associated with liver damage (OR 3.3).

How should occupational health and safety professionals use these data? A further decrease in the occupational health standard for vinyl chloride in China should be the immediate reply. How about the data on polymorphic *CYP2E1*?

We are on the threshold of a new revolution in understanding the interaction of genes with the environment. The relative roles of heritable and environmental causes in occupational hazards are an important scientific issue, with

many practical consequences. Traditional geneticists have emphasised genes, while epidemiologists have argued for the environment. The literature on disease causation is full of overstatements, but recent data from twin and family studies offer more scientifically-based estimates of the apportionment of disease causation. With the emergence of the versatile tool of single nucleotide polymorphisms, studies on “gene-environment interactions” have become popular. The studies have produced a number of reports with no or only modest impacts of gene-environment interaction on environmentally-induced disease.² Furthermore, there are many embedded controversial issues. Mass reporting of results has occurred, with little consideration of the functionality of single nucleotide polymorphisms or the tissue of expression of the relevant genes in subgroups with little biological rationale. It is ironic that the traditional roles of epidemiologists and geneticists appear to have been reversed:

the proponents of gene-environment interactions seem to be stressing the overwhelming importance of genetic factors acting in concert with environmental factors, while geneticists are raising concern.³

The setting of permissible occupational exposure limits is a practical example of the importance of understanding the relative contributions of the environment and genes. The role of polymorphic genes in occupational disease risks has been the subject of extensive research for several decades. Some polymorphic genes do not present a risk in the absence of a given exposure but do so when the exposure occurs.

As Schulte points out in his editorial, “it remains unclear to what extent identifying susceptibles can be applied in occupational safety and health”.⁴ Unlike most occupational exposures, which can be reduced or eliminated if proven to cause harm, inherited gene variants cannot be changed and can be passed on to subsequent generations. Given the number of metabolising enzymes and the wide variation in their expression, it would be too simplistic to propose that one gene at a time be examined in relation to disease risk. Therefore, methods and techniques have been developed for examining whole pathways, containing tens to hundreds of genes, and their expression patterns in relation to disease risk. In a shifting strategy, researchers are using whole-genome scanning to search for disease genes. This technique casts a wide net over the genome, allowing researchers to