Felix qui potuit rerum causas cognoscere

As undergraduates, in my medical school, we had a grey booklet that listed the courses that we had to attend and have signed up in order to fulfil the requirements for taking our final examinations. We all went elsewhere after completing the pre-clinical course and at clinical school I found that those of us who had migrated north, alone among our new colleagues, were required to show that we had performed 5 post mortem examinations under supervision. We quickly learnt that we had missed much in examining the patient while alive and began to understand the importance of this final audit on the medical care of patients. Later, as a houseman I learnt how to approach the difficult task of requesting bereaved relatives to permit an autopsy with sensitivity, and subsequently taught this to generations of my own house physicians. Throughout my career, I continued to learn from the autopsy and subsequent discussions of the histopathology with colleagues in pathology, a learning process now seriously curtailed by the weak response of the medical profession to the Alder Hey scandal.

Virgil’s line, happy he who was able to understand the causes of things, found an echo in the first great pathology textbook, published in the 80th year of Morgagni’s life, *De Sedibus et Causis Morborum*, on the sites and causes of diseases of 1761. The doctors of the Enlightenment were already beginning to find an answer to Voltaire’s contemporary comment that they gave drugs, about which they knew little, to cure diseases, about which they knew less, to patients about whom they knew nothing. Morgagni, professor in Padua, was to live another 10 years and influenced all future generations of doctors who looked to morbid anatomy to elucidate the causes of their patients’ symptoms. Perhaps the best known of these was Läennec, the Breton who became professor of medicine in Paris and who in 1819 published *Traité de l’Auscultation Médiate* in which he correlated clinical findings, especially with his stethoscope, with pathological changes at autopsy. But anyone writing these essays must sense Jeff Aronson peering over his shoulder. When I use a word… What causes disease? From ancient times up until the anatomical exploration of human and animal bodies pioneered by Vesalius, doctors remained happy to ascribe illness to external forces which from the time of Hippocrates came to be recognized as what we would now characterize as lifestyle and seasonal influences—weather, diet, exercise and so on. After Morgagni, the profession had a more obvious feature of illness to focus on—a disordered heart valve, narrowed coronary and cerebral arteries, tumours. My copy of his book, published in 1779, gives details of hundreds of post mortem and surgical examinations intended to elucidate the causes of the symptoms. From that time onwards, we have looked inside for the causes of disease. But looking inside only gets us so far.

As time has passed, the look inside has become more detailed. Leeuwenhoek’s simple lenses revealed previously invisible creatures and structures, Hooke found cells, Virchow systematized pathology and, in my time, electron microscopes have shown ultra-structural features including chromosomes. As Swift remarked

So naturalists observe, a flea
Hath smaller fleas that on him prey
And these have smaller fleas to bite ‘em,
And so proceed ad infinitum.

Now we can visualize molecules and nano-sized particles, can manipulate genes and investigate the genomes of ourselves and even of the anthropoid second cousins of our distant ancestors. These technological triumphs have perhaps allowed us to lose sight of what our ancestors thought important, the more distant rather than the proximate causes of disease. As Morgagni showed, a narrowed vessel in the head can lead to stroke, but what caused the narrowing? Was Hippocrates right in pointing to the influence of the environment? This is the territory of the epidemiologist, but the epidemiologist thinks...
in terms of patterns of health and illness in populations and of their determinants. The clinician is concerned mainly with the illness of individual patients and the proximate cause. Can we marry these two different views of causation? Do we need to?

As clinicians, we strive to make a diagnosis that explains our patient’s symptoms and signs. If we are right (of course a diagnosis implies much more than a simple label; it is critical to appreciate this\(^1\)), this allows us to plan appropriate treatment and to give a prognosis, based on the known natural history of the disease, a process of deductive logic. We hope, from our understanding of therapeutics, that the treatment will alter the prognosis for the better though, sometimes, the prognosis allows us to temper our hope for a cure by prescribing a kinder regimen. In any case, treatment and prognosis interact with each other. A different, but analogous, inductive logic is used by the epidemiologist, who might be thought of as seeking the greater fleas, as De Morgan expanded Swift’s verse:

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\text{And the great fleas themselves, in turn, have greater fleas to go on} \\
\text{While these again have greater still, and greater still, and so on.}
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The epidemiologist describes the patterns of health and illness in populations and then may be in a position to make predictions and plan interventions. If so many people smoke, then a proportion is likely to suffer lung cancer but public health measures to reduce smoking should reduce the incidence of the cancer. But is the epidemiologist right or is he or she just scaremongering, as some sceptics might have us believe? After all, the epidemiologist relies on statistical tests of probability and only an incalculable one is prepared to say that the demonstrated associations are causative rather than chance or a consequence of some bias or mysterious confounding factor. So often, fingers have to be firmly crossed when the (rarely done) intervention study is embarked upon.

The greatest of recent epidemiologists, Richard Doll, modestly attributed his success to having worked in his early years with Austin Bradford Hill. Bradford Hill tried to help us out of this quandary by proposing a series of tests, not criteria, whereby the strength of the evidence on causation might be assessed. We are to consider if the evidence is statistically strong, consistent and coherent, if the time between exposure and onset is consistent with the known natural history of the condition, if there is an exposure–response relationship, if the association is specific to a particular agent, is biologically plausible, if there is experimental evidence in support of the association, and if there are helpful analogies derived from other fields. Of these, the strength and consistency of the association and the presence of an exposure–response association are the strongest pieces of epidemiological evidence, but it often takes biological plausibility and experimental evidence to convince the sceptic. Bradford Hill made the point that biological plausibility was not necessary since it depended on the state of knowledge at the time, and I came across this in air pollution research where the very consistent associations in many large studies with heart attack were still widely thought to be the consequence of some confounder such as temperature change until a plausible biological mechanism involving ultrafine particles, lung inflammation and changes in blood coagulability was proposed.\(^2\)

So the clinical doctor is mostly interested in the internal, proximate causes and the epidemiologist in more distant risk factors. If Virgil’s observation may be generalized, the clinician is more likely to be happy than the epidemiologist, who is always troubled by uncertainty. And, as we all know, faced daily with the reality of death, pathologists are the jolliest of doctors. But, perhaps more often than we might think, the two views on causation come together at the bedside of our patients and arouse our curiosity. Some months ago I was asked to see a patient whose breathlessness was accompanied by radiological signs of lung fibrosis. His lung biopsy showed changes of sarcoidosis in the upper lobe and what is called UIP ( usual interstitial pneumonitis) in the lower, though there were granulomata also in the fibrosis. His lungs were packed with aluminium, and he had worked some years before in a smelter and been exposed to aluminium oxide fume. Did he have sarcoidosis, whatever causes that, or a sarcoidosis-like reaction to aluminium? The epidemiology is not very helpful; some outbreaks of lung fibrosis in relation to exposure to powdered aluminium oxide have been described, but not in smelting. Large studies of aluminium smelter workers have shown no evidence of an increased risk of lung fibrosis. A couple of case reports of sarcoidosis-like lung disease describe an association with exposure to aluminium oxide, and I happen to have seen a similar case myself some years ago. The proximate cause is lung granulomatosis and fibrosis but the more distant cause may be aluminium exposure, perhaps in someone programmed to develop a sarcoid-like lung response. Or it may not; we can never know for sure. For the clinician and the patient, a response to steroids provided a satisfactory outcome. The epidemiologist is left wondering.
Causation is a complex issue. In Virgil’s time, there were two views on pathogenesis, imbalance of the humours and attack by demons, internal and external. Happiness lies in sorting these out. Now, what is happiness?

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References

