BEHIND THE HEADLINES

Behind the Headlines reproduces selected clinical articles which have been published online in *The Bulletin* in the preceding quarter, in order to disseminate this topical clinical information to a wider audience (including those Fellows and Members without internet access).

The reproduced articles aim to educate and inform the wider College membership about specialist items that have been reported in the international medical and mainstream media: to the non-specialist it may not always be clear how accurately such stories – whether reporting results of scientific studies or issues of concern to health professionals – have been reported. To clarify such situations, expert clinical comments are commissioned on matters that are recurring in the international media, or about which different reports have caused conflicting messages for those practising in other specialties.

It is hoped that this section will, in time, become an invaluable source of independent and authoritative advice for Fellows and Members interested in updating their knowledge of new developments in other specialties.

IN THIS ISSUE

- The Severe Acute Respiratory Syndrome outbreak – what lessons have been learned?;
- Air pollution and stroke: is a causative association plausible?; and
- Getting a handle on why good drugs sometimes don't work.

THE SEVERE ACUTE RESPIRATORY SYNDROME OUTBREAK – WHAT LESSONS HAVE BEEN LEARNED?

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BACKGROUND

Readers of *The Journal* will remember the article on SARS which the College commissioned at the height of the SARS epidemic last year. In parallel to recent reports of SARS survivors encountering delayed side-effects (avascular necrosis) attributed to the initial treatment regimes and also of new cases of SARS in China, it was decided to commission a further commentary on SARS.

Severe acute respiratory syndrome (SARS) is the first new infectious disease of the twenty-first century that poses a threat to international health. Originating in southern China in November 2002, it was brought to Hong Kong in February 2003 and then rapidly spread worldwide, though mostly to Asian countries. At the end of the epidemic in July 2003, the global cumulative total was 8,098 cases with 774 deaths in 29 countries or regions on five continents (mortality 9·6%).[1] Of the ten most-affected countries or regions, seven were in Asia (mainland China, Hong Kong, Taiwan, Singapore, Vietnam, the Philippines, and Thailand).[1,2] Mainland China and Hong Kong together accounted for 87% of cases and 84% of deaths. It was a terrible experience for all of us, with tremendous suffering from morbidities and loss of lives, break-point straining of healthcare resources, disruption of everyday life and a great setback for travel and business around the world, particularly in Asia. In Hong Kong, for instance, commercial aircraft movements dropped by 49% during the peak of the SARS outbreak in May 2003,[3] and hotel occupancy rates plunged to an all-time low of 17%, against 83% in May 2002.[4] The devastation inflicted on tourism, business and the economy was unprecedented in the history of modern medicine.[5]

It is now the right time to reflect on what we have learned from this outbreak. On the positive side, medical scientists and healthcare professionals have stood up to the challenge, and have shown the highest level of dedication and professionalism in fighting bravely in the front line to contain the infection, and in disseminating promptly information regarding clinical features, radiological features, modes of transmission, and the results and problems of different treatments.[6–10] Using modern molecular technology and the coordination of the World Health Organization (WHO), medical scientists have been quick to identify and characterise the novel coronavirus as the causative virus of SARS (SARS-CoV).[11–13] Laboratory tests, though far from ideal, have been developed to detect antibodies and SARS-CoV RNA.[14]

However, governments and medical and health authorities now realise that we were poorly prepared for this SARS onslaught and our response was less than satisfactory. The Government and Hospital Authority of Hong Kong have

therefore commissioned the independent SARS Expert Committee and the Hospital Authority Review panel on the SARS outbreak respectively to conduct reviews on the capacity of the healthcare system and propose ways to prepare better for any future outbreaks. The Reports chronicled the outbreak, defined the deficiencies of the system, and made recommendations for strengthening surveillance and reporting systems, for comprehensive contingency planning, for clear command and control structures, and for developing effective communications.[15] A Centre for Health Protection will be set up with the responsibility, authority and accountability for the prevention and control of communicable diseases.

A number of questions regarding the virus and the disease remain unanswered. The SARS-CoV is a new pathogen for humans, thought to have originated in wild game animals such as Himalayan palm civet cats, which 'jumped species' to infect humans in the recent past. Anecdotal reports together with a study in the wild game animals market in southern China show a higher seropositivity for SARS-CoV in wild animal traders than controls, appear to support this hypothesis.[16] Its precise origin, animal reservoirs and pathogenesis, modes of transmission other than by droplets and fomites, infectivity during the incubation period and after clinical recovery, and endemicity, are still unknown. A recent report found no transmission on an aircraft by a person with presymptomatic SARS.[17]

The treatment for SARS is largely anecdotal, and there are no controlled trials to support or refute any treatment modalities. Current understanding, obtained from observational studies, combined with general virology principles, suggests three pathogenic stages of SARS, namely viral replication, inflammatory pneumonitis and residual pulmonary fibrosis.[11, 18, 19] While these stages can be identified conceptually, one should appreciate that they often overlap chronologically and vary remarkably in duration, as some patients appear to have rapidly progressive disease while others present in a more indolent fashion.[20]

Historically, before SARS was even defined by the WHO, early patients were treated with a broad spectrum antiviral agent, ribavirin, and corticosteroid.[6] The apparent good progress and recovery of the first few patients led to the adoption of this combination as the standard treatment for SARS in Hong Kong and elsewhere,[6, 7, 9, 18, 21, 22] although there was considerable skepticism about its safety and efficacy.[23–5] Ribavirin was considered to have caused significant anaemia, haemolysis and liver dysfunction in Canadian SARS patients, although the incidence of these was lower among Hong Kong patients who received a lower dose.[7, 9] High dose corticosteroid has been associated, as expected, with sepsis, particularly ventilator-associated pneumonia and even systemic fungal infection.[26] More recently, about 12% (49/418) of Hong Kong patients with SARS were found to have avascular necrosis (AVN) of the hips and knees on MRI examination (unpublished and preliminary data). This high incidence strongly suggests that SARS-CoV may have been a contributory factor to AVN as corticosteroids are not uncommonly used in patients suffering from rejection of transplanted organs without such a high incidence of AVN. This is supported by the other extrapulmonary manifestations in SARS, including residual diastolic cardiac dysfunction and liver dysfunction in SARS.[27, 28] Further cross-sectional analysis might help delineate the pathogenesis of AVN in SARS.

Ribavirin and corticosteroid as an initial treatment for SARS is now considered scientifically unsound in Hong Kong and worldwide. However, there is consensus that high-dose methylprednisolone, 250–500 mg daily for three to six days, can be lifesaving for patients with radiographically deteriorating pulmonary consolidation, increasing oxygen requirement and respiratory distress (e.g. a respiratory rate of 30/min), i.e. the syndrome of 'critical SARS'.[29] A recent retrospective study revealed that administration of a combination of Kaletra (lopinavir 400 mg and ritonavir 100 mg), an antiprotease designed for treatment of HIV infections, and ribavirin appeared to be associated with a reduction in steroid usage and nosocomial infection, and these patients had a decreasing viral load and rising peripheral lymphocyte count[30] Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level. This finding, the only clinical observation showing some efficacy of a combined antiviral treatment, has been adopted in the design of a controlled trial in Hong Kong, in case SARS should ever recur.

Other sequalae of SARS include inability to concentrate, hair loss, anxiety and depression, which could be stress-related, consequences of 'SARS treatment' or a complication of SARS-CoV infection. Longitudinal assessment of lung function is being studied in Hong Kong in survivors of SARS, and preliminary findings suggest a restrictive defect. This is consistent with findings of residual fibrosis and sometimes traction bronchiectasis revealed by high resolution CT studies.[31] Reassuringly, SARS patients, who were typically discharged after two to three weeks, do not appear to have infected their close contacts, strongly suggesting that recovering patients are probably not very infective.

The SARS outbreak is a sobering reminder in this age of heavy air travel and globalisation that any emerging infectious disease can spread rapidly around the world. A number of important lessons have been learned. First, to control an emerging infection quickly and to prevent spread across boundaries, outbreaks must be reported as early as possible to neighbouring countries and regions and to the WHO. Second, health authorities must be prepared for major outbreaks,

by having infection-control and quarantine guidelines capable of being implemented as soon as the outbreak is reported.[15] Third, the WHO has demonstrated its unique value in issuing international alerts, coordinating international medical and scientific efforts and collating and disseminating information and advice. The WHO website must have been one of the most frequently visited in the first half of the year. And fourth, with the distinct possibility that this new SARS-CoV has crossed the species barrier from animals to human, we need to revisit the human-animal habitat, especially the closeness between man and animals in southern China where wild game cuisines are so popular. This provides an ecosystem for the interaction of wild game animal virus and human virus, allowing genetic recombination or assortment to produce deadly new variants to infect humans. The south China live animal market study[16] should lead to sobering reflection on the wisdom of the wild game eating habits in Hong Kong and southern China.

At this time we cannot predict whether the SARS epidemic will return (12 January 2004). However, we must remain vigilant, and the two laboratory-acquired cases (Singapore announced on 9 September 2003 and Taiwan announced on 17 December 2003) and the one confirmed case and two suspected cases in Guangzhou, Guangdong, China to-date (12 January 2004) – none laboratory-acquired – serve as a grim warning to us all.[32] This time, the lesson has been learned, and the international medical and health community has reacted promptly to disseminate information, provide appropriate quarantine and to implement train and airport health check measures. The WHO has also drawn attention to the most recent biosafety guidelines for SARS laboratories handling SARS specimens,[33] and has sent a team to China to help investigate the source of the infection. The press announcement on 5 January 2004 by the University of Hong Kong and Guangzhou Institute of Respiratory Diseases that the strain of the virus in the Guangdong patient confirmed to have SARS is almost identical to the strain in civet cats has led to prompt action from the Guangdong authorities. They have slaughtered 10,000 civet cats in the province and have imposed an immediate ban on the farming, transport, sale, and consumption of civet cats, badgers and raccoon dogs.[32] Tens of thousands of people travel between Hong Kong and Guangdong province every day, and the port control, health and hospital authorities and healthcare professionals in Hong Kong are on full alert. With such alertness and preparedness at regional and international levels, we should be able to contain and control not only a major SARS resurgence, but any outbreak of other major infectious diseases in the future.

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NOTE

Asia has borne the brunt of the SARS outbreak, and *Respirology*, official journal of the Asian Pacific Society of Respirology, published a SARS Supplement in November 2003, covering clinical virology and pathogenesis, epidemiology, radiology, clinical features and diagnosis, pharmacotherapy, ventilatory and intensive care, prognosis, outcome and sequalae, hospital infection control and admission strategies, and public health measures. The articles are written by hands-on clinicians, public health experts and medical scientists at the forefront of the battle against SARS who have contributed significantly to the current literature on the disease. Interested readers are invited to read the Supplement by visiting the website (www.blackwell-synergy.com/links/toc/res/8/s1).

AIR POLLUTION AND STROKE: IS A CAUSATIVE ASSOCIATION PLAUSIBLE?

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BACKGROUND

This article was commissioned following the publication of a large-scale study in stroke that suggested an association between air pollution and stroke. The study, which attracted considerable media interest, reported that stroke admissions to hospitals in Taiwan increased at times when high pollution levels and temperatures in excess of 20°C were reported.

I well remember the air pollution episodes of my childhood in the 1940s and 1950s: cold, still, winter days when coal was used for all domestic heating and the smoky fog obscured the houses on the opposite side of the street. It did not take a great leap of the imagination to believe that this was in part responsible for the huge number of patients with end-stage bronchitis and emphysema we saw in the wards as students and young doctors in the late 1950s and 1960s. Some half a century later, in 1992, I was asked to chair a committee responsible for recommending Air Quality Standards to the United Kingdom (UK) Government. Over those 50 years there had been dramatic reductions in air pollution in the cities of the UK, and yet epidemiologists were still able to demonstrate associations between what appeared to be trivial levels of particulate pollution, of the order of a few tens of micrograms per cubic metre, and death rates from respiratory and cardiovascular disease. Yes, cardiovascular disease! And when

we looked at the data it became apparent that although the relative risk of death from lung disease was greater than that from heart disease, the absolute risks (since many more people died of heart attacks) were greater for cardiovascular disease. Did it make sense? Could about one milligram of soot, inhaled over 24 hours, cause people to die from heart disease?

A possible explanation of this association came to me in 1994 on picking up my copy of the *Lancet* and reading a paper that reported the variations in clotting factors in the blood of older people in relation to season.[1] With colleagues, I proposed the hypothesis that the nanometre-sized particles that largely comprise combustion-generated air pollution cause alveolar inflammation sufficient to alter blood coagulability and thus increase risks of adverse cardiovascular events.[2] Since then, evidence has accumulated in support of this hypothesis.[3] We have taken it further by suggesting that since the lung's defences are directed at eliminating microorganisms with the potential to invade and multiply, it makes teleological sense that the lungs should respond similarly to other small inhaled particles, both by local alveolar inflammation and by triggering a systemic, acute phase reaction.[4] It is important that any hypothesis should explain the known facts, and another observation that is now generally accepted is that not only are air pollution episodes associated with acute episodes of cardiovascular disease but also lifetime experience of pollution modifies long-term risks of heart disease.[5] In other words, if you are brought up in a polluted city, you are more likely to develop heart disease than if you have lived in the country. Alterations in risk factors, such as fibrinogen concentrations in the blood, would explain this. But if this mechanism were responsible for the observed associations, air pollution would be expected to influence other diseases where blood coagulability or platelet aggregation is of pathogenic importance. Is this the case?

A problem in investigating these effects of air pollution is that they are weak, and hard to demonstrate except in very large populations. The confidence with which one can state that there is an epidemiological association depends in part on the frequency of the event one is studying, and such conditions as stroke and pulmonary embolism are very much less common causes of death than heart attack. Nevertheless, a number of studies have now shown such associations. To take two that seem reasonably convincing, in the Netherlands, a 4% increase in risk of death from both stroke and thromboembolism has been shown to accompany a rise of 40 $\mu g/m^3$ in exposures to particulate pollution; the association with stroke was statistically significant, while that for thromboembolism was not quite.[6] In Taiwan, a recent study has shown associations between stroke, both ischaemic and haemorrhagic, and particulate pollution, nitrogen dioxide (NO_2) and carbon monoxide (CO).[7] These associations were present only in the hot season, except that with CO, which persisted in the cooler weather.

Air pollution research is made complex by the presence of multiple factors that vary simultaneously – temperature, atmospheric pressure, wind speed and different sources and mixtures of particles and gases. There is still much discussion about the plausibility of these associations representing a cause-and-effect relationship, part of the difficulty being the extremely low doses of pollutants being associated with serious health effects. Current research therefore is directed at understanding mechanisms and ingenious epidemiological designs are necessary to link this with real-life experience of individuals. My own view is that the most likely mechanism is increase in blood coagulability and/or decrease in fibrinolytic ability together with changes in endothelial and platelet function as a response to alveolar inflammation. I am not disturbed by the fact that some reports note associations of disease with particles, some with gases such as NO_2 and CO, and some with all of these. All simply represent the same pollutant, combustion exhaust, now mainly from diesel vehicles in the UK, and all are confounded by the same hitherto unmeasured pollutant: nanometre-sized particle numbers.[4] For the past couple of years these particle numbers have been counted in major UK cities and it should soon be possible to relate such counts to health end-points. When I tell you that on a moderately polluted day, about 100 $\mu g/m^3$ in the air means that some 1,000 billion of these particles are deposited in our alveoli in 24 hours, compared to the 50 billion that the lung is used to, you may see why such reactions are possible.

In 1964–5 I spent a year in Stoke-on-Trent as a medical registrar, and was impressed with the frequency of aspirin-taking in the patients I saw there with gastric haemorrhage. When I asked why they did so, the answer was always the same – 'to keep off the dust'. This was the dust from the potteries, notorious for causing silicosis, but Arnold Bennett's Five Towns had also been extremely polluted from the coal-fired kilns. Decades later, I began to wonder if these patients had a point.

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GETTING A HANDLE ON WHY GOOD DRUGS SOMETIMES DON'T WORK

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BACKGROUND

Following widespread media reporting of comments attributed to a senior scientist at GlaxoSmithKline, in which it was reported that most drugs only work in 30–50% of people, it was decided to commission an authoratitive overview on

'Most drugs work in 30–50% of people' was a front-page headline in the *Independent* 8 December 2003, over an interview with a senior scientist at GlaxoSmithKline (GSK) on how new findings in genetics may improve the reliability of pharmacotherapy. The headline and story probably resulted from the flammable combination of the interviewer's quest for newsworthiness and the interviewee's enthusiasm for pharmacogenomics. Such new fields often have a honeymoon of hope-begotten hype.

The dose-dependent magnitude of actions of many medicines are indeed highly variable. In 1991, Carl Peck and John Harter published a landmark analysis of the sources of variability in drug response.[1] They focused on theophylline, the recommended dose of which, given to an average-sized patient with mild asthma, could produce any response from none to maximal. It is akin to the elevator in a 20-story building that goes to random floors, only occasionally to the one selected. Such behaviour in elevators is completely unacceptable, but theophylline was in use for years, though recently introduced medicines have gradually replaced it.

In the 1980s, therapeutic drug monitoring had promised to eliminate such variability, but its cheerleaders failed to grasp a basic fact that variability in drug response has multiple sources that interact nonlinearly to create variability in the relation between prescribed dose and effect.

The nonlinearity, as Peck and Harter showed, arises from the fact that variability in the prescribed dose–effect relation is the square root of the sum of the squares of the variabilities of each component of the system that transforms a prescribed dose into a measurable effect. This nonlinearity has the unhappy consequence that a major reduction in the variability of one component of the system has only a minor effect on the overall variability of the dose–effect relation. In order to achieve a major reduction in overall variability, one must reduce the variability of each component of the system. Finally, when the last major source of variability has been greatly reduced, one can end up with a relatively reliable dose–effect relation whose range of variations in response to a mid to upper-range prescribed dose does not reach as low as zero.

The foregoing is a loose rendition of the theory of reliability improvement, which has been tested and repeatedly proven in industrial and other systems. It applies as well to biomedical systems. Under the banner of 'statistical quality control', it was pioneered by the late W Edwards Deming, who is credited with teaching the Japanese to manufacture high-quality (i.e. low-variance) products.[2] Why Japan? After the Second World War, Deming tried to convince Western automakers to adopt his methods, but their customer demand was at an all-time high – hardly an incentive to invest in quality improvement. The Japanese were reconstructing their demolished factories, and embraced Deming's teachings in the hope of changing their pre-war reputation for shoddy products. The results not only reversed their old reputation but provided the quality basis for steady growth in Japanese products' shares of many markets. Deming achieved great renown in Japan, and the annual Deming Award, started in Japan, but now

open to all, goes to firms that make exceptional improvements in quality.

There are useful lessons for the reliability of pharmaceuticals in Deming's work. To see that, we turn to some pharmaceutical details and their associated numerical values.

A CLOSER LOOK AT THE PECK-HARTER MODEL

The Peck-Harter model of variability in drug response listed the following subsystems that, acting together, create the dose–effect relation:

A. The drug formulation, its drug-release kinetics, and the absorption of drug into the bloodstream.
B. Patient compliance with the prescribed drug regimen.
   Whether a prescribed dose is taken but not absorbed, or not taken at all, has the same functional result of interrupting the patient's exposure to the drug.
C. Pharmacokinetics.
   What the body does to drug that has entered the body, creating the ingested dose-concentration relation.
D. Pharmacodynamics.
   What the drug does to the body, creating the concentration-effect relation.

Subsystem A has three variable components, (a) drug content of the dosage form and the kinetics of (b) its release from the dosage form *in vivo* and (c) its absorption. Modern manufacturing has driven variance in drug content down to *de minimus* levels, but the kinetics of drug release and absorption remain variable and subject to improvement.[3]

Subsystem B posed intractable problems until the advent of electronic methods to compile ambulatory patients' dosing histories. These methods rely on time-stamping microcircuitry incorporated into pharmaceutical packages, automatically recording time and date whenever the manoeuvers occur that are necessary to remove a dosage from from the package.[4–6] Findings with this method were the topic of my Al-Hammadi Lecture at the College's St Andrew's Day Therapeutics Symposium in 2001. New since then is the definition of a new discipline within biopharmaceutics, called pharmionics, which is the study of what patients do with prescription drugs.[7] Pharmionics brings reliable measurement to the quantity and timing of drug intake. As a disciplinary focus, rather than a judgemental pronouncement about patients' behaviour, it sidesteps the long-running, sterile argument over whether patients' execution of prescribed dosing regimens should be called 'compliance', 'adherence', or 'concordance'. The focus goes onto patients' reliably compiled drug dosing histories and on how variations in the quantity and timing of dosing create variability in drug response.

Subsystem C, pharmacokinetics, has a 50-year history. It, too, had to await the advent of sensitive-enough methods to allow measurement of drugs and their metabolites in small samples of body fluids.

Subsystem D, pharmacodynamics, poses great difficulties for measurement because of the great diversity of drug actions, many of which either evade reliable measurement, or require difficult interventions for measurements to be made.

Deming taught that one should begin by rank-ordering the sources of variation by their size: biggest first, smallest last. Next, they should be re-ordered by tractability, i.e. the existence of technical means to achieve improvement. It is pointless to try to attack a problem without satisfactory methods for measurement, analysis and improvement.

The keystone is measurement. Deming taught that 'what wasn't measured didn't happen', and 'if it can be measured, it can be improved'. A further point is that a problem that is intractable this year may become tractable next year, with new, more sensitive methods of measurement, new understanding of underlying mechanisms from which variance can emerge, and new methods of data analysis.

HOW THE PECK-HARTER MODEL WORKS

It is revealing to look at some numerical aspects. Peck and Harter formulated the sources of variance in drug response by using coefficients of variation (CV (the standard deviation as percentage of the mean)) for subsystems A, B, C, and D using values that they believed applicable to theophylline, the drug they chose as model. From available data, they estimated a CV of 20% for subsystem A, 50% for B, 50% for C and 30% for D. The sum of the squares of each is thus 400 + 2,500 + 2,500 + 900 = 6,300, the square root of which is 79% – the CV for the overall prescribed dose–effect relation. A CV of 79% corresponds to the deranged elevator mentioned earlier, and projects that as many as half the patients prescribed a mid-range dose will have zero response. Even when full-strength dosing is prescribed, about one patient in seven would be projected to have a zero response.

CHANGING THINGS

As an exercise in simulation, let's assume that application of new pharmacogenomic information allows a reduction in the CV of item C from 50% to 10% – a big improvement. To see the overall result, we redo the sum of squares with the new number in italics: 400 + 2,500 + *100* + 900 = 3,900, the square root of which is 62·5% – a disappointingly small reduction in the overall dose–effect relation, notwithstanding the big reduction in pharmacokinetic variability.

Going further, suppose we apply some of the promising methods of improving compliance,[7,8] taking the CV of subsystem B from 50% down to 20%, and, still keeping the improvement in C, we now have a sum of squares of 400 + 400 + 100 + 900 = 1,800, the square root of which is 42·5% – still big enough that many patients would manifest very small or zero responses, though almost half of the original variance is gone. Next, if we could do better with compliance, carve out some of the pharmacodynamic variance (maybe also based on pharmacogenomics), and use a rate-controlled drug delivery system to tame the kinetics of drug release,[3] we might end up with something like a 10% CV of A, a 15% CV of B, a 10% CV of C, and a 20% CV of D. The sum of squares of this mix is 825, the square root of which is 29%. Now we have reached a degree of variability small enough that a dose aimed at eliciting a mean response that is, e.g. 75% of maximal, would still show some detectable response in low-end outliers,

One can only guess at how much further reduction might reasonably be achieved by further refinement of the approaches used to get the overall CV from 79% down to 29%. The key point, however, is that no single approach can reduce to a low level the variability of the overall system when its sources are distributed throughout the system. A system-wide approach is needed. One can challenge the choice of figures that Peck and Harter selected, or the sizes of possible improvements described above, but the basic nonlinear features of the interactions of the variabilities of the various components of the system cannot be evaded by changing numbers.

The foregoing is, of course, somewhat simplified, chiefly the assumption that variability in each subsystem has a gaussian distribution. In reality, some distributions are markedly skewed: in subsystem B, for example, underdosing is four times more likely than overdosing.[10] One should naturally use observed rather than assumed distributions. Also, rarely occurring complete absence of a drug receptor or a metabolising enzyme can of course dominate the entire picture. Likewise, drugs don't work in patients who don't take them, and the clinical estimation of a patient's drug intake is no better than a coin-toss.[11] Thus, a reliably compiled dosing history can rule in or out poor execution of the prescribed dosing regimen as a single-source cause of non-response or of highly variable response. For example, Burnier, Brunner and colleagues found that about half of persistent nonresponders to triple-drug antihypertensive therapy simply weren't taking the drugs; their pressures normalised when their dosing histories were compiled electronically and used as a management tool.[9]

NOT ALL MEDICINES ARE UNRELIABLE

Some pharmaceuticals are highly reliable in use. The inhalational anesthetics, for example, are devoid of variance in the relation between their partial pressure in plasma and their anesthetic effect,[12,13] and modern methods of administering them have driven their pharmacokinetic variance to essentially zero. The combined, oestrogen-progestin oral contraceptives appear to have zero variance in their pharmacodynamics, and insufficient variance in their pharmacokinetics to prevent a patient from achieving an almost zero risk of conception, given punctual dosing. The need for strict punctuality in dosing, however, is the Achilles heel of oral contraception, for the conception rate degrades 50-fold, from 0·1–5·0% per year, between 'perfect use' and 'typical use'.[14] Long-acting depot or implant formulations bypass the variability created by delayed or omitted oral doses.[3] Monthly depot penicillin injections completely prevented recurrent acute rheumatic fever, while the results with daily oral penicillin were highly dependent on compliance with the prescribed dosing regimen.[15]

IS PATIENT COMPLIANCE MORE IMPORTANT THAN PHARMACOGENOMICS?

Several years ago, pharmacogenomics was the subject of a major annual public lecture in the Netherlands. Custom dictates that the lecturer comes from abroad, and that a number of Dutch professors write chapters on related topics in a companion volume. A waggish colleague invited me to write on the topic of the above subheading; it was translated and published in Dutch,[16] so few are privy to the answer. As the foregoing analyses show, the improvements that can be made through pharmionics and medication management, and those that can be made through application of genetic knowledge, seem about equally likely, but it is probably less costly first to assure that drug intake is adequate before pursuing other possibilities that entail expensive tests.[7,9]

SUMMARY

Success in reducing variability comes from continuing application of measurements, analyses and interventions to attack the usually multiple sources of variability. These improvements can be expected to occur under different

disciplinary banners, e.g. pharmacogenomics, pharmionics and compliance improvement, elimination of food–drug and drug–drug interactions. It is costly, time-consuming and undramatic work in its early and middle stages – not something that a flighty management, seeking quick fixes, is likely to support to a successful conclusion.

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