The Contribution of Research in Anaesthesia to Clinical Medicine

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The theme of this paper is that research in one speciality often has applications into much wider medical fields. In 1942, almost a century after the first demontration of surgical anaesthesia, Harold Griffith of Montreal introduced curare into anaesthetic practice, and almost overnight, there became the need to turn an imprecise craft into a clinical science.

My career as an anaesthetist started not too long after this event, and consequently has spanned almost the whole period in which anaesthesia has changed from an inexact art to a very precise science. What made the introduction of a paralysing drug so important? Some advances in science are conceptual, many are technical, and most would surely consider the introduction of the neuromuscular blocking drugs to be the first conceptual advance in anaesthesia.

It is not a new drug. Sir Walter Raleigh brought curare to England in 1595 from South America, describing how it caused death by paralysis of breathing in conscious individuals.

In 1857, in a classical series of experiments, Bernard demonstrated that its action occurred entirely at the neuromuscular junction. He could think of no use for such a drug in medicine, but for once he was proved wrong. Curare was the first drug used by anaesthetists whose action was specific, a truly "clean" drug, with one action only, namely to block conduction at the neuromuscular junction.

Why did the anaesthetist need specifically-acting drugs?

In the past, anaesthetic agents had been used in a blunderbuss fashion, one agent being used to produce everything – unconsciousness, analgesia, muscle relaxation, and depression of stress responses – a crude technique with many disadvantages, not least being the prolonged period before metabolic and other systems recovered. The use of neuromuscular blockers helped to introduce the concept of "balanced anaesthesia" – the triad of hypnosis – muscle relaxation – suppression of stress response – and enabled anaesthesia to be separated into these components, each of which could be separately controlled using small doses of specific agents, thus minimising side-effects and hence toxicity of large doses.

Curare thus introduced an era when the anaesthetists gradually learned how to control, safely and effectively, most of the physiological systems.

Muscle paralysis provides the surgeon with an easily accessible operating field, gives the anaesthetist the means of inducing anaesthesia quickly and easily,

bypassing the "excitement" phase and sparing the patient at least some of the dangers of recovery, and also the energy of muscle work. The need to use the artificial pulmonary ventilation triggered research into all aspects of lung function, and a realisation that anaesthetists needed to be more highly trained in wider fields than previously. It soon led to demands for our expertise in managing pulmonary ventilation in patients outside the operating theatre, such as neurological diseases including tetanus, coma, chest trauma and respiratory failure. The use of curare has led to a more intensive study of respiration, the need for training in basic sciences, to the care of respiratory problems in other than surgical patients, and to the development of intensive care units.

The improved circulatory state of patients under light anaesthesia and curare, plus the increasing complexity and delicacy of surgery soon led to requests from the surgeon to provide a "bloodless field". This entails control of arterial and venous pressures and peripheral blood flow, including the use of controlled hypotension by a variety of methods – ganglion blocking drugs, adrenergic blockers, spinal and epidural analgesia, etc., but all have in common the need to protect the blood flow and oxygen supply to the vital organs – brain, heart, liver, kidneys. This gave other benefits, by reducing work-load, the metabolic demand of the tissues can be met at least at cost, and whilst this was first thought to be safe only in patients with healthy cardiovascular systems, it is now known to be an essential part of dealing with the ischaemic and failing heart as well and is practised in medical wards and coronary care units regularly. Light anaesthesia does not protect against unwanted and extravagant autonomic responses, and the understanding of these in trauma and severe illness was much advanced by the concept of "balanced anaesthesia".

Under light anaesthesia and paralysis, it is essential to avoid having a conscious but paralysed patient. The margin between sleep and wakefulness is close, and processes of memory and recall are not fully understood. It has long been known that there is a level of anaesthesia where patients will respond to command even during an operation but are apparently pain-free and have no recall after, and also the typical "awake" patterns on the EEG have been observed in patients who by all other standards appear to be asleep, again with no memory for events. It has also been shown that certain stimuli, including auditory, and spoken suggestion can, under certain circumstances such as under hypnosis, be recalled in patients who were undoubtedly very deeply anaesthesised. Anaesthetists must remember that they are doctors as well as scientists, and that the patients' psychological reactions, their fears and anxieties are important, although anxiety may sometimes need to be relieved pharmacologically, that communication, understanding and reassurance are even more important.

Thus, the first quarter century of the new era in anaesthesia was marked by "control". No one would claim that the anaesthesised patient had become a controlled experiment – though to an extent, because of enormous individual differences between patients, one might claim that every anaesthetic is a controlled experiment in intensive care.

The original inhalational anaesthetic agents were simple hydrocarbons and hence very easy for the pharmacologist to manipulate – instead of testing large numbers

of drugs indiscriminantly, it was possible to construct drugs whose chemical formulae could be predicted to produce a particular pharmacological action. Thus small changes led to halogenating ethers, etc., and the development of agents with greater potency and less toxicity, and also important in anaesthetics, non-flammability. Halothane was the first such drug, other better ones have followed.

Pharmacokinetics and dynamics are fields that are relatively new, hardly existing some 20 – 25 years ago, and the acute changes of anaesthesia make it a particularly good field for studying these. Anaesthetists are rare amongst doctors in that our ordinary work involves the administering of drugs ourselves, titrating of dosages and careful monitoring of their immediate effects on all systems. Monitoring thus enormously improved our standards of safety and our whole approach and understanding of drug uptake, distribution and elimination.

Anaesthetists are in a good position to observe adverse drug reactions and to study their mechanisms – far better than the physician who has difficulty in identifying a cause-effect relationship in slower acting drugs over longer periods. Hence, adverse drug reactions in drugs used in anaesthesia have contributed significantly to knowledge of the nature of the immune response, partly becasue reactions can be investigated immediately they are suspected, and appropriate treatment instituted before serious harm ensues.

All our apparatus must be carefully designed to be fail-safe in operation, properly equipped with warning devices; recently, the use of computers with functional feedback loops almost renders the anaesthetist redundant. Unfortunately, though this is now almost possible, whereas public opinion demands the expense of equipping aircraft this way, it does not provide the National Health Service with means of similarly protecting the patient in the theatre.

Has this research activity made anaesthesia safe? There is no doubt it is more pleasant for the patient, it is easier to administer, and it is much easier for the surgeon to operate, and in some cases we have made the impossible become possible. Mortality and morbidity are very difficult to assess. Data are hard to come by – studies are not comparable: mortality is now very low indeed and usually not from a single clear case; we may sometimes know the numerator of the equation, but we cannot know the denominator.

In anaesthetically developed countries, deaths where anaesthesia contributes seem to be about 0.08 to 0.2 per thousand. Where studies are comparable, deaths seem to have fallen over the past decade quite considerably. Can it ever be zero? With human fallibility, this seems unlikely and studies from several countries reveal a proportion of deaths which might be avoidable, due to technical errors which should not have occurred, or which should have been identified and corrected, so we are not yet at the lowest possible level. This implies not so much the need for research as for better education, in particular, educating for being alert when something is going wrong. We educate so much to prevent people getting into trouble; then, when they do, they are ill-equipped to get out of it! Perhaps, like aircraft pilots, we should have practice in simulated emergencies. For the future, no doubt, there will be continued improvement in ventilators, machines, monitoring, perhaps better working environments.

A new development is the use of high frequency ventilation – a new concept in that in the past, our efforts have gone towards ventilating as close as possible to normal physiological breathing. High frequency jet ventilation is quite different, the lungs are ventilated at anything from 80 – 200bpm with very small tidal volumes and consequently very little movement of chest wall – merely an oscillatory air flow through partially distended lungs. It is proving to be a means of oxygenation in adult respiratory distress syndrome and in other cases where it had previously been virtually impossible, and these are conditions which are becoming much commoner.

A surprisingly neglected field is postoperative analgesia, where we do not apply what we already know. Patient-controlled analgesia has been made safe and feasible with use of computers to prevent overdosage either inadvertently or deliberately. Several methods are available, whereby patients activate on injected IV and IM dose of a powerful analgesic. Other methods such as spinal or extradural opioids are now commonly used, and it would probably be fair to say that given more intensive nursing areas (and hence trained nurses), we have the knowledge to render the postoperative period almost painfree.

There have recently been exciting developments at cellular and molecular levels. Modern research techniques have forwarded this field greatly, even though we are still without knowledge of a mechanism of anaesthesia which fits all agents in all their diversity of structure.

It was once thought that inhalation agents were excreted unchanged through the lungs, but the introduction of radioactive labelling showed that significant amounts were metabolised – this is very variable – methoxyflurane 50%, halothan 25%, enflurane 2.5%, isoflurane 0.2% and probably accounts for the nephro and hepatotoxicity potential of some of the agents. Cytotoxicity has been demonstrated, and this field is one where new knowledge is imparted almost weekly – depression of cell multiplication; mitotic abnormalities in nuclei; reduction in synthesis of DNA, etc. Does this matter in practice? It now seems clear that all volatile agents including N2O inhibit neutrophil activity at relevant clinical concentrations. Does this reduce resistance to pathogenic organisms postoperatively? Does it inhibit the tumour killing function of leucocytes in cancer? Are immunocompromised patients at risk? We do not know because the effect is rapidly reversible on breathing air.

We also know that N2O depresses the activity of methionine synthase in brain and liver. In rodents, it needs only a short exposure (1/2 – 1 hours) to reduce to less than 30% activity, but it is much slower in man – it occurs after 10 hours of 60% N2O, when neutrophenia and inactivation of methionine synthase result in depression of vitamin B12 which in turn interferes with the production of DNA (Nunn 1985, 86). The clinical importance of vitamin B12 depression was dramatically shown in 1978 in a paper describing 15 patients suffering from symptoms of sub-acute combined degeneration of the cord: 14 were dentists and one was a hospital technician, all were exposed (some by addition) to N20 frequently. Since it has been shown that exposure either continuously for many hours or intermittently results in a change in erythropoeisis to the megaloblastic form typical of B12 deficiency, and this is reversible after withdrawal of N2O.

The above evidence points clearly to a need to study the effects of long-term exposure to trace concentrations of anaesthetics as a possible health hazard to theatre staff. Retrospective studies suggested some alarming trends though none of these reached statistical significance: increased incidence in female staff and wives of male staff of spontaneous abortion and subfertility; some tumours of reticuloendothelial system and lympoid tissues were increased.

Active steps are now being taken in operating theatres to reduce pollution by scavenging of expires gases and two major prospective studies are under way in UK and USA on health of women working in theatres.

Anaesthesia is essentially teamwork. However, we know the dangers that where several people are responsible, then no one is. Patients need a single identifiable personal doctor to relate to, and teams need a clear leader.

Anaesthesia has great educational potential. A period spent in an anesthetic department gives unique opportunities to students and doctors of other disciplines to see a very wide spectrum of medicine including the whole field of surgery, a large amount of acute medicine in ICU, accidents and emergency skills in immediate treatment of critical situations. Our daily work consists largely of the application of the basic sciences to clinical practice, the pharmacology of drug actions; the demonstration of physiological principles; and their modification by trauma and disease.

Summary: I have discussed how the relatively controlled situation of the anaesthetised patient has provided research possibilities which have been seized and acted upon over a very wide field, and have extended knowledge of respiratory function, cardiovascular function, neurophysiology and psychology principles of pharmacology including metabolism, stress responses and immunology, as well as mechanism of drug action and elimination.

Our use of complex apparatus has led to advances in engineering and application of automation by computer and other means in both monitoring and delivery of treatment. Attempts to elucidate the mode of action at cellular level of anaesthetics has contributed significantly to knowledge in basic sciences.

Finally, the nature of our work demonstrates the potential benefits to patients of teamwork, and the educational value to all doctors of management of critical situations in patient care.

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