Charles Clifford Macklin (1883-1959): Pioneer Canadian pulmonologist

NORMAN C STAUB MD
Cardiovascular Research Institute and Department of Physiology, University of California San Francisco, San Francisco, California, USA

A prophet is not without honour save in his own country.
Matthew 13:57

MACKLIN, THE MAN

Charles Clifford Macklin, eldest son of William Macklin and Carolyn Clifford, was born October 23, 1883 in the village of Todmorden on the bluffs above the Don River, just east of Toronto, Ontario.

Charlie's grandfather, Marshall Macklin, emigrated from Ireland in 1828 to farm in Scarborough, northeast of Toronto. In 1839, he married Mary Jackson. Their 1851 stone house, a Canadian historical trust landmark, stands on Macklin Gate Court in the midst of a suburban housing project and near the recently dedicated Macklin school. Their twelfth child, William, born in 1854, was Charles Macklin's father.

Carolyn Clifford, the daughter of Samuel and Carolyn Clifford, met William when she was a school teacher in Scarborough and boarded with the Marshall Macklin family. William married Carolyn in January 1883.

When Charles was two years old, the family moved to their own farm in nearby Milliken's Corners. He attended Scarborough School #2. "When I started school in the early 90s ... we walked across the fields two miles to the little country one room school ...."

At 14 Macklin's education abruptly ended because he was needed on the farm. However, two years later with $100 given to him by an aunt he "... left the farm ... to take a business college course ...". He attended Central Business College of Toronto, where he learned shorthand and typing (Figure 1). Throughout his life, Charlie, as his family and friends called him, was a prodigious correspondent. He entered the University of Toronto Medical School in October 1908 because "... I was in the Medical Department of the Canada Life Assurance Company and, since two or three of my chums decided to study medicine, I thought I had better have a try at it ...".

Macklin blossomed intellectually and graduated in June 1914 with honours. He won the first James H Richardson Fellowship to do research in anatomy. The fellowship paid $500, which in 1912 was great riches indeed. The year in anatomy was a turning point in his life. His description of the skull of a 40 mm human fetus was published in 1914 and attracted the attention of Franklin P Mall, the renowned educator and chairman of the anatomy department at Johns Hopkins Medical School. Mall invited Charlie to Baltimore as an instructor in anatomy at $600 per year.

Shortly after Macklin moved to Baltimore, he met Madge DeGrofft Thurlow, a freshman medical student. Madge was bright, 19 years old and a women's rights advocate. In the anatomy department, there were several fellows whose first name was Charles, so Professor Mall gave each a distinctive nickname. Macklin received the German name Karl, from

Correspondence and reprints: Cardiovascular Research Institute and Department of Physiology, University of California San Francisco, San Francisco, CA 94143, USA

Figure 1) *Charles Clifford Macklin in 1900 in Toronto*

which Madge derived the affectionate nickname 'K' by which she frequently addressed him throughout their lives.

In September 1917 Madge and K were married in Philadelphia, where her parents lived. The newlyweds went by train to Toronto to visit his parents on their farm, then on to Pittsburgh, where K taught anatomy for a year. They did not have a proper honeymoon until the following summer, when they canoed up the Madawaska River into the Algonquin Park wilderness. They pitched their tent on an island in the river and lived on fish, wild berries and barley soup.

Their first child, Carol, was born in October 1918. Two more daughters, Sylva and Margaret, followed in 1921 and 1927, respectively.

During the First World War, Macklin tried to enlist in the Canadian army but was not accepted because of a minor congenital foot deformity. However, he did serve as a contract surgeon for the United States Army under Professor Louis Weed in the neurosurgical laboratory at Johns Hopkins University, where he studied brain trauma and repair.

In 1921 Paul McKibben, Dean of the Faculty of Medicine at Western University, London, Ontario recruited Charlie as Professor of Histology and Embryology, based upon a strong recommendation by Weed:

> *... Dr Macklin, who had been made an Associate Professor here last Spring, is interested in learning about the opportunities of the post. You know, of course, Macklin's qualifications; his publications have been numerous and of the highest quality ....*

Figure 2) *Charlie in his academic gown at Western University in 1928*

As of 1921, Macklin had not published any work on the lung. However, in 1922 a paper appeared in the *Anatomical Record* entitled "Elastic membrane of the bronchial tree and its functional significance". Many years later K wrote that he had begun to work on the lung in Weed's laboratory, but he never gave any explanation as to why he switched to lung research from his productive studies of brain injury, cellular division, and bone development and repair.

In 1929, Macklin published an extensive review, "The musculature of the bronchi and lungs". It is a keystone of our modern knowledge of structure and function of the airways and of lung expansion during breathing. In the 1920s K was about the only scientist interested in movements of the lung (Figure 2). Regional lung expansion was not studied further until after the Second World War.

The Macklins' move to the University of Western Ontario (UWO, renamed from Western University) was probably a mistake. The university had been among those recommended to be closed in the Flexner report on medical education in

1910. Recruiting the Macklins was an attempt to improve its quality. It did not become a first class school until after the Second World War.

Madge worked with her husband as an instructor, teaching embryology and also participating in histology; she was an outstanding teacher. Charlie, however, turned out to be a rather ineffective teacher. Although he was an innovative histologist, he was never popular with the medical students. His examinations were difficult, and he expected students to be capable of teaching themselves.

From the mid-1920s on, Macklin was unhappy at UWO. Either he or Madge was constantly doing battle with the medical school administration. In a letter to Louis Weed, K wrote,

> *It is apparent to me now that I made a mistake in leaving your laboratory before acquiring a department of my own. For I am having to carry on here under some disagreeable conditions ...*

and later to his lifelong friend Edmund Vincent Cowdry of Washington University, St Louis,

> *Mrs Macklin and I would like to get into a wider field at work. We are both primarily interested in research, and have managed to get something done up here, but the time has come to look for something better.*

Although Charlie continued to complain about conditions at UWO and to seek positions elsewhere, he never reached the point of accepting any offers.

The Macklins' family life was fairly typical of middle class people in the '20s and '30s. His $4000 a year income was not bad for those times; taxes were low, housing and food were cheap. They could afford a fulltime housekeeper and an automobile.

At home Charlie could be difficult and quixotic on the one hand, and affectionate and encouraging on the other. One daughter told me that when her father came home in the evening, the family held its collective breath waiting to learn whether he was in a good mood or not. Another recounts how her father would suddenly jump in his auto and, taking one or more of his daughters, drive up to Milliken's Corners to see his parents. Nevertheless, the family prospered and the girls dearly loved their parents. They went on vacations every year to the Great Lakes, Baltimore, Philadelphia or to Woods Hole, Massachusetts.

An important aspect of Charlie's otherwise modest social life was his membership in the Baconian Club of London, which consisted of a group of men who met several times a year. At each meeting, one or more members would give a talk on a subject he had researched; Macklin was fond of Hamlet and of Napoleon. The main purpose of the Club seems to have been to argue and to pick apart the carefully prepared presentations.

In 1934, Macklin published a brief article on alveolar pores. In 1936, he first mentioned the effects of lung overinflation. His papers of that period (1936-1944) are still quoted as the authoritative research on interstitial emphysema.

K regularly presented demonstrations and papers about his research at the American Trudeau Society (American Thoracic Society) and American Anatomical Society meetings. In the Anatomical Society he served a term on council and chaired a roundtable discussion about the existence of an alveolar epithelium at the 1936 meeting.

Charlie loved to travel. In 1936 he attended the International Congress of Anatomists in Milan, Italy. When he returned home, he wrote articles and gave talks about the congress. Naively, he praised the organization of the meeting by the fascist government of Mussolini. When interviewed by the London Free Press, he said that the people of Europe, including Italy, were desirous of peace.

The next year he took Madge and Margaret to Ireland, England and Germany. In Berlin he was elected to the German Anatomical Society. Towards the end of his life, Macklin wrote that he had always been much more appreciated in other countries than in Canada or at UWO.

In 1938, as war loomed in Europe, Sir Frederick Banting toured Canadian universities to determine their preparedness to undertake war-related research. Overall, he found them ill-prepared, with some notable exceptions. One of these was the laboratory of Charles and Madge Macklin. Banting was impressed by Macklin's work and recommended that his research be funded.

Charlie thought that his experiments in cats of osmic acid inhalation, which caused alveolar epithelial damage, would be a valuable starting place for a study of war gas lung injury, so he submitted a grant application to the Canadian National Research Council. It was not approved. The Deputy Minister of the Department that reviewed the grants concluded, "I do not think the research in question would be of any assistance ...".

Fate soon contravened that rejection. The next year (1940) Professor FJW Roughton of Cambridge University wrote to Banting that Sir Joseph Barcroft was anxious for someone to work out the detailed anatomy and histology of the alveoli on various species of animals used in laboratory experiments on war gas. He wrote, "It appears that Dr Macklin would be highly qualified to do this work ...".

So in October 1940 Banting sent a telegram to Macklin "Grant $5,000 awarded. Proceed". Although $5000 is trivial in the light of today's awards, in 1940 it was among the largest grants ever given by the National Research Council of Canada.

Macklin recruited Stanley Hartroft, a senior medical student in Edmonton, Alberta.

> *Through Professor Shaner, you have been offered a salary of $125 per month as my research assistant .... Professor Shaner has informed me ... that you will accept this offer .... Please let me know when you expect to arrive.*

Stanley Hartroft's availability was fortuitous. In Banting's 1938 tour, he had found a dearth of young men who were trained to do basic research and even fewer who had a medical degree. Stanley met both qualifications. He arrived

Figure 3) *Macklin's wartime team in the laboratory preparing to fix the lung of a monkey. Left to right: Charles Jarvis, lab technician; Stanley Hartroft, research fellow; Edna Cunningham, typist and laboratory assistant; Professor Macklin. The picture is dated October 11, 1941*

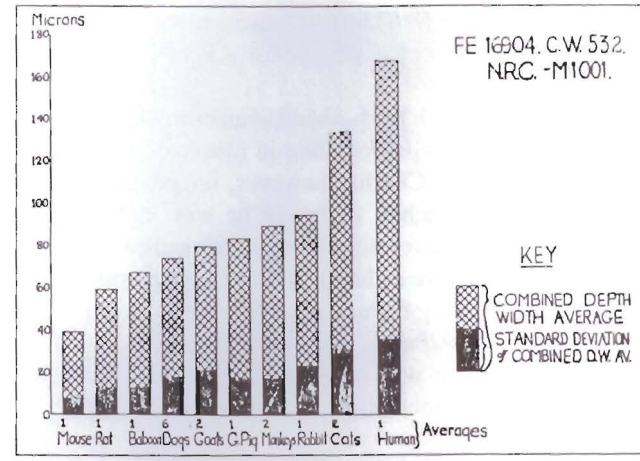

Figure 4) *A bar graph summarizing the data on the size of the alveoli of the lungs among 10 mammalian species. Note that only one or two specimens of each species were measured, except for the dog. The figure was made by Stanley Hartroft. From Report to Section of Physiology, Chemical Warfare Laboratories, Ottawa, Canada, June 30, 1943*

in London, Ontario at the end of January 1941. He was the only research fellow Charlie ever had.

In Macklin's laboratory between 1941 and 1943, in addition to Madge and Professor (as Stanley always referred to him), there were Charles Jarvis (Macklin's histology technician), Edna Cunningham (a typist crippled by rheumatoid arthritis) and Stan Hartroft (Figure 3).

Although the quantification of pulmonic alveolar size is probably what pulmonologists most frequently associate with Macklin's name, it was not, in my opinion, one of his major achievements. The measurement of alveolar size did not require any great intellectual leap forward and, in retrospect, there was certainly no theoretical basis for Barcroft's notion that the size of individual alveoli affected the response to inhaled gases among species.

It took two-and-a-half years to complete the project and to write the long report (classified 'SECRET'), which was submitted to the Sub-Committee on Physiological Aspects of War Gas Injury of the National Research Council of Canada, which forwarded it to Sir Joseph Barcroft. In spite of strict wartime censorship, most of the data were eventually published in a series of short articles in *Transactions of the Royal Society of Canada* in 1943 and 1944. I obtained the last copy of their report from the Canadian government archives in Ottawa in 1960.

The results of the experiments are well known and still valid, and they included some innovative lung preparation methods, including perfusion-fixation. Macklin and Hartroft found a fairly good correlation between alveolar dimensions and body size, although the cat had disproportionately large and the goat disproportionately small alveoli relative to body size (Figure 4). Macklin thought these differences reflected the ability of different species to perform sustained exercise; an important insight into function based on structure. The data proved to be useful a decade later when work on alveolar surface tension and surfactant depended on knowing the size of the alveoli.

In 1943 Stan Hartroft joined the Canadian Medical Corps. After the war he trained as a pathologist at the University of Toronto and later was Professor of Pathology at Washington University, St Louis, Missouri.

Shortly after the war things began to change rapidly at UWO Medical School. George Hall, who had been at the Banting and Best Institute in Toronto during the war, became the dean. Although the Macklins had their troubles with the medical school deans over the years, those were mere skirmishes compared with the main battle which now took shape.

Hall was something of a whiz kid, rising rapidly in medical administration. After only two years as dean, he became president of the UWO.

Among Hall's changes at the medical school was a decision to get rid of Madge Macklin, ostensively because her teaching of embryology did not fit in with Hall's plans for the medical school curriculum, but almost certainly also because of public antagonism to her long-standing espousal of eugenics in relation to inheritable diseases. On August 9, 1945 Hall wrote to Charlie,

> *... a great deal of consideration has been given to the arrangements whereby the teaching of histology, embryology, and anatomy might be coordinated within the University as a whole ... you are advised, as head of your department, that the teaching of embryology will ... become the responsibility of the Department of Zoology ... the services of Dr M T Macklin, who is employed on a part time basis, will not be required ...*

The Macklins were devastated by this abrupt termination. Madge was in the prime of her career and was becoming internationally recognized for her work on human heredity and the genetic basis of disease. She was one of the first investigators to establish a genetic factor in breast cancer – a topic of great interest in the 1990s. Later, she was a councillor

and served as president of the American Society for Human Genetics.

Through friends and associates Madge was able to obtain a research position and continue her human genetics studies in the zoology department at Ohio State University; there were no departments of genetics in those days. She worked there from 1946 to 1959, returning to London one weekend per month and spending her summer vacations with K. In a letter to Cowdry, Macklin summarized the events with some bitterness:

Dr Madge Macklin goes to Columbus the end of this week ... I will miss her greatly, of course; but fortunately, it is not so very far to Columbus, and she will be able to come home fairly often ... We thought it was the only thing to do under the circumstances. I do not know of any other so-called University that would turn out one who had done two dozen years of brilliant work like Madge Macklin has done here ...

Several months later, Hall replaced Macklin as Head of Histology with Murray Barr, making Charlie Research Professor of Experimental Histology.

In spite of these troubles, Macklin continued his investigations and opened new imaginative lines of research. He showed that when the lung expands, the pulmonary vascular volume increases; even more so if the alveolar wall microvessels are excluded by high alveolar pressure (zone I conditions). Thus, he discovered what we now call 'alveolar' and 'extra-alveolar' vessels.

He also realized the importance of breathing in relation to the circulation of blood. He referred to the lungs as an 'accessory heart', a feature that has become central to our understanding of cardiopulmonary resuscitation.

In 1950, Macklin published another important review, "The alveoli of the mammalian lung", summarizing 15 years of work on the pulmonary alveoli.

In 1953, Macklin was forced to retire, which brought another difficulty (Figure 5). The university retirement fund had not been in existence long enough for Macklin to be qualified to receive a significant pension. The Board of Governors refused to extend Macklin's tenure for one year, so that he would receive a larger pension, although they did vote to give him one year's salary ($5700).

Charlie did not go quietly into oblivion. He wrote to his cousin,

... They gave me a nice silver tray and so I am out for good. This symbolizes the end of everything but the final stage of the 'unhousing process', which is finalized in the expulsion of the one-time professor and his abandonment to the outer world ....

K was never one to understate his position or to avoid self pity. In another letter to his cousin he included the following:

I was heartbroken when they turned me out of university space here. I would gladly have gone on doing what I could voluntarily. But they said they had to treat all

Figure 5) *Professor Macklin in his office about the time of his retirement in 1953*

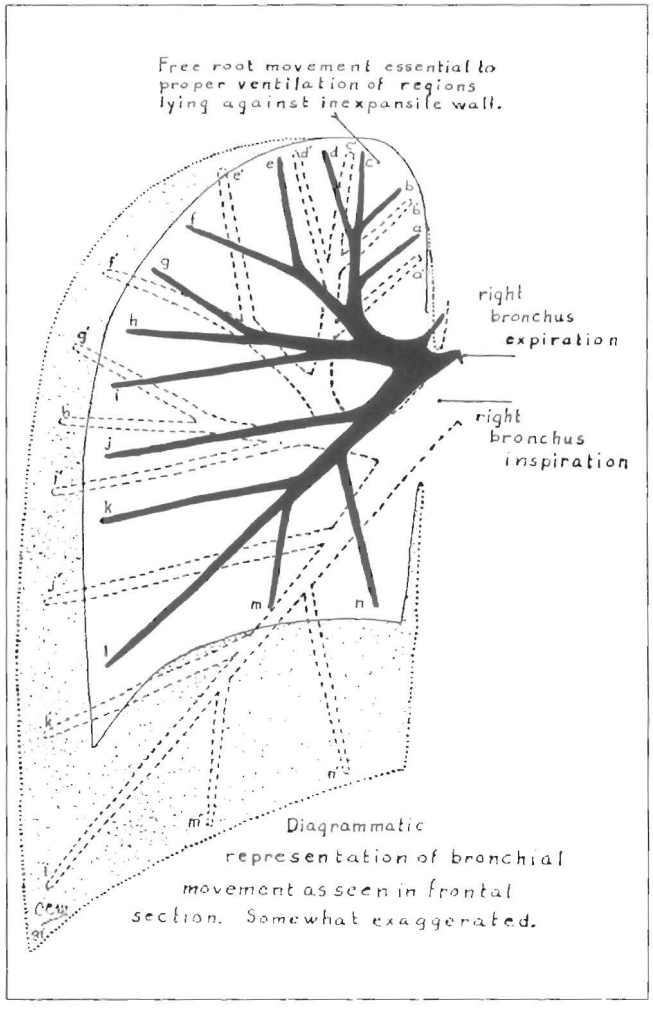

Figure 6) *Expansion of the lung occurs in all directions. The bronchi become longer and wider and the trachea moves downward permitting the upper lung to expand without distortion. Macklin made this figure; see CCM 311 in the lower left corner of the lung. From* Am Rev Tuberc *1932;25:393-417*

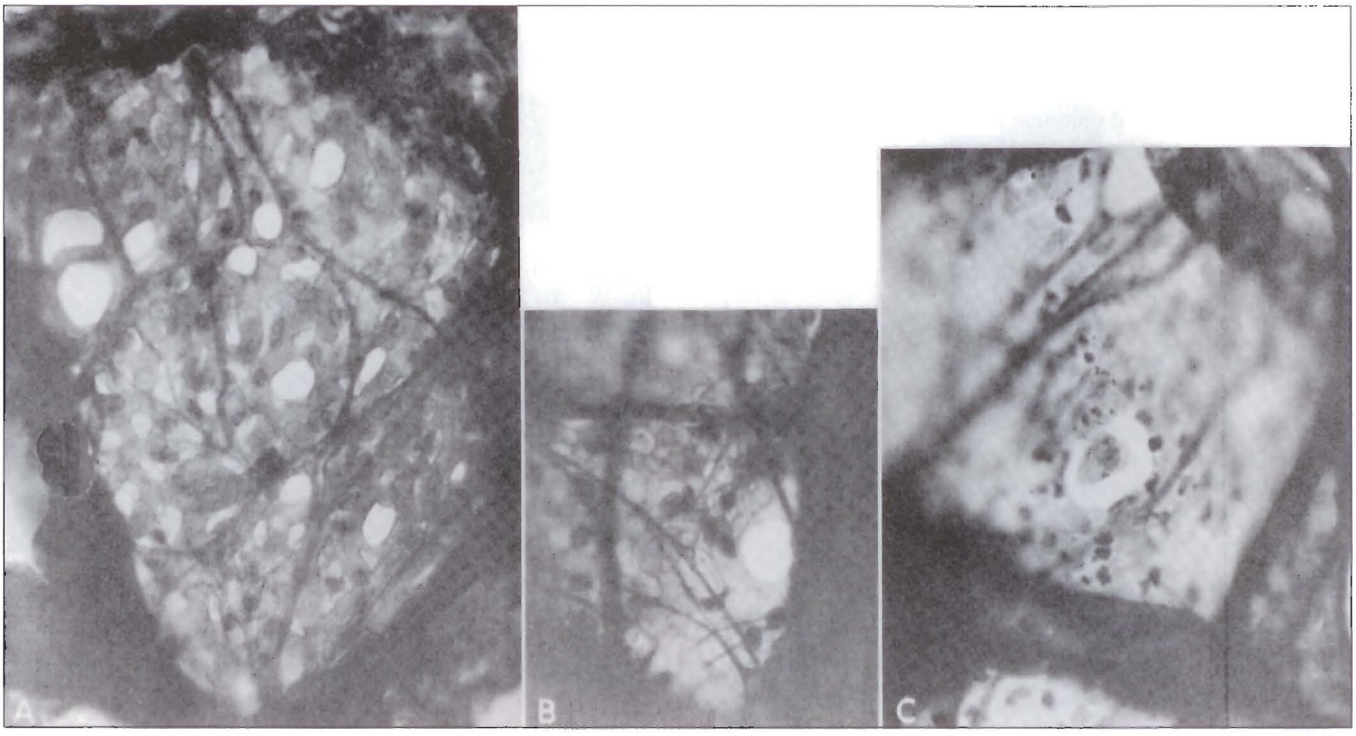

Figure 7) *Microphotographs of alveolar pores and fenestrae in thick sections of expanded lung. Macklin noted that the pores could not be seen in lungs fixed at low volume, suggesting that stretch of the alveolar wall occurred with lung expansion. From* Arch Pathol *1936;21:202-16*

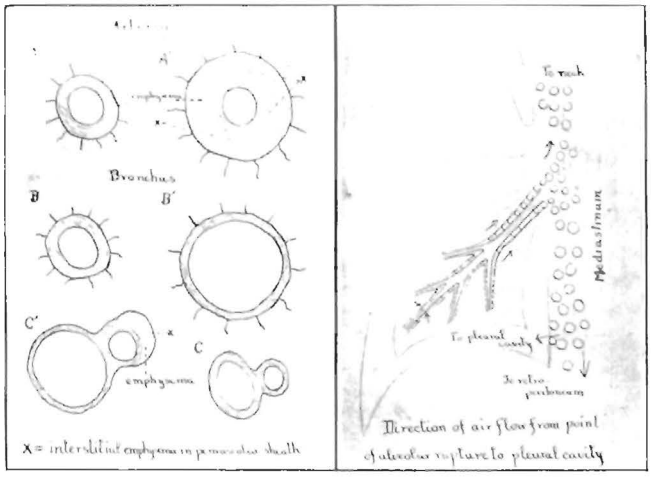

Figure 8) *Macklin's rendition of peribronchovascular air (x) and how air tracks along the loose, binding connective tissue into the mediastinum. From* Can Med J *1937;36:414-20*

alike .... However I still manage to do a little, although it is not ideal being alone all of the time ....

That 'manage to do a little' included three major papers about the function of the type II alveolar epithelial cell (granular pneumonocyte).

In 1959, the same year that Madge Macklin retired from Ohio State, K was invited by Giles Filley of the University of Colorado to be the honoured guest at the Second Aspen Conference on Emphysema. Charlie declined, stating that he did not feel well enough for extensive travel. I would have met him at that meeting. In November he wrote to his daughter Carol, "... I do not read anymore, except the newspapers.... This afternoon I sat on the back porch and enjoyed the last lingering rays of the sun ...".

The day after writing that letter, Charlie decided to go downtown to do some errands. He put on his greatcoat, Homburg hat, took his walking stick and, saying goodbye to Madge, walked a block to the bus stop. When the bus arrived in central London, the driver noticed Macklin slumped over on a rear seat. An ambulance was called and Charlie was taken to the Victoria Hospital where he was pronounced dead. He was buried in Ebenezer Church yard near his boyhood home. Madge died in 1962 and was buried beside him.

MACKLIN, HIS RESEARCH ACCOMPLISHMENTS

The subtitle of the present biography is pioneer Canadian pulmonologist, which I chose in order to emphasize Macklin's extraordinary ability to deduce function from structure. One need only compare his work with that of William Snow Miller (1858-1939), Professor of Anatomy at the University of Wisconsin, whose career overlapped that of Charlie's. At different times both had been students of Franklin Mall, but Miller remained a strict anatomist. Charles Macklin was the better scientist, not just as an innovative histologist but as a pulmonologist. However, Miller is better known because he did one thing that K did not do. He wrote a book, *The Lung* (1937), summarizing his studies. Interestingly, he did not mention any of Macklin's discoveries concerning lung expansion or anything else.

Macklin's investigations of lung structure and function extended over nearly 35 years (1922 to 1956). His papers and abstracts contain remarkable physiological and pathophysi-

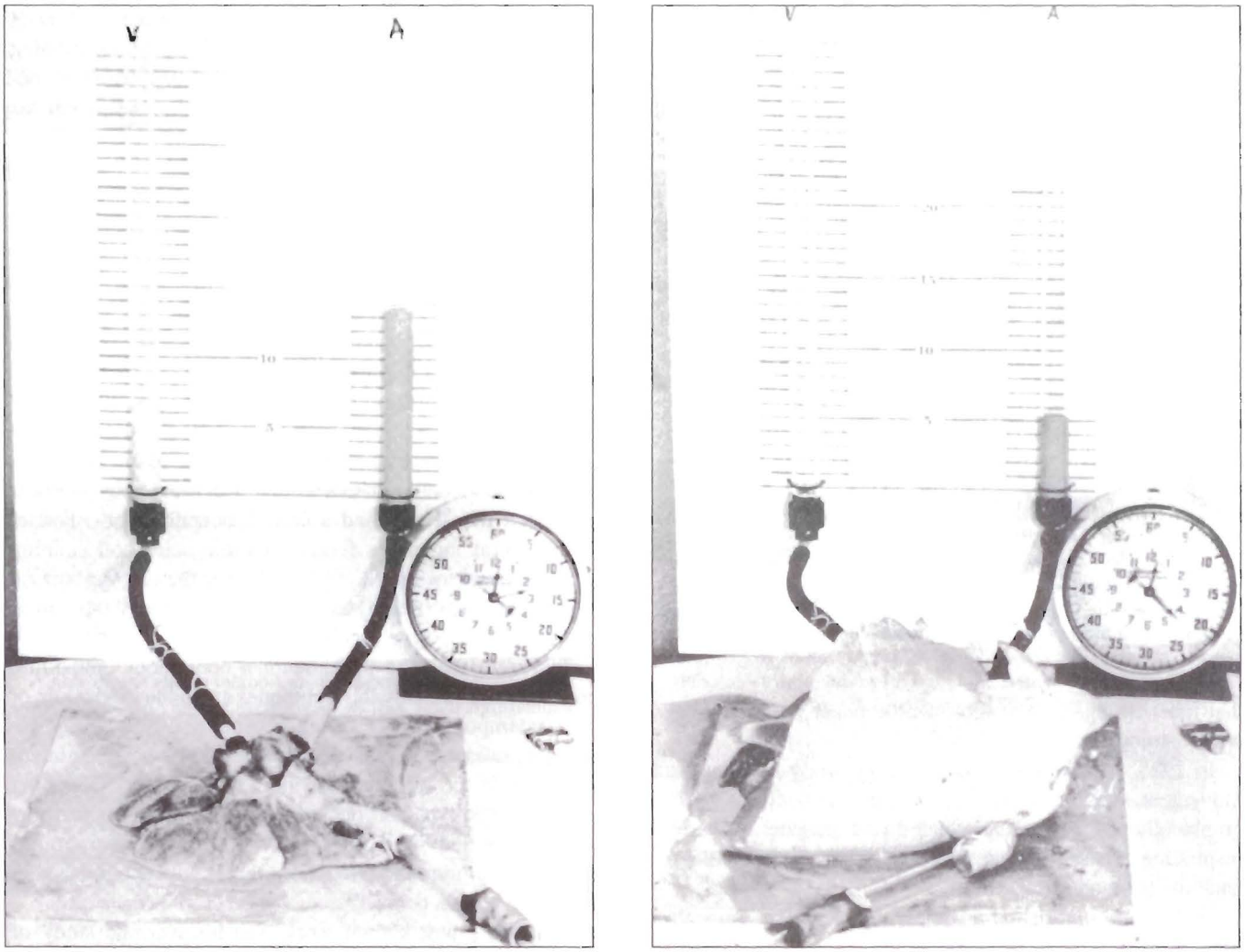

Figure 9) *Figures from Macklin's landmark paper proving that lung vascular volume increased as the lung was inflated.* **A** *The levels of white (vein, V) and coloured (artery, A) latex when the lung is collapsed;* **B** *The levels of both latex solutions fall (6 to 8 cm) when the lobe is expanded. The clock shows that 10 mins elapsed between the pictures. From* Rev canadienne Biol *1946;5:199-232*

ological insights. His work was a beacon during the years before the Second World War, when pulmonary physiology was largely unknown.

In these days of huge grants and laboratories full of equipment, fellows and technicians, it is important to remember that essentially all of K's accomplishments were made while working alone and with few funds.

The trends in Macklin's thinking as he progressed from one concept to the next can be traced rather easily. He had many original ideas, often based upon chance observation made during the course of experiments. Professor Stanley Hartroft described Charlie's discovery of alveolar rupture with subsequent interstitial emphysema as follows:

... he ... got some calf lungs ... and attached the trachea to the compressed air line ... and turned the valve and ... he overfilled them. ... [the air] all came bubbling out at the hilum into the mediastinum. ... he said, 'Now isn't that interesting. Look! The air came bubbling out around the root of the pulmonary arteries and veins.' ... to me, nothing could be less interesting. He had ... blown the lungs to pieces by putting too much air in them. ... Just throw them away and get some more lungs and don't turn the air pressure on so hard. ... [After getting another lung] he left the pressure on lower ... and it finally did dry the lung. ... and using a very sharp knife he cut sections through the dried fixed lung. And lo and behold, here were all the ruptures in the lung at the bases of the alveoli along the bronchovascular bundles. ... and he said, 'Ah, ha. That is how the pathogenesis of pulmonic interstitial emphysema occurs'. (From a tape-recorded interview with Stanley Hartroft, 1978).

Macklin's first lung research in 1922 dealt with the functional significance of the elastic membrane of the bronchial tree; that is, the inner lining of the bronchi which contain a interdigitating spiral network of elastic fibrils and bands of smooth muscle. He demonstrated that the recoil of the trachea or lobar bronchi when stretched depended on the integrity of

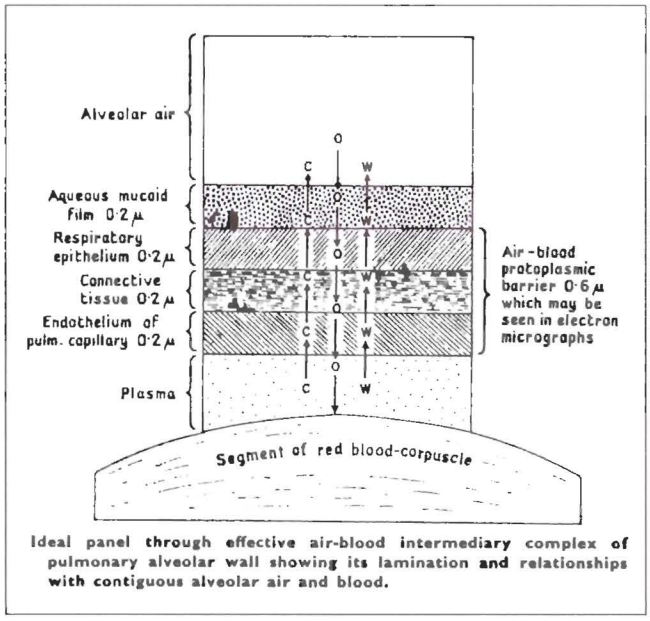

Figure 10) *The alveolar-blood barrier to gas exchange, as conceived by Charles Macklin. An alveolar lining layer is shown. From* Lancet *1954;i:1099-104*

that inner lining. This insightful little paper has little to do with histology but a great deal to do with physiology.

In 1925, Charlie published an x-ray study of bronchial movement, demonstrating conclusively that all the radiographically visible bronchi dilated and lengthened during inspiration. Plate 5 of that paper was used in textbooks of anatomy for three decades.

In 1929, he published a review article, "The musculature of the bronchi and lung" in which he synthesized a remarkably modern view of lung mechanics. For example, he concluded that the anatomical dead space ('bronchial capacity') must increase as lung volume increased. A few years later, based on careful chest roentgenograms, he clearly described how regional lung expansion occurs, particularly the necessity for movement of the lung hilum during breathing and the concomitant movement of the pulmonary arteries and veins in relation to breathing (Figure 6).

In 1934, Charlie moved on to study the pulmonic interlobular air passages (alveolar pores and fenestrae). Although alveolar pores had been described by Ogawa in 1920, what turned Macklin on to them was Van Allen's and Lindskog's demonstration of collateral ventilation in 1931. Using thick (25 μm) sections, Macklin confirmed the existence of pores, showed that they were easy to miss if the lung was not well-inflated at the time of fixation, and concluded that these interalveolar communications equalized pressure and volume among alveoli (Figure 7). As a demonstration of the physiological direction of his thought, he noted that

> *... the vents in the alveolar wall attached to the pleura are of larger size ... and ... that vents of large size characterized the walls attached to the adventitia of the blood-vessels and the smooth-walled air tubes.*

He made his next leap forward in 1937 when he showed that rupture of the alveolar bases along the loose, binding interstitial connective tissue was the path by which air entered the interstitium (Figure 8). When he completed his studies, which are summarized in a review in *Medicine* (1944), he had almost completely settled the issue.

The quotation above from Stanley Hartroft is, unfortunately, apocryphal because Charlie published his studies of interstitial emphysema in the calf lung two years before he met Stan. Still, the tale, which Macklin probably recounted or demonstrated to Stanley, is wonderfully insightful about Macklin's originality and readiness to appreciate chance observations.

Charlie entered the debate between the German researcher Max Clara, who believed the alveoli contained only residual non-nucleated pieces of epithelium (epicytes or squames), and the American William Snow Miller, who stated categorically that the alveoli had a complete epithelium. Macklin used several ingenious fixation (osmic acid) and staining (silver nitrate) methods to try to delineate the alveolar surface cells. This led eventually to his investigations of the granular pneumonocytes (type II cells).

Unfortunately, the problem of a continuous epithelium could not be solved by the techniques available to Macklin or his contemporaries, not so much because of the limited resolving power of the light microscope (as is so often claimed) but because the technique of thin (1 to 1.5 μm) sectioning using glass knives had not been invented. The controversy was not settled until Frank Low's electron micrographs showing a continuous alveolar epithelium were published in 1953.

Macklin's best-known work was his wartime study of alveolar size among mammalian species. As it was mainly applied anatomy and did not contain any original ideas, I have already recounted it in the section about Charlie's life. He summarized most of his work on the alveolar structure and function in a lecture at the Institute of Medicine in Chicago in 1950.

In 1946 Macklin published one of his most inspired physiological discoveries. He described exactly how the

> *... lengthening of the blood vessels must occur from the pull of the surrounding connective tissue of the expanding lung. The branches of both blood and air tubes are fastened directly to the bases of alveoli, and the expansion of these must necessarily increase the length of the tubes, and may also have a dilating effect ...*

(Figure 9). Later he referred to the changes in intrapulmonary blood volume with breathing as the accessory heart. He used the metaphor of a bridge to describe the relation of the pulmonary circulation to the right and left hearts.

Three of K's last four papers deal with the function of the osmiophilic granules secreted by the type II cells and the clearance of dust and cells from the air spaces. He accepted Terry's 1926 conclusion that there is free liquid on the alveolar surfaces (alveolar lining fluid). As early as 1936, and again in 1946, he confirmed, on the basis of his silver staining

of the alveolar surface, earlier suggestions that the type II cells "... contributed something to the circumscribing fluid film of the alveolar capillary wall which is advantageous in external respiration ...".

In his 1954 paper in *Lancet* and again in *Acta Anatomica* (1955) he showed his excellent understanding of what was going on in the air spaces of the lung (Figure 10). He presented evidence for an active secretion by the type II cells and that the secretion contained myelin figures (phospholipids) and lowered alveolar surface tension.

In regards to alveolar clearance he hypothesized that dust, liquid and alveolar macrophages had a special route of exit from the air spaces into the interstitium in the region of the bronchoalveolar junctions, which he called pulmonary sumps.

His final publication dealt with the preferred sites of bronchogenic carcinoma in relation to the airway concentration of particles during clearance.

MACKLIN, SUMMING UP

How can I epitomize the amazing physiological insights of Charles Macklin? Was he a prophet? a visionary? He was clearly far ahead of his contemporaries in relating lung structure to its function. Historically he was largely ignored; his colleagues were not ready for his expanding view of lung physiology. For example, Thomas Hale Ham, author of a leading textbook of histology and a contemporary at the University of Toronto, told me that he never realized Charlie's work was important. Charles Clifford Macklin was truly a stranger in a strange land.

ACKNOWLEDGEMENTS: My gratitude to Carol, Margaret and Sylva Macklin, who contributed many reminiscences, pictures and other mementos of their parents. I also thank the librarians and archivists at the University of Western Ontario, the Alan Mason Cheney medical archives at Johns Hopkins University, and the University of Washington, St Louis. Many former colleagues and students of Charles and Madge Macklin also shared their memories.

REPRESENTATIVE BIBLIOGRAPHY FROM MORE THAN 130 PAPERS AND ABSTRACTS BY CHARLES MACKLIN

1. A note on the elastic membrane of the bronchial tree of mammals, with an interpretation of its functional significance. Anat Rec 1922;24:119-35.
2. The musculature of the bronchi and lungs. Physiol Rev 1929;9:1-60.
3. The dynamic bronchial tree. Am Rev Tuberc 1932;25:393-417.
4. Alveolar pores and their significance in the human lung. Arch Pathol 1936;21:202-16.
5. Pneumothorax with massive collapse from experimental local overinflation of the lung substance. Can Med Assoc J 1937;36:414-20.
6. Vital staining of the mammalian pulmonic alveolar wall and its bearing on the problem of a continuous epithelial layer. Proc R Soc Canada (Sect V) 1938;32:156. (Abst).
7. Ageing in the respiratory system. In: EV Cowdry, ed. Problems of ageing, 2nd edn. Baltimore: Williams & Wilkins, 1942:185-253.
8. The size of pulmonic alveoli based on measurements of their outlines in 25 µm microsections of human and common laboratory animal lungs fixed in the state of expansion. Report to Section of Physiology, Chemical Warfare Laboratories, Ottawa, Canada, June 30, 1943.
9. Evidences of increases in the capacity of the pulmonary arteries and veins of dogs, cats and rabbits during inflation of the freshly excised lung. Rev canadienne Biol 1946;5:199-232.
10. Alveoli of mammalian lung; anatomical study with clinical correlations. Proc Inst Med Chicago 1950;18:78-95.
11. The pulmonary alveolar mucoid film and the pneumonocytes. Lancet 1954;i:1099-104.
12. Pulmonary sumps, dust accumulations, alveolar fluid and lymph vessels. Acta Anat 1955;23:1-33.
13. Induction of bronchial cancer by local massing of carcinogen concentrate in outdrifting mucus. J Thorac Surg 1956;31:238-44.