Alberta Doctors' Digest

Mixing clinical work, research and business in medical practice

In September, I took WestJet from Calgary to Edinburgh, hired a car and drove to Cobham (south of London) to attend the wedding of a former classmate at Edinburgh Medical School. We'd remained in contact over the years and had also worked on several bone-related clinical research projects. This was his third wedding, and I'd been asked to speak, focusing on his career rather than his future third wife, Dame Joan Ruddock, an ex-cabinet minister in the U.K. It sounded like an interesting event. There would be guests that one doesn't normally get to meet, for example Baron Neil Kinnock, former Leader of the British Labour Party and Leader of the Opposition.

The drive was easy at first, picking up a friend in Northumberland, but became harder the further south we went. We stayed overnight north of London at The George Hotel in Buckden, a one-hour drive north of the dreaded M25. This we hit the morning of the wedding on a Saturday around 10 a.m. and crawled along the M25 as signs announced traffic delays due to several accidents. We reached the Hilton Cobham at 1 p.m.

The speech went alright – just ensure a few chuckles and stick to the time allotted. I focused on our early years. I'd known John (now professor John Antony Kanis) since we were medical students. He was a bright young man, and we teamed up as partners in the second- and third-year physiology course. John planned and carried out the experiments while I focused on the social side. As a result, I progressed stress-free to fourth-year clinical medicine. John, however, was selected to do an extra year of physiology, which resulted in a first-class honours physiology degree, and our academic paths parted, though we remained friends.

I even mentioned in the speech that on one occasion we'd opened together for the Incredible String Band (a group which seemingly few of the younger generations have heard of) at the Stockpot, in Edinburgh, playing *The Bridges of Paris*, jazzed up, with me on fiddle and John on guitar, before Mike Heron shooed us off the stage and started singing *October Song*. I also mentioned John doing a fire-eating trick the night before an important event (his first wedding), which went wrong and resulted in eyebrow loss and facial injuries.

That John was smart is illustrated by his student summer jobs. Most of us were happy as labourers on building sites (perhaps becoming "the nipper" who nipped into town for the men's lunch or placed their bets with the local bookie.) John, in contrast, was hired at his father-in-law's building company and took the role of site manager. I thought this was only because his father-in-law was the boss, but no – he was fascinated by carpentry, plumbing and electrical work and performed effectively. It obviously worked – no Scots tradesman would ever put up with an ignorant junior medical student telling him what to do.

John's path was the academic pathway, being appointed to professorial units for our mandatory year of "houseman" slavery, while I worked in the clinically more varied regional hospitals for six months in medicine and six months in surgery.

A chance reunion and interesting outcomes

Our paths then parted for about 18 years until well after I came to Edmonton's Cross Cancer Institute, having trained in the new field of oncology, while John had spent five years at Oxford University in renal research and from 1979 to 2002 was professor in human metabolism (and then in 1991 was appointed director of the Centre of Metabolic Bone Disease) at Sheffield University, England.

That might have been the end of it but for a chance meeting in Montreal Airport in 1988 while I transferred flights from the USA for Edmonton and he was waiting for a flight back to the UK in the airport sitting area. It was a consequential meeting.

By then, I was participating in breast cancer clinical trials especially in the National Surgical Adjuvant Breast Project (NSABP) based in Pittsburg, and John had become an international expert in bone biology and was looking to start clinical trials in bone oncology. He'd become not only an expert in bone biology but had participated in setting up a new pharmaceutical company as a director and medical expert. The name of the new company was "Shire" and their initial products were bone products: calcium supplements (e.g. Calcichew-D3) for treating/preventing osteoporosis. He had also become involved with Leiras, a Finnish company. This company had an agent they wanted to test as an inhibitor of bone metastases in early breast cancer, but before that, studies in more advanced disease were needed in those patients with overt bone metastases.

At the time I had been communicating with professor Trevor Powles at the Royal Marsden, London, to look at working together to introduce treatments for patients with bone metastases. The scene was set for a collaboration in clinical research – one that has benefited patients with breast cancer.

We rapidly put together a protocol for the use of the bisphosphonate, di-chloro-methylene diphosphonate – "clodronate" – in patients with metastatic breast cancer involving bone. The study was completed quickly and published in 1992 by Eugene McCloskey of Sheffield University as first author. We then took the next step (promoted by professor Trevor Powles, who had joined the investigators group) to set up a protocol assessing whether bisphosphonates could inhibit the development of bone metastases in women with early breast cancer. We recruited centres in Canada, Britain and Europe and eventually, after also recruiting the USA-based NSABP with help from the British Breast Group, showed that it did reduce bone metastasis incidence in post-menopausal women.

During the early period of my visits to Britain to see family and friends, I would interrupt my drive to Edinburgh and stop at Sheffield to see John. One time, after a discussion on the progress of the clinical research, John got up and brought through a typed document held together by a blue plastic spine. He explained that (as medical advisor) he was recruiting potential investors in the development of a new pharmaceutical company. It looked interesting, though the document was untidy and a bit tatty. I said (though I still had a mortgage) that I might be interested in popping in $5,000. Sorry, he said, the minimum was 20,000 pounds.

The name of this novel pharma company focusing on bone agents? "Shire Pharmaceuticals," he said. Shire was founded in 1986. "Nice name," I said and left. Shire became a highly successful company and was eventually taken over in 2019 by

Takeda, a Japanese company. “How much would I have made had I invested?” I asked. John tapped on his pocket calculator: “Around six and a half million pounds,” he said.

A year or two later, John teamed up with a pharmacist who had also been involved in Shire, Harry Stratford, to form another company, “Strakan” (named for the combination of Stratford and Kanis.)

This company would be focusing on bone medications – vitamin D, calcium compounds, bisphosphonates and the like. Well, like many others of John’s friends and acquaintances, I wasn’t going to miss out this time and popped in some cash. The company lasted five years, lost money, and then was merged in 2004 with a French firm Proskelia (an Aventis spin-off) in an all-stock deal to form “Prostrakan” with no return of funds to the original Strakan investors. This new company survived and has done quite well.

One significant event in John’s career occurred in 1990, when the NHS was trying to reduce costs and close some clinics in the Sheffield area. The Hospital Trust decided to stop funding professor Kanis’s now well-reputed Bone Research Clinic. This would ordinarily mean the clinic closing, but John decided to fight and offered to put his own money into Sheffield’s Royal Hallamshire Hospital to save the clinic. The remaining funding would come from a public appeal. He recruited many funders and influential backers, so this became a successful campaign that succeeded in keeping the clinic funded. The somewhat shamed Health Authority agreed to continue with cash support.

From then on, John was sheltered from the threat of closure and continued his research and clinical trials without much interference, leading to many advances in osteoporosis management including the establishment of the now internationally used fracture risk assessment tool (FRAX) that focuses on preventing bone disease and fracture by screening people at high risk of osteoporotic fracture for therapy.

Avoiding the quicksands of ethical conflict

John’s academic achievements have been extraordinary: over 1,000 peer-reviewed papers, a Royal Society of Medicine award for his textbook on osteoporosis, editor-in-chief of *Osteoporosis International*, and founder of the European Foundation for Osteoporosis (now the International Osteoporosis Foundation.) He’s been a long-standing advisor to government departments and NGOs in nine countries including China and Russia. He continues as director of the Centre for Metabolic Diseases in Sheffield. He’s patron of Osteoporosis 2000, has had the Freedom of the City of Florence bestowed on him and has had two Vatican papal audiences. His achievements include elaborating diagnostic criteria for osteoporosis based on assessment of bone mineral density that have become international standards including significant contributions to fracture risk assessment in the development of FRAX, now used worldwide. John has been ranked in the world’s five top experts in metabolic bone disease from 2013 to present.

I honestly don’t know why he’s not received an award for his career achievements in the UK’s New Year or King’s Birthday Honours Lists, although the pathway to those awards (and similar Canadian awards) has always been a wee bit of a mystery to me, perhaps requiring some political connections.

The ethics of all this is important in understanding the relationship between pharmaceutical companies and clinical medicine. Clinicians regularly interact with pharmaceutical representatives, most of the time listening to the spiel about latest drugs or therapies and assessing the clinical studies' data. While good pharmaceutical companies certainly do consider the ethics of their practices, like any business, they tend to reward moneymakers with rewards. It's really up to the clinician to determine the neutral position – reviewing the relevant data as to the benefits and potential problems. If a medical meeting is being organized, it's common for requests to pharma companies for support in financing. If a therapy looks promising, companies commonly form an "advisory committee" to give advice on presentation of their data. The members of the committee will usually receive an attendance fee for the advice. All this is usually reasonable.

However, conflicts of interest can become significant. Where things become cloudy is if a company ups the incentives and offers a clinician personal payments based on the magnitude of use of the therapy benefitting company profits. At the extreme limit is a clinician receiving a percentage of the gross earnings from the therapy produced by the company (so-called "percentage of gross.") This is not allowed and can run an individual into serious conflict with a professional college or the institution where they work. In some countries (e.g., Russia) however, these arrangements are not uncommon and not viewed as unusual.

The proper way to prescribe is to use the generic names for drugs in prescriptions rather than the brand name. The Colleges of Physicians & Surgeons of Alberta and Ontario, as well as the British Medical Association, have full instructions regarding ethical behaviour and in many instances the key is full disclosure to colleagues and perhaps even to patients.

If this is not done, doctors can end up being promoters of a particular brand of an agent. They may end up prioritizing profit over patient well-being. This really becomes a problem if the agent is not the best in the field.

It's clear that professor Kanis has navigated this maze successfully and, importantly, ethically.

A successful formula for medical research and business

So what is the formula for a successful career in clinical medicine, performing ground-breaking research but including a significant interest in the business side of medicine?

First of all, you must be an expert in at least an area where there is potential for a useful diagnostic test or new treatment. You then have to be able to liaise with business types who may want to appoint you as an advisor, or even as a board member. However, you have to be quite clear about not letting your work or advice to the company influence your clinical practice or receive any payments directly related to the company's income from the therapy. Fixed emoluments on "advisory boards" are permissible – but payments directly related to the success of sales of a medication or therapy are not justifiable to ethics committees.

In addition, you have to be a consistent producer of good research papers to justify your research appointments. And you have to be honest with your colleagues.

It’s a busy life that can be rewarding but does not necessarily result in any great financial rewards. Professor John Kanis has succeeded in navigating these quicksands and made many contributions to the well-being of patients with bone disease.

Editor’s note

The views, perspectives and opinions in this article are solely the author’s and do not necessarily represent those of the AMA.

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