Prof. Mike Hughes – Pulmonary Function 1954-2010 – ARTP Conference 2010

Thank you Martyn for your kind and generous introduction and for all your support with this project. I do enjoy visiting PF labs as a "volunteer guinea pig", and staff always treat me with great kindness and expertise. You should all, justifiably, be proud of your contribution to Pulmonary Medicine.

I have always been a supporter of and an advocate for the ARTP. When my proposal for a book on the Physiology and Practice of Pulmonary Function, to be written primarily for ARTP members, was enthusiastically endorsed by Brendan Cooper and Damian Muncaster, past and present Chairmen of the ARTP, and by the whole of your present Committee, I was very pleased and determined to do my best. From this talk, you will get, amongst other things, a flavour of what is in the book.

1. The setting for this lecture is the development of pulmonary function over the past 55 years, though the origin of your speciality probably goes back to 1940, 70 years ago. Why should you be interested in such history? There are many reasons; one of them is that the discoveries and methods of 50 years ago are still applied by you today, and the physiological concepts of the 1950s still influence our thinking.

2. Julius Comroe really put Pulmonary Function, as we know it, on the map with his Beaumont lecture in 1954, followed by the book based upon it. Comroe was a formidable scientist, and a natural teacher and leader.

3. From Chairman of Physiology in Philadelphia, he became the founder of the CVRI, the cardiovascular research unit in San Francisco, which became a byword for excellence.

4. The publication of his book The Lung was opportune because there had been an explosion oif knowledge about pulmonary physiology and function in the preceding 15 years and I shall briefly refer to the researchers and scientists of that "Golden Age". Then, I shall take one of Comroe's case histories from his 1955 book and compare it with present practice, illustrating the development of Pulmonary Function by referring to the Figures and Tables in my book.

5. Comroe in his preface laid great store on good illustrations, and I have tried to follow his precepts as shown on this slide. In particular, I was determined to use the medical artist I had worked with from my Hammersmith Hospital days for over 20 years, Doig Simmonds. He is in the audience. Perhaps he will raise his hand!

6. Examples of his excellent diagrams (my colleagues are very envious) with their clean lines can be seen on the cover of the book together with his name and that of Neil

Pride, who read every page of the book in manuscript, and of the ARTP, your society and the publishers.

7. The second world war and its aftermath was a great stimulus to research into pulmonary physiology and lung function. One of the most famous departments was at Rochester, and when Fenn, a most distinguished physiologist, recruited his young and raw graduates, Herman Rahn and Arthur Otis he said modestly "we are working on positive pressure breathing, which will enable our Air Force to gain a little altitude". Little did they or anyone know that the spin–off would be a series of famous diagrams of the pressure–volume relationships of the lung and chest wall, and the O2–CO2 diagram, all so fundamental to our understanding to this day.

8. A decade later, Rahn trained two respiratory physiologists, LF and JBW, who also contributed much to our understanding. You will have heard of John West through his beautifully produced books, such as The Essentials series. I worked for John in 1966-8, so I can trace my ancestry back to Rahn and Fenn.

9. Another famous centre for applied physiology was the Harvard School of Public Health. Jere Mead was a pioneer in so many ways – you may have heard of the EPP, the equal pressure point; with Mel Avery, a paediatrician in Montreal, he highlighted the surfactant deficiency in Respiratory Distress of the Newborn. I was fortunate to spend 15 months in his Department. I wish it had been longer.

10. Jere Mead trained Peter Macklem and Milic-Emili. Both became leaders in clinical respiratory physiology, and their names will be familiar to many of you.

11. Dick Riley worked with Cournand in New York, and then became Chairman of the Respiratory Department at John's Hopkins; a brilliant respiratory scientist whose concepts of ideal alveolar PO2, physiological dead space, venous admixture (physiological shunt) are still used today.

12. Two of Riley's protégés were British Physicians, Moran Campbell and Neil Pride, both associated with Hammersmith Hospital, though Moran emigrated to Canada. I was Moran's House Physician for 6 months, and was Neil Pride's colleague at Hammersmith for nearly 30 years. Both made immense contributions.

13. Modern pulmonary function was born, not in Comroe's laboratory, but in Cournand and Richard's Department at the Bellevue Hospital in New York. Not only did they receive the Nobel Prize for the introduction of cardiac catheterisation, measuring pressures for the first time in the R atrium, R ventricle and pulmonary artery, but they described, with their colleagues, an accurate measurement of absolute lung volumes (which is being revived today), proposed the classification of obstructive and

restrictive disease, and unravelled many of the complexities of gas exchange, such as VA/Q mismatch and alveolar–capillary block.

14.   All this work was a solid foundation and springboard for Comroe's book The Lung, Clinical Physiology and Pulmonary Function tests when it was published in 1955.

15.   Important contributions had been, or were going to be made, by its authors, notably Robert Forster (the single breath diffusing capacity or transfer factor), Arthur Dubois (the name is of Dutch, not French origin) for the body box, and Ward Fowler (a member of the team but not an author as he had moved to the Mayo Clinic) for the single breath and multi-breath nitrogen tests.

16.   Roughton came from Cambridge, UK, to work with Robert Forster; using Roughton's rapid reaction apparatus they measured "theta", the rate of reaction of CO with blood, and formulated their famous equation which is the key to the understanding of the physiology of the TLCO.

17.   Another giant was Arthur Dubois who solved the problem of measuring alveolar pressure by gas compression in the body box, enabling him to measure FRC and airways resistance. Comroe and Botelho had been working on this problem for 1-2 years before Comroe put Dubois onto it. When Dubois told Comroe he had cracked it, Comroe was apparently pleased that Arthur had got it to work, but irritated that it had only taken him a week! Dubois had the advantage of a new pressure transducer with hundred fold increase in sensitivity.

Is this catalogue of personalities boring? I hope not. They were all great scientists, and I knew most of them. Several were my teachers, just as I am teaching you now, thus linking you to what I call "a golden age". More importantly, their discoveries and concepts are still relevant today.

18.   We come to Part II of my talk; consideration of a pulmonary function profile, one of ten, taken from Comroe's book. The clinical details suggest asthma. Although the slow vital capacity was measured before and after a bronchodilator (increasing by 0.8 L), you will be surprised to see that the dynamic measurement was not the FEV1 but maximum voluntary ventilation over 15 seconds.   Like the VC, this was considerably reduced but responded to the bronchodilator. The cause of the reduced MVV was reduced maximum expiratory flow (inspiratory flow was 4.5 times greater).   Also recorded was the presence of air trapping from a spirogram trace.

19.   This diagram, from Comroe's book, shows [schematically] spirograms of resting breathing, expiratory and inspiratory VC and 15 s MVV. The MVV is reduced in airflow obstruction, whether due to bronchial narrowing and constriction in asthma, or to loss of lung elastic recoil as in emphysema, but is relatively well preserved in restrictive lung disease with fibrosis. We know now that the MVV and the FEV1 are closely related in normals and airflow obstruction (MVV being 35 to 40 times the FEV1), and it was inevitable that this exhausting test would be replaced by the single breath timed vital capacity, as foreseen by Comroe in 1955.

20.   Air trapping. You should be familiar, in patients with severe airflow obstruction, with the slow return to the relaxed end expiratory level (true FRC) following a deep inspiration, and that it is important to take account of this when measuring FRC in the body plethysmograph or after closed circuit helium equilibration. But another cause of air trapping in asthma is the bronchoconstriction induced by a deep inspiration.

21.   A modern way of observing air trapping in asthma compares maximum expiratory flow, at the same lung volume relative to TLC (after 60% FVC expired) following an MEFV curve starting from TLC versus a partial flow volume curve starting from end tidal inspiration. A maximum–partial flow ratio less than 1.0 (on the right) indicates deep inspiration induced bronchoconstriction, often seen in spontaneous asthma, but the reverse is seen [M/P ratio > 1] in bronchoconstriction induced with methacholine.

22.   Today, in contrast, our young man would have a measurement of FEV1 and FVC before and after bronchodilatation, calculation of the FEV1/FVC ratio (a good index of intrapulmonary airflow obstruction) and a maximum expiratory flow volume curve.

23.   The FEV1 had in fact been described 8 years before Comroe's book appeared, but in French in a French journal, so time passed before much notice was taken in the United States. Tiffeneau was a pharmacologist in Paris; Yernault gives a good account of the development of the FEV! and the FEV1/FVC ratio. The FEV1 was originally the CPUE, capacité utilisable à l'effort, and 1 second was chosen as it was the expiratory time for normal subjects during exercise. The FEV1 became a standard measurement in the late 1950s. You can see that I have indicated the FVC at 6 seconds (FVC6); this has been proposed as a way of standardising the FVC which, in severe airflow obstruction, may become dependent on the forced expiratory time (sometime a volume plateau is never reached), and sometimes patients quit early. Whether the FVC6 will replace the FVC is controversial; the severer the obstruction, the more the FVC6 and the FEV1/FVC6 ratio will underestimate values using the true FVC.

24.   The next advance in spirometry, probably stimulated by the availability of X–Y persistence oscilloscopes, was Fry and Hyatt's description of the maximal expiratory flow volume curve, which revealed patterns not easily seen from spirographic plots of volume versus time. Here we see, taken from my book like the previous spirogram, MEFV curves in young and elderly normals, and in moderate and severe COPD.

25.   The FEV1 is such a reliable test in patients with airflow obstruction because it is largely effort independent. The reason for effort independence is explained by the isovolume pressure flow curve – one of the classical diagrams of respiratory mechanics – in which expiratory flow was measured at different levels of alveolar pressure at a series of lung volumes (by interpolation). Palv was derived from pleural pressure which was an index of the amount of muscular effort. You can see a plateau of expiratory flow, at a given lung volume, once a critical threshold of effort (or Palv) had been achieved. All the original IVPF curves were measured on Bob Hyatt since Don Fry refused to swallow the oesophageal balloon, but Hyatt still didn't get first authorship. The Fry Hyatt collaboration was extremely productive as you have seen in this and the previous slide. They met by chance. Fry said "one afternoon, a young man walked into my lab looking for the men's room (the loo). We struck up a conversation …". The rest they say is History!

26.   Our young man with variable airflow obstruction would today have had a sprogram and MEFV curve before and after bronchodilator.
Note that with MEFV curves before and after a bronchodilator, flow comparisons must be done at the same lung volume relative to TLC (so-called isovolume) rather than relying on FEF75 because FVC has changed. Incidentally, I am not a great fan of FEF75 (aka MEF25); the normal range is so wide; there is sufficient information in the shape of the MEFV and MIFV curves. Note also that bronchodilatation may reduce dynamic hyperinflation and FRC and RV.

27.   Technical innovation frequently makes an important contribution, and our understanding of diurnal variation in asthma was advanced after Wright and McKerrow introduced a simple hand held peak flow meter which could be used by patients in their homes.

28.   This rather complex slide shows 4 phases of increasing asthma severity, from Stage I with almost normal mean PF with minimal diurnal variation, few if any symptoms or bronchodilator use, no corticosteroids and normal bronchial hyperreactivity on the basis of a methacholine challenge to Stage IV with low mean PF, much diurnal variation, more symptoms and b.d. use, oral and systemic corticosteroids and increasing bronchial hyperreactivity with a clearly abnormal methacholine challenge.

29.   In 2010 we recognise that the cardinal features of asthma are bronchial hyperreactivity, as shown on the previous slide, and airway inflammation. In the presence of normal spirometry a bronchial challenge (with methacholine, or increasingly with an osmotic challenge such as mannitol) would be carried out which would likely be positive if airway inflammation was also present. With abnormal spirometry, it is more likely that a standard bronchodilator test would be done.

30.   In the future I think PF laboratories may be asked to assess airway inflammation, either by inducing sputum with hypertonic aerosols for harvesting eosinophils, or by measuring NO production from single or multiple exhaled samples.

31.   The most rigorous method of measuring bronchial NO production is to take 2-3 exhaled samples over a range of fixed flow rates, plotting exhaled NO production on the Y-axis against expiratory flow. The slope represents alveolar concentration (in asthma the slope is the same as in normals) and the intercept reflects the increased NO production due to airway inflammation.

32.   Back again to our case history and the measurement of lung volumes. Little has changed in 55 years in terms of output; the same lung compartments are measured. A statistical improvement is that we quote standardised residuals (SRs) as well as % predicted. Srs are the number of SDs by which the result deviates from the regression coefficient for a normal population. The important point is that SRs tell us the probability of a result being normal or abnormal. Less than $\pm$ 1.645 SRs means that the result is within the 90% confidence limit for a normal population. 80 or 120% predicted normal does not give you that likelihood.

33.   The most usual method of measuring absolute lung volumes since 1955 ha been the closed circuit helium dilution technique described by Meneely and Kaltreider in 1949, though their first report cam out in 1941. With sophisticated breath by breath analysis, there has recently been a revival of interest in the earlier nitrogen washout method of Darling and Cournand.

34. The advantage of the Dubois body box technique published in 1956 is that trapped gas in bullae or cysts can be measured. Most of the time, if careful attention is paid to technique (for both methods), there is good agreement between the box and washin–washout methods. Dubois in the same year described the measurement of airways resistance, also using the body plethysmograph.

35. A more portable technique, though it may not look it from this slide, for measuring resistance (total respiratory, not airway) is that of forced oscillation, also described by Dubois also in 1956, his *annus mirabilis.* Its clinical application has been much helped by computer analysis, and laptops mean that measurements can be made outside the confines of a laboratory, for example in OPD or intensive care or overnight in a sleep laboratory. It is suitable for children over 7 years old. There are confounding effects of the upper airway and the chest wall, but there is useful information in the pattern of frequency dependence of resistance and reactance.

36. Back again to 1954. DLCO/TLCO measurements had not yet become routine and were not measured in this patient. Under the influence of Ward Fowler, the Comroe lab was keen on assessing uneven ventilation distribution, as evidence for or confirmation of peripheral bronchial involvement. This was done by analysing the phase III slope of the SB–N2 test following a breath of 100% O2, as here, or by measuring the delay pattern in a multi–breath N2 washout. Uneven ventilation distribution was likely to lead to low VA/Q areas and hypoxaemia. Note the reduced oxygen saturation which is not unusual in uncontrolled asthma.

37. This slide shows the phase II slope of the SB–N2 washout. In addition, there is an inflexion on the latter part of the curve, leading to phase 4. This was first noticed by Milic-Emili et al in 1967. They called the inflexion point the *closing volume.* It was shown subsequently that after expiring to volumes below FRC, the bronchioles in the dependent zones closed, leaving expired gas concentrations dominated by the nitrogen–rich upper zones. Closing volume is only seen in relatively normal lungs, and increases with age. It was thought that an increase in closing volume might be a sensitive marker of early smoking–related lung damage, a hope that, unfortunately, has gone largely unrealised.

38. The multibreath N2 washout during 100% O2 breathing was described and validated in Cournand's laboratory in 1940, and is having a renaissance, as I have mentioned earlier. The shape of the N2 washout curve can be analysed, more quantitatively than the single breath N2 test, for uneven ventilation in terms fast and slowly ventilated compartments.

39. The synthesis is to measure the phase III slope for each breath of a multi-breath N2 washout. The analysis is complex, and the subject must breathe at a fixed rate and tidal volume, but the information content is potentially very novel. Uneven ventilation can be separated into two anatomical compartments; an acinar or bronchiolar, and a conducting airway or bronchial compartment. Since we have tests for alveolar function (the KCO), for the intrathoracic airways (the FEV1), a test specific for the "silent" zone in between, the bronchioles, might be very useful.

40. So, we come back for the last time to our 17 year old young male. In 2010 we would measure the single breath TLCO, KCO and VA. A normal result, as here, would (with evidence of variable airflow obstruction) clinch the diagnosis of asthma. Comroe in his book commented that emphysema could not be excluded in this young man, though it was unlikely. The normal KCO means that we can exclude emphysema. The TLCO, introduced in 1957, together with the FEV1 and FEV1/FVC ratio are the most important routine lung function tests.

41. The single breath TLCO or DLCO originated a long time ago in Copenhagen for the purpose of showing that there was sufficient gas exchange surface area in the lung to explain the quantities of oxygen taken up during maximal exercise. It was a battle between Bohr and Haldane who held that the lung, particularly at altitude, could secrete O2 into the arterial blood, and Marie Krogh [seen here] and her husband, August, who held that passive diffusion was sufficient. The Krogh's won the argument hands down. Here is Marie defending her thesis and the KCO, hopefully not against Haldane or Bohr!

42. The set-up and procedure for the single breath TLCO will be very familiar to you. It was validated and assessed rigorously way in Forster's lab in Philadelphia by

43. Colin Ogilvie, a well known chest physician from Liverpool, and a keen ornithologist.

44. The SB-TLCO consists of two parts; measurement of the alveolar uptake of CO – a linear slope on a semilog plot as shown (this was what Marie Krogh described in 1914), and a measurement of the volume of distribution of inhaled CO using helium dilution (this was the addition to Krogh's test suggested by Ward Fowler in 1952). The TLCO is the **product** of the slope (the KCO) and the alveolar volume (VA), so a low TLCO can only be interpreted by looking at its two components, the KCO and the VA.

45.   For the interpretation of the TLCO and KCO, it is important to understand the physiological influences in terms of blood flow, Hb concentration and lung expansion. I have written extensively, and in my book, on how lack of alveolar expansion, loss of alveolar units and alveolar-capillary damage all have different effects on the KCO.

46.   We leave our case history for the third and final part of my talk which documents still more changes which have taken place since 1954, driven often by technical advances and inventions.

We take measurements of PaO_2 and $PaCO_2$ for granted today, but before the days of platinum and glass electrodes it was very difficult to get reliable measurements. O2 and CO_2 contents could be measured in the van Slyke or Haldane blood gas apparatus, but using the dissociation curve to calculate PaO_2 was a problem because of the flat shape of the ODC at PaO_2s > 8 kPa. The Riley bubblewas extremely demanding technically. $PaCO_2$ was somewhat easier because there was an independent measurement of pH. After Clark and Severinghaus, it was all too easy!

47. Oximeters have improved their accuracy, calibration procedures and convenience over the years. The discovery of the pulse effect by Aoyagi, and the development of the pulse oximeter was a real breakthrough.

48. As I have mentioned, technological advances are oiften the key to progress. Without a good method, one cannot do anything. Lilly increased the sensitivity of pressure transducers 100 times enabling Dubois to measure alveolar gas compression in the body box. Where would we be without stable and accurate flowmeters and instantaneous X–Y plots? Rapidly responding gas analysers, culminating in the respiratory mass spectrometer now permit breath by breath and within breath analysis at rest and on exercise.

49. A really important advance, though a low tech one, was the introduction of an oesophageal balloon to measure the surface pressure over the lung, the pleural pressure. After writing his thesis, Buytendijk never did any more research! But, how important was his discovery! Pulmonary resistance, lung elasticity, pleural pressure for estimating respiratory muscle effort and diaphragm strength, and the intraoesophageal EMG to record diaphragm activation.

50. The measurement of maximum static inspiratory and expiratory pressures, first reported by John Hutchinson in 1846, was rather neglected in the 1950s which is surprising in view of the polio epidemic early in that decade, but it is now recognised as an important part of the pulmonary function portfolio.

51. Sniff nasal pressure was proposed by the Brompton group as a more user friendly measure of maximal respiratory muscle strength; I have some sympathy with that point of view as sniffing is easier than the Valsalva or Mueller manouvre for MIPs and MEPs (PEmax and PImax). In this example, sniffing has occurred after oesophageal and gastric balloons have been swallowed; the difference between them, the transdiaphragmatic pressure is a measure of diaphragm strength, and low pressures on the R. ndicate diaphragm weakness.

52. There are times when patients cannot cooperate to activate their muscles fully for strength assessment, such as in the ITU, or they may be inhibited by pain. Direct stimulation of the phrenic nerves or nerve roots in the neck is required. These are called "non–volitional tests"; a new technique for doing this is cervical chord magnetic coil stimulation.

53. The origin of the diaphragm weakness in systemic lupus erythematosus (SLE) has been controversial. In this slide, taken from my book, transdiaphragmatic pressure (Pdi) and its components (Poes and Pga) are measured during a normal breath (shaded); Pga becoming negative during inspiration is abnormal, termed "paradoxical", and suggest diaphragm paralysis, or inhibition. The diaphragm "twitch" pressure after involuntary stimulation of the phrenic nerve roots in the neck is normal, suggesting that the diaphragm weakness during normal respiration is due to "inhibition", possibly from pain due to pleurisy. After immunosuppressive treatment in B, and with less pleuritic pain, the voluntary inhibition or "paradox" is less. Non–volitional strength, the "twitch" remains normal.

54. Time is running out. Exercise testing is described in Chapter 8 of my book. This slide just makes the point that nowadays simple tests such as 12 or 6 minute walk and shuttle tests (all of which originated in thiis country) are recognised as having an important role in the assessment and rehabilitation of the more disabled patients.

55. So, other chapters in my book should be consulted for those aspects of pulmonary function I have been unable to cover today. In taking on responsibility for sleep disordered breathing and non-invasive ventilatory support, the modern Pulmonary Function Laboratory has assumed responsibility for patient welfare and wellbeing in addition to functional assessment. Where will the ARTP be in 2020?

56. So, if you have bought it or are thinking of buying it, I hope you enjoy it!