

# The 'worried-well', insulin resistance and metformin therapy

**To the Editor:** I would like to respond to the letter with the above title that appeared in a recent issue of the *Journal*.<sup>1</sup> The authors wrote: 'The decision whether to use insulin sensitisers in patients with impaired glucose tolerance is still being debated, but there is certainly no evidence that these drugs will either help the patient lose weight or prevent progression to diabetes in individuals without dysglycaemia.'

Metformin has been tried in obese individuals without diabetes as a tool for inducing weight loss. Several studies<sup>2-5</sup> found that metformin decreased body mass index (BMI), waist-to-hip ratio and total cholesterol and increased high-density lipoprotein cholesterol in obese but non-diabetic patients.

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# Zebras and bergkwaggas – the case for research on rare and very rare genetic diseases in South Africa

**To the Editor:** I recently had the privilege of learning firsthand about some very uncommon genetic diseases during a clinical infectious diseases rotation at the National Institutes of Health (NIH) in Bethesda, Maryland. Most of our patients had rare inherited immunodeficiency syndromes, such as chronic granulomatous disease and Job's syndrome, resulting in chronic intractable infections with unusual mycobacteria and fungi. These patients came from around the USA, sometimes even from other countries, for periodic elective admissions to the hospital section for a full workup. One of our patients had befriended a patient from another clinical section, and they shared a ride from Virginia when they came for their annual admissions. When I discreetly enquired what 'zebra' (the US medical student term for a very rare disease) the friend might have, the nurse replied: 'Oh that must be the guy from Tangier Island with Tangier disease.'

It turns out that Tangier disease (TD), an extremely rare (less than 50 cases reported worldwide) genetic disorder of



cholesterol transport, is named after an island – really a large sand bar – located in the Chesapeake Bay, just off the coast of Virginia.<sup>1</sup> Settled by English watermen in the 1680s, Tangier Island has remained a secluded enclave for more than three centuries. The inhabitants still speak a quaint Elizabethan dialect, and most of them bear one of four surnames from the original group of founders. It is therefore not surprising that a founder gene defect would eventually be expressed in such a small gene pool. TD was first identified in a 5-year-old boy from the island who had characteristic orange tonsils, very low levels of high-density lipoprotein (HDL), and an enlarged liver and spleen.<sup>2</sup> Importantly, the low (or absent) levels of HDL in the blood predispose TD patients to premature coronary heart disease (CHD). The recent discovery of ABCA1 (ATP-binding cassette A1) as the defective gene product in TD is a major advance in lipoprotein research and has shed light on the role of low HDL levels in CHD.<sup>3</sup> ABCA1 is a cell membrane protein that mediates the efflux of excess cholesterol from cells, particularly macrophages, into the HDL metabolic pathway for transport to the liver. Defective function of ABCA1 in TD therefore leads to sterol-laden macrophages in tissues and atherosclerotic plaques, as well as reduced plasma HDL. Because of its ability to deplete macrophages of cholesterol and to raise plasma HDL levels, ABCA1 is a promising therapeutic

target for preventing CHD, not only in TD patients but also in the general population.<sup>3</sup>

Zebras, and even bergkwaggas, are of course not that rare in South Africa. Several genetic disorders occur with an unusually high frequency among South Africans. These include founder gene disorders such as variegate porphyria (South African genetic porphyria), familial hypercholesterolaemia, Fanconi's anaemia, and keratolytic winter erythema (Oudtshoorn skin disease), which are seen particularly in the Afrikaans-speaking population. Research on these rare, and very rare, genetic diseases should be supported because the latter provide the extreme conditions in humans that could show up solutions for diseases that are much more prevalent in all South Africans. Recent identification by the Cape Town group<sup>4</sup> of the gene mutation prevalent in South Africans with variegate porphyria has already led to better diagnosis of this common and debilitating disorder. In the era of the genomic revolution and bioinformatics there are currently unprecedented resources available to aid the study of genetic diseases, including an ever-expanding number of free Internet genetic databases from the National Center for Biotechnology Information (NCBI). In addition, the NIH has established an Office of Rare Diseases (ORD) to help stimulate and co-ordinate research on various 'orphan diseases' (less than 200 000 cases in the USA). The



opportunity to access these powerful resources, which enable the concentration of clinical, molecular, and computer approaches, should be seized in order to obtain a deeper understanding of the various genetic diseases that collectively afflict so many South Africans.

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## SAMA and sexuality – breaking the silence

**To the Editor:** Jon Larsen's letter entitled 'Doctors and sexuality'<sup>1</sup> is commendable for its clear, forthright approach. It adds an important dimension to the politically correct view offered by the SAMJ's Deputy Editor on the subject.<sup>2</sup>

Yes, SAMA is silent on these issues, but it should speak out against all practices that affect the mental, physical, emotional and spiritual health of the population. Jon Larsen's comments are particularly pertinent. It is indeed amazing that despite every major religion denouncing premarital and extramarital sex, the medical profession remains silent on the issue. To be practical these goals may not be attainable for the majority in our present culture, but do we give up promoting abstinence before marriage and faithfulness within it? Do we simply cut our losses and promote safe sex for all irrespective of any moral considerations, even those that may impact on health?

We are inextricably linked to our consciences and if our sexual practices do not fall in line with the fundamental teachings of our churches, mosques and synagogues then surely internal tension and in some cases even turmoil may result. That this must impact on individual health is logical. We therefore have the choice of either trying to modify our consciences to stay in line with society's changes, or attempting to halt that change by speaking out against the practices we believe will affect us and our patients at some level at some point in time. The morality of modern day society moves continuously in small increments in the direction it pleases, but never without consequences. Individually and collectively the medical profession has the choice to stand firm or follow. If we choose the latter then what we believe to be unacceptable today we may find acceptable tomorrow, and our practice of medicine will become progressively more devoid of absolutes. (It is worth recalling that in this country the legal abortion of healthy babies on request was once regarded as morally beyond consideration).

In the past medical practitioners were viewed as more than physical healers. We were held in high esteem for our professionalism, our ethics and our adherence to high moral standards highlighted by our Hippocratic oath.

Our silence on these aspects of sexuality may be interpreted by many as condoning the practices outlined by Jon Larsen while showing no regard for the health consequences of such behaviour. It is quite likely that this will lead to our further diminishment in the eyes of those we care for.

Yes, SAMA should not be silent, but perhaps it is time to stop and think about how to break that silence. If we only adhere to what seems politically correct then the medical profession, which has the ability to set a precedent, may lose the opportunity to take the lead on those moral issues that impact on the physical, mental, emotional and spiritual health of our people.

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## Legal, but is it right?

**To the Editor:** Specialists in private practice have the legal right to charge whatever fees they wish, but sometimes they leave behind frustrated people.

A 59-year-old widow developed a breast lump. The surgeon told her that she would need 'an operation and a reconstruction' and that 'medical aid will take care of the payment'.

Medical aid paid the hospital fees. The surgeon's fees were three times higher than the medical rate. The medical aid refused to pay the reconstructive surgeon, demanding an adequate motivation as to why she needed reconstruction. The widow had no extra finances. A relative paid R4 000 to the primary surgeon over the medical aid rate and R8 000 to the second surgeon.

When the patient tried to obtain a motivation for the reconstructive surgery to send to the medical aid, the primary surgeon's practice refused to provide one. 'This is a super-specialist practice and not a discount supermarket. The patient was fully informed about our fee structure,' she was told. This was not true! She was also told that 'the reconstructive surgeon must write the motivation'.

The old medico-legal adage applies. If it was not written down, it was not done.