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CLINICAL

Wondering…

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Does anyone ever wonder nowadays? Or, are we slaves of the many search machines and the cyber world, which undermine or suppress original thought? Are we so obsessed by texting or tweeting that wondering appears to be a waste of time, of no consequence or without any fruitful outcome? Are answers to our diffident and hesitant questions so immediately available at the touch of a button that few discover the joy of wondering? Ranging into the unknown, with or without the constraints of logical thought can be a fascinating luxury. Wondering is curiosity and bringing together disparate pieces of information. It can be rewarding, even inspirational, but also a hopeless quest. Nevertheless, human minds should never be shackled by the orthodox but must be allowed to wonder (and wander) freely.

Do young doctors, scientists or medical researchers ever have (or make) time to wonder? I have two personal examples.

THE SEEDS OF HYPOTHESIS 1

In 1950, I had been newly appointed as a junior research fellow with Dr A Rae Gilchrist and he asked me to study arteriosclerotic heart disease (ASHD) and in so doing to learn how to use a medical library. Successive Registrar General's reports of 1945–49 indicated a great excess of ASHD in young men compared with women. Extraordinarily, the word 'coronary' was not yet included in these national or international reports. Men aged 35–39 had seven times the death rate from ASHD, those aged 40–49 had five times and those aged 50–59 had twice the rates for women of the same age. Why was this? I wondered about the burden of work for men and about cigarette smoking. This was very common in men and much less so in women after WW2. But Doll and Hill had not yet produced their devastating indictment of cigarette smoking. So, what might account for the excess in young men. I wondered particularly about its relative rarity in young women. Might this point towards an explanation for the differing death rates?

One year later, after daily blood sampling of 12 healthy women over five weeks, Boyd and I could report that cyclical changes occurred in plasma cholesterol with significant reductions coinciding with ovulation, timed by a rise in temperature.[1] Men showed no cyclical changes and had higher concentrations of low density lipoproteins (LDL) compared with young women. This suggested that naturally-occurring oestrogens might be protective against what became known as coronary heart disease (CHD), leading to several publications demonstrating that administered oestrogens lowered total cholesterol and LDL.[2] Twenty years later, we were able to show that both bilateral ovariectomy and/or a spontaneous menopause before age 35 were associated with a CHD excess.[3,4] In other words, those women had lost the protection of naturally occurring oestrogens. This had not previously been reported. The research resulted entirely from wondering about gender differences in the incidence of CHD.

THE SEEDS OF HYPOTHESIS 2

A second phase of wondering also bore fruit. Why do some patients with acute myocardial infarction die within hours of the onset of symptoms? Orthodox thinking in the 1950s was that they all had large infarcts. But, three months spent in the autopsy rooms with a pathologist examining these patients' hearts, convinced me that this was not the only reason. Out of 50 consecutive autopsies on patients with a clinical diagnosis of a coronary heart attack, there were at least 16 with no apparent myocardial damage and no other cause for death. Yet all had had classical symptoms of acute myocardial ischaemia. So, I wondered. Might there have been an interruption of normal sinus rhythm or of normal conduction of the cardiac impulse? Stokes-Adams attacks were well recognised; however it seemed unlikely that 16 out of 50 deaths could be explained this way. I wondered, therefore, whether their deaths might have been due to an acute failure of, or alteration in, myocardial energy supply.

Meanwhile, when studying electrophoresis as a means of separating plasma lipoproteins, I had noticed a fast-moving band which did not stain for cholesterol but did stain for fat (using Oil Red O). After several months I realised that this was present only in blood taken from patients with acute myocardial ischaemia. Why was this; what caused it? After further analysis, it turned out to be free fatty acids (FFA), known to be the principal substrate

for normal myocardial metabolism but, now appearing in excess during acute coronary syndromes. It was already known that adrenaline activates tissue lipolysis leading to an efflux of FFA into plasma. It seemed likely that patients undergoing acute myocardial ischaemia who had intense pain and great fear would also have high adrenaline concentrations (which suggestion we later demonstrated) causing excess FFA. Kurien and I then found that the higher the plasma FFA during the first six hours of acute ischaemia the greater the mortality and arrhythmic complications.[5] We proposed that a metabolic crisis can occur with excess FFA and relatively less glucose available as substrate for the acutely ischaemic myocardium.[6] The relationship between high concentrations of plasma FFA and arrhythmias during acute myocardial ischaemia was soon confirmed[7] and more recently with an analysis of 1,834 patients from the TIMI II trial of thrombolysis for STEMI.[8] This would explain the deaths of the 16 patients without evident myocardial damage, mentioned above. It also provided a strong argument for very early intervention.[9]

Wondering was rewarded. I think it most improbable that either of these hypotheses would have been formulated or answered by use of the Internet search resources now available.

In my own lifetime, there have been two of the most fundamental biological discoveries that resulted from wondering. In 1935, recognition that a mould in Petri dishes might be antibacterial set Alexander Fleming wondering, leading to the isolation of and therapeutic uses of penicillin. Francis Crick and Jim Watson hypothesised in 1953 that a double-helix of two nucleotide chains, comprising four nitrogenous bases, two purines and two pyrimidines, was the basis of deoxyribonucleic acid or DNA and the key to our understanding of inheritance. Crick wondered about such a structure for DNA in a pencilled diagram drawn on the back of an envelope!

THE FUTURE OF WONDERING

A great challenge now is the mind. What is it? Will current neuroscience research identify and characterise it? How is the mind related to the hundreds of thousands of brain synapses and the neurotransmitters? Will computer images and robots ever reflect brain activity with any accuracy? Functions of the mind may be related anatomically to certain areas of the brain but the relationship with psychology will be hard to grasp. The mind appears to be led by the senses, particularly vision, but how does it allow memory, provide creative thinking, instantaneous recall and the huge range of subtle propositions and emotions included in the wonderful facility of wondering?

Keep wondering. Google does not have all the answers! Let's continue to be inventive.

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