T.H. Pullar Memorial Address. Pathology: the study of structure and function in health and diseases

Robin Fraser

Dr T.H. “Thos” Pullar, the champion and friend of New Zealand medical laboratory scientists and technologists would no doubt have received great support from Christchurch Pathology, which is celebrating its 100th Anniversary. Because of earthquake-munted venues we are so grateful for your invitation to celebrate in Wellington.

Pullar’s idea of teamwork, in my opinion, has so enhanced New Zealand pathology.

Our Christchurch pathology began in 1912 with the appointment of Dr. AB Pearson from Edinburgh. His first autopsy report (No.1 Christchurch) was dated September of that year. The following year Pearson appointed Mr. T Ross (bacteriologist). Christchurch soon built up a collegiate of scientists, technicians and medical pathologists, so making a huge contribution to patient care, diagnosis and inevitably to medical research.

Pathology rapidly expanded and WWII saw Pearson’s assistant pathologist, Dr. Denis Stewart in the Middle East fighting yellow jaundice (hepatitis A) with occasional cases of fulminant hepatitis and death of several of our troops. Denis returned to take over the Christchurch department, while Pearson joined his son Colin in his pioneering private pathology practice.

Dr. Edgar Thomson (RPA Hospital) and Dr. Fred Gunz (Sydney Hospital), both having worked previously in Christchurch, encouraged me in 1974 to become senior lecturer in Professor Roy McGiven’s new academic-hospital pathology group (Christchurch School of Medicine, now University of Otago, Christchurch). I was stunned with the depth and beauty of our discipline this side of the “ditch.” Please let me explain why I believe pathology is team-dependent and so important for our nation’s health.

Pathology, or the study of disease, is central to the endeavours of clinicians and biomedical scientists. However, the normal (anatomy and physiology) must first be understood (1). Changes in structure and function of the body, arising from either environmental or genetic defects, lead to physiological compensation. If compensation fails, then disease or even death occurs. Pathology is therefore concerned both with the pathogenesis or the events leading to the disease, as well as the disease itself. For these reasons, pathology, as well as medicine and surgery, have been traditionally the three major departments in the clinical training of medical students.

Our discipline permeates all aspects of endeavor in our medical schools, hospitals and community. The study of abnormal structure and function occurs at the gross level where the coroners’ pathologist dissects a body to determine the cause of death following an accident, disease or homicide. This is the setting in which students learn of morbid conditions within the community or hospital, and audit clinical treatment. Structure and function is also important at the microscopic level, where the hospital histopathologists, clinical lecturers and surgeons discuss biopsies with the aid of the light microscope, giving clues as to diagnosis, treatment and prognosis of various diseases.

Normal and abnormal structure and function extend to the ultrastructure, as determined by electron microscopy. For example, abnormalities of the fenestrated endothelium lining of the liver sinusoids or “liver sieve” (Figure 1) affect lipoprotein metabolism, so playing a role in the pathogenesis of diseases as diverse as atherosclerosis, hepatitis, cirrhosis and even cancer. Our own experimental work gives explanation to public health findings on dangerous life-shortening habits, such as smoking, excess alcohol intake and some diets on the prevalence of atherosclerosis, the trigger to so many sudden deaths we see as pathologists in the mortuary (2-6).

But structure, function and their abnormalities extend way beyond those elucidated by electron microscopy. Molecular changes alter the trafficking of messages within the cell, to and from its nuclear DNA and cytoplasmic RNA synthesising (rogue) proteins. Cytokines and hormones are messengers to surrounding cells or distant organs. All these pathways may involve specialised disciplines of pathology. Avogadro’s number allows the structure of lipoproteins to be calculated from their size (electron microscopy) and composition (lipid chemistry), so important in cholesterol metabolism (7,8).

At the other end of the scale, the changing structure of the universe may influence disease. A lack of sunspots may lead to a mini-ice age, the retreat of citrus trees and the scourge of scurvy, defenestration of Prague and the Thirty Years War (9). An asteroid strike may kill the dinosaurs or may bring new forms of life to earth. The greenhouse effect may alter the distribution of mosquitoes and malaria.

Our Christchurch department includes biomedical researchers, such as the protein group, seeking mutants of serum proteins leading to haemorrhage, thrombosis, infarction, emphysema, dementia and...
death. Mutant proteins named by the group read like a page from Thomas Cook, since abnormal proteins tend to be named after the town or region in which the patient lives (specimens came from all over the world).

The original leader of our protein group was Emeritus Professor Robin Carrell, now of Cambridge, U.K. Continuing with his innovative work, our scientists in Christchurch have discovered several protein vectors of similar configuration transporting enzymes and hormones to specific sites of activity. These transporters have been named “serpins.” Mutant serpins, mostly synthesized by hepatocytes in the liver, but also by neurons, because of their abnormal dimensions may be trapped in the cells of origin, leading to inclinations which eventually result in necrosis, hepatitis and cirrhosis or, when synthesized in the brain, dementia (10-12).

Because of the research activities of hospital scientists, technologists and their postgraduate students, Christchurch pathology is capable, within weeks of a new test being described in an overseas journal (such as mutant DNA for the diagnosis of haemochromatosis, cystic fibrosis or Huntington’s chorea), of having the test up and running for the benefit of those in Canterbury and beyond.

Blood cells are examined by hospital and university haematologists, scientists, students and technicians for the diagnosis, treatment, prognosis and understanding of haematological and other diseases. A major research effort concerned the dendritic cell. This cell presents foreign antigens to lymphocytes, so the body can reject non-self. There is also research into the problem of patients with bone marrow transplants being susceptible to fungal infection due to immune depression. Haematologists, microbiologists and virologists are improving techniques for diagnosing fungi, bacteria and viruses from their DNA foot prints.

The microbiologists of the clinical school and hospital laboratories research bacteria in the kidney, protected by chemical osmolites. There is a real tapestry of endeavours in Christchurch, with a geology student from the University of Canterbury liaising with urologists and hospital scientists into the structure of kidney stones and their shattering by ultrasound. The microbiologists also join in world wide crusades against the pneumococcus, bird flu, HIV and have interests in ultraviolet exposure.

The manner in which white blood cells kill bacteria with the release of oxygen radicals again links biomedical research with microbiology, respiratory pathology and the health of premature babies. Thus our free-radical group meshes nicely with hospital health efforts and extends into the community, advising on the place of foods and vitamins protective against free radical damage.

Throw some students into this tapestry of knowledge, jumble of clinicians, scientists, researchers, technologists and administrators and it makes the curriculum committee wince as to what is our core teaching. It is not just laboratory diagnosis, it is not just biomedical research, it is not just haematology, microbiology, virology, immunology, cytogenticities or forensic pathology. It is indeed the study of disease and health, abnormal and normal structure and function. To our students, both undergraduate and postgraduate in a wide spectrum of health and medical pursuits, one of our major resources is the museum. Not only are there macroscopic specimens of diseased organs, but also an enormous collection of slides and power-points for projection of specimens and their histopathology (13).

More recently genomics and epigenetics have become tools to alleviate familial diseases such as hyperlipoproteinaemias, amyloidosis, haemophilia and even tumours by inserting DNA to replace mutant genes or siRNA to inhibit rogue proteins. Suitable vectors carry the genetic material to reach the appropriate organ (most often the liver). The size and composition of these vectors is all important, since to reach the hepatocytes they are first filtered by the liver’s fenestrated sinusoidal endothelium sinusoids (capillaries) (14-16).

In the future, I predict that the porosity of the liver sieve will be recognised of importance not only in the pathogenesis of atherosclerosis, from both environmental and familial hazards, but also in diseases related to immunity and inflammation. I believe our champion, Dr Pullar would have approved of my request for your scientific input into our Australasian Liver Sieve Research Group’s recent dreams or hypotheses. These are:

1. To develop a simple clinical liver function test for liver sieve porosity, for example:
   i. BSP test for albumin uptake, a common LFT from 50 years ago (17).
   ii. A cholesterol C13 breath test (18).
   iii. Imaging of filtration of suitably labelled nano-spheres, as by a spectral CT device (19).
   We urgently need a safe test to translate this experimental work to the bedside.

2. The role of immune tolerance, related to hepatocytes presenting their proteins as antigens to circulating T cells by contacting them through fenestrea, (a process called trans-endothelial hepatocyte lymphocyte interaction, TEHLI) which depends on a porous liver sieve (20) (Figure 2). We hypothesise that hypo-fenestration brought about by alcoholism (4), nicotine (5) and sedentary old age (2) leads to lack of immune-tolerance, immune hepatitis, active chronic hepatitis and cirrhosis. For example, the carrier state of hepatitis B (derived from being born of an infected mother) may become active hepatitis when defenestration occurs, so leading to T cells without tolerance.

3. The sieve’s place in the treatment of septic shock syndrome (due to TNF alpha and other inflammatory cytokines) from endotoxin activation of the reticulo-endothelial system, especially the liver macrophages (Kupffer cells) being negated by infusion of chylomicrons (21). These lipoproteins which adsorb endotoxins, when small enough pass through the fenestrea (Figure 1) to contact hepatocytes. Their adherent endotoxins are detoxified by the liver and excreted in the bile (21). Artificial fat emulsions (eg Intralipid) may act similarly (22). The latter, however has variable results, which might reflect the use of rabbits as experimental animals (with smaller fenestrae) rather than rats (23). Another factor maybe that TNF alpha decreases the sieve’s porosity (24). Sepsis has been shown to correlate with decreased sieve porosity and hyperlipidaemia (25). We also wonder if the saturation of
triglycerides, by changing the proportion of free cholesterol to cholesteryl ester may alter the adsorption of endotoxins by chylomicrons (6,26). One must get in early with treatment.

4. Chylomicrons from the jejunum may lead to endotoxins from within the gut lumen being transported up the thoracic duct to the neck veins to reach the lungs as their first organ of call. If the endotoxins activated the alveolar macrophages might this lead to the shocked lung syndrome? (Fortunately the small gut is usually relatively free of gram-negative bacteria; however, Dr Bruce Dobbs, the CDHB hospital surgical scientist who for thirty years has researched chylomicrons and the liver-sieve with me, points out that colonic lymph mixes with chylomicron-rich lymph in the thoracic duct, where gut endotoxin-chylomicron complexes may occur.) A fascinating editorial raises these possibilities (27). The pathogenesis of diabetes may also be affected by endotoxin-bearing chylomicrons from the gut (28), the excretion of which may be inhibited by our previous findings of less porous liver sieve in diabetes (29).

I am proud to have been associated with the discipline of pathology within our hospital-university environment, which despite financial restraints, clashes over funding, recognition and scientific philosophy, still delivers research-based training to our clinicians and patients and our ethos of translational medical research. The collegiality of New Zealand pathology, with our various national specialist meetings are tribute to Dr. T.H. Pullar’s vision of teamwork.

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