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“The expertise of the average person who gave anaesthetics...” before World War II “was a technical expertise which had evolved from many years of empirical practice, rather than a mastery of some field of academic knowledge” from his inaugural lecture “The Edge of the Knife” in 1968[1].



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The practice of anaesthesia has changed dramatically in the last fifty years of the twentieth century.

Ed Cooper worked in the Department of Medicine at the University of Birmingham as a National Coal Board Research Fellow prior to moving to Newcastle upon Tyne. He was first assistant (1957-62), then a consultant, and became Professor of Anaesthesia in May 1967, until 1980 when he resigned from this appointment.<sup>ii</sup>

His inaugural lecture[1], “The Edge of the Knife”, delivered on Monday 4<sup>th</sup> March 1968 covers many aspects of his work and indicates a sense of humour. “When I called on Professor Miller to kneel and kiss hands on my appointment to the Chair he assured me that he was sorry I’d got the

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<sup>i</sup> Photograph courtesy of Gary Enever, RVI, Newcastle-upon-Tyne.

<sup>ii</sup> Before 1963 the medical school in Newcastle was part of King’s College of the University of Durham, the 1964 intake of students became graduates of the new University of Newcastle-upon-Tyne.

job. He had hoped someone bright would have applied.”

He followed similar interests as his predecessor (Edgar Pask) in Newcastle in that he studied the interactions between man and respiratory equipment and the measuring equipment used in the studies. Equipment-related work will be described first and then the physiological studies.

## Equipment and Measurement

In the 1950s the measurement of carbon dioxide in gas mixtures was a problem (Ramwell 1957)<sup>iii</sup> because the molecules of the diluent gas caused an alteration in its infrared absorption spectrum, the pressure broadening effect. Previous work by Coggeshall and Saier<sup>iv</sup> had indicated that if the partial pressure of the diluent gas was large; although the pressure broadening effect may be large, it would be fairly constant over small changes in concentration.

In 1957 Cooper simplified the measurement of carbon dioxide in the presence of nitrous oxide by producing a single calibration curve that could be used for concentrations of nitrous oxide between 60% and 80% [2]. It was determined that when using a calibration chart for 60-80% nitrous oxide the error in the measurement of carbon dioxide was less than 7.5%. The effect of water vapour was very small <0.03%. There was much discussion on the source of errors.

Scientific methodology is of paramount importance in research, a sine qua non, and part of the methodology is error elimination. Cooper was meticulous in this aspect of his work. He discussed the errors in measuring expired gases in Anaesthesia (1959) [3]. The slip of gas past valves, the pervious nature of Douglas bags, the peculiarities of dry gas meters, distensibility of tubing, compressibility of gases and the use of complete respiratory cycles to measure volumes per unit time rather than using fixed time periods.

The Lancet in 1960 carried a description of a tapered PVC bag that had

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<sup>iii</sup> Ramwell PW. The infrared analysis of carbon dioxide during anaesthesia. *British Journal of Anaesthesia* 1957;29(4):156-9.

<sup>iv</sup> Coggeshall ND, Saier EL. Pressure broadening in the infrared and optical collision

been designed to measure expired gases[4]. The gas was collected over a known number of respiratory cycles and then a rod was used to roll up the bag, like rolling up a tube of toothpaste, until the bag was tense. The volume was then read off a scale, simple, but, presumably, effective.

Two further papers by Cooper in 1960 investigated the work involved in breathing through respiratory equipment[5,6], obviously of great importance to rescue services in mines, self-contained breathing apparatus of any kind, and in anaesthesia. Respiratory protective devices (gas masks, filters and closed circuit breathing apparatus) were studied by producing pressure volume diagrams from the application of a sine wave pump to the breathing system under test. Flow through such apparatus was rarely laminar and previous workers, Silverman et al[7], had suggested that "a limit on external respiratory work appears to be the best basis for stating tolerable limits of resistance". Work by Cooper, comparing man with a sine wave pump at different minute volumes, had demonstrated that the correlation was such that apparatus could effectively be tested using a sine wave pump. Six breathing systems were tested and the total work increased with increasing minute volume - work done against elastic forces becoming negligible at high minute volumes, work done against friction forces becoming dominant.

$P = kn (V)^n$  - Reynolds showed that  $n$  could be determined for any system and could be used to describe roughness or tortuosity of the system. On a logarithmic plot of  $P$  vs.  $V$  the gradient is  $n$ . Through some mathematical contortions it was shown that constant flow bench tests correlated well with physiological testing using pressure volume loops. A set of standards for breathing apparatus was laid out. One stated that expiratory work had to be less than 50% of total respiratory work at high minute volumes.

Minute volume estimation[8]; this must have presented a problem at this time as the device described was produced as an alternative to the vagaries of the pneumotachograph which were considered bulky, complex, a fire risk, and were associated with zero drift. In addition the changing composition of anaesthetic

gases affected their accuracy. The mechanism was ingenious, involving the measurement of a fraction of the total flow by allowing flow through a shunt in parallel with the main respiratory circuit. It had the inherent fault of manual, discontinuous, measurement of flow using a moving soap film. Needless to say the pneumotachograph has survived to the electronic age (and the use of non-explosive anaesthetic agents); this device did not. It seems extraordinarily complex and was developed through 'trial and error'.

The indirect estimation of arterial pCO<sub>2</sub> had been attempted by many methods to avoid the invasive procedure of arterial puncture<sup>v</sup>. In 1961 Cooper addressed the problem[9]. Arterialised ear-lobe capillary blood was shown to be acceptable if the patient was not in a state of 'autonomic upset' (pallor, sweating, abnormal pulse or blood pressure). Rebreathed gas - having the same tension as mixed venous blood - was shown not to have this problem, although the systematic error was large. Collecting blood from the back of the hand during unimpeded flow was also acceptable, the pCO<sub>2</sub> difference between hand and artery being 1.6 mm Hg, SD ± 4.2 mm Hg. End-tidal carbon dioxide, collected by an automatic sampler, underestimated arterial carbon dioxide by variable amounts, in bronchitic patients by the order of 10-15 mm Hg. However, the conclusion drawn was that the rebreathing technique was the technique of choice.

The rebreathing technique was originally suggested by Plesch<sup>vi</sup>. It involved the prefilling of a 'rebreathing bag' with carbon dioxide (either from a pre-mixed cylinder or by the subject rebreathing oxygen in a bag for 90s) and at the end of an inspiration the subject began breathing from the bag, in only a very short time the concentration in the bag equilibrated with the alveolar carbon dioxide and the gas concentration could then be measured.

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<sup>v</sup> Collier CR. *Journal of Applied Physiology* 1956;9:25.

Campbell EJ, Howell JB. The rebreathing method of estimating arterial and mixed venous carbon dioxide tension. *British Journal of Diseases of the Chest* 1960;54:137-8.

Campbell EJ, Howell JB. Simple rapid methods of estimating arterial and mixed venous pCO<sub>2</sub>. *British Medical Journal* 1960;1(5171):458-62.

Apart from a teaching article on the measurement of ventilation[10] twenty years passed before the next equipment related paper was published, passing from the era of valves to that of transistors and micro-chips. The ability of a chemical-sensitive field-effect transistor for on-line measurement of  $K^+$  was investigated[11]. Intermittent blood flow through a 'butterfly needle' enabled the measurement of  $K^+$  and it was found to be slightly lower than that measured by flame photometry, 3.8 mmol L<sup>-1</sup> compared with 4.1 or 4.03 mmol L<sup>-1</sup> using Corning 450 and 902 flame photometers. Blood was sampled for 8s at 32s intervals, the main problem was maintaining anticoagulation.

## Physiology

"On the efficacy of intragastric oxygen" (1960)[12] was the title of a detailed study into a method of resuscitation that must rank only second to 'cupping' as a stupidity. It highlights the state of medicine<sup>vii</sup> in the late fifties although more logical means of resuscitation had been considered for centuries. Newborn kittens were rendered severely anoxic and were given intragastric or intra-intestinal oxygen. Survival time, rate of haemoglobin desaturation and rate of fall of oxygen tension were measured, as was the rate of loss of oxygen into the blood stream from the gut and the effect of minimal pulmonary oxygenation. Although this technique was widely used this study provided no evidence to suggest physiologically important amounts of oxygen were transferred from the gut to the circulation. Under optimal conditions less than 0.02 ml min<sup>-1</sup> of oxygen was absorbed but the anoxic liver probably consumed this. The average newborn kitten required 0.3 ml of oxygen per minute for 'bare and tenuous survival'.

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<sup>vi</sup> Plesch JZ: *exptl Path Ther* 1909; 6: 380

<sup>vii</sup> "Nearly one millennium ago, authors recommended ventilating via a bellows and a tube in the trachea. In 1767, the Dutch Humane Society published guidelines for resuscitation of victims of drowning, stating: 'keep the victim warm, give mouth-to-mouth ventilation, and perform insufflation of smoke of burning tobacco into the rectum'." Michael Ardagh. A brief history of resuscitation. *The NZ Medical Journal*, 2004;117, 1193

The Infant Resuscitation Committee at the Maternity Pavilion of the Winnipeg General Hospital, in 1956, stated that “Carbon dioxide and intragastric oxygen are not advised by the committee” for the resuscitation of neonates<sup>viii</sup>, citing Waller, and Morris<sup>ix</sup>. A commentary on the inappropriateness of intragastric oxygen was published in the BMJ four years later<sup>x</sup>. Cooper’s work was supported by a similar study by Coxon<sup>xi</sup>. It is an interesting commentary in that it reviews the origin of the use of intragastric oxygen; the idea originated with A Yllpö, (*Acta paediat. (Uppsala)*, 1935, suppl. 1, 122 (referenced from BMJ commentary)) but was later described by Y Akerren and N Furstenberg<sup>xii</sup>.

The bottom line was - “This method should now be abandoned, particularly as its use may delay more effective measures.”

In 1967 Cooper published two papers on physiological dead space during passive ventilation[13,14]. As the sole author, as with the majority of his papers, he by necessity must have personally carried out the work. The first paper describes the detailed methodology and incorporates much of the experience from previous studies -measurement of gas tensions, gas volumes, minimising leaks, criteria for assuming steady state and so on. The final measurement of  $V_D/V_T$  at what he terms 'constant ventilator activity' was such that "the standard deviation of individual values about the mean for each subject was 0.83% (range -1.9% to 1.8%).

The second paper presents the results from patients studied. The units used were a mixture of imperial and metric. Patients were ventilated at a 'standard' rate, the tidal volume was 80 ml per stone (12.6 ml kg<sup>-1</sup>) at a frequency of 15/min.

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<sup>viii</sup> Schmidt O, McLandress M, Cruickshank L: An evaluation of infant resuscitation. *Canadian M.A.J* 1956; 75: 503-6

<sup>ix</sup> Waller HK, Morris D: Resuscitation of the newborn with intragastric oxygen; Akerren's method. *Lancet* 1953; 265: 951-3

<sup>x</sup> Intragastric oxygen. *British Medical Journal* 1962: 483-4

<sup>xi</sup> Coxon RV: The effect of intragastric oxygen on the oxygenation of arterial and portal blood in hypoxic animals. *Lancet* 1960: 1315-7

<sup>xii</sup> Akerren Y, Furstenberg N: Gastrointestinal administration of oxygen in treatment of asphyxia in the newborn. *Journal of Obstetrics & Gynaecology of the British Empire* 1950; 57: 705-13

Ninety eight percent of recorded physiological dead space was  $>4\text{ml kg}^{-1}$  and with increasing tidal volume the dead space became larger. Radford et al. in 1954 had produced a nomogram that was said “to estimate proper ventilation during artificial respiration”, these assumptions were said to be not valid under conditions of general anaesthesia and passive ventilation<sup>xiii</sup>, since the volume of the dead space in ml was not numerically equal to the patient’s body weight in pounds. The mean value for  $V_D/V_T$  was 52.2% (range 33.5% - 68.8%), much larger than during spontaneous, conscious breathing. This paper of Coopers confirmed work by others that the Radford nomogram was not suitable for use during anaesthesia<sup>xiv</sup>, this included work by Nunn’s team<sup>xv</sup> and by Thornton in Sheffield<sup>xvi</sup>.

As the subjects, or patients, age increased so did the  $V_D/V_T$  ratio. By 'standardising' the results of other workers Cooper either produced a correlation with age where previously none existed or improved the correlation. Thornton's series matched Cooper's best. Combining the results from his patients (50) and the other workers' patients (70) Cooper was able to produce an equation relating physiological dead space to age with a correlation coefficient of 0.70. His 'rule of thumb' equation was:

$$V_D/V_T \% = 33 + \text{age} / 3 \quad \text{SD} \pm 6.93\%$$

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<sup>xiii</sup> Radford EP, Ferris BG, Kriete BC: Clinical use of nomogram to estimate proper ventilation during artificial respiration. *New England Journal of Medicine* 1954; 251: 877-884

<sup>xiv</sup> Gain EA: The adequacy of the Radford nomogram during anaesthesia. *Canadian Anaesthetist's Society Journal* 1963; 10: 491-500

<sup>xv</sup> Campbell EJ, Nunn JF, Peckett BW: A comparison of artificial ventilation and spontaneous respiration with particular reference to ventilation-bloodflow relationships. *British Journal of Anaesthesia* 1958; 30: 166-75  
 Nunn JF, Hill DW: Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man. *Journal of Applied Physiology* 1960; 15: 383-9

Nunn JF: Predictors for oxygen and carbon dioxide levels during anaesthesia. *Anaesthesia* 1962; 17: 182-94

<sup>xvi</sup> Thornton JA: Physiological dead space. Changes during general anaesthesia. *Anaesthesia* 1960; 15: 381-93

This study must have involved a great amount of personal work and should be noted as contributing to the confirmation of the fact that changes in respiratory physiology under general anaesthesia, in particular during passive ventilation, are different to those occurring in awake subjects.

Other papers by Cooper are of a miscellaneous nature, 'Tracheostomy and controlled respiration', 1961, is a review[15], and, in essence, states that the bigger the hole and the bigger the tube the better. 'Oral neomycin and anaesthesia', 1963, was one of the early descriptions of the neuromuscular blocking properties of antibiotics[16]. Other publications are listed in the references[17-22]; a few have been omitted because, although referred to in various texts, they could not be located.

The cartoon below returns us to the beginning of this report as it reflects a man of varied interests and a sense of humour; the individual graphics reflecting the variety of topics in his writing[1].

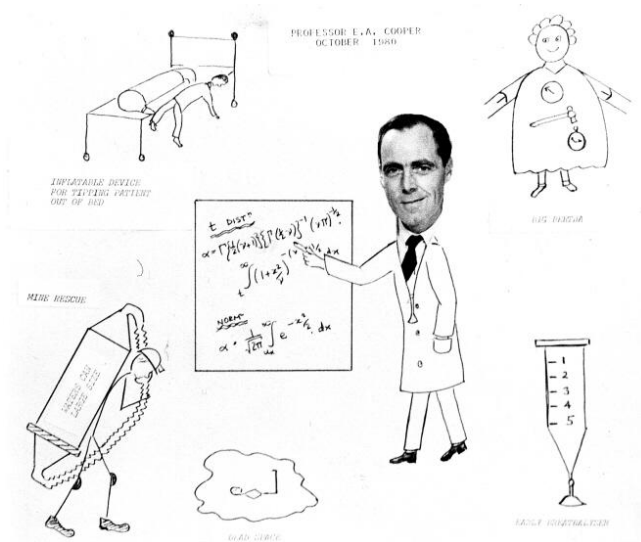
A final quote from the inaugural lecture:

"But wherever academic anaesthesia may lead: the skies, the seas or the solid dry land<sup>xvii</sup>, our prime function is to protect our patients from the agony and the danger of the edge of the surgeon's knife. This we do by standing at the edge of another knife, the knife edge about which their existence see-saws and swings, for it is our job to stabilise and prevent the platform from reaching the limits of its traverse – wakefulness or death."

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<sup>xvii</sup> This is a reference to the work of his predecessor Professor Edgar A Pask who worked during WWII on safety equipment for military personnel both at sea and in the air.





Cartoon courtesy of Dr Gary Enever, Department of Anaesthesia, RVI, Newcastle upon Tyne, dated at the time of EAC's resignation from the Chair.

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