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John Dundee’s academic career virtually spans the whole period covered by this book, his first publication being in 1950 and the last reference in 1998. He was a lecturer in 1953 and senior lecturer in Liverpool 1957/8, where he was awarded his PhD, and moved to Belfast in 1958 as senior lecturer and founder of the academic department there. (Queen’s University). He became a professor in 1964. He was dean of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland between 1970 and 1973 and retired in 1987, but continued writing.

John Dundee’s output was prodigious and so to cope with this massive body of work only an overview of a selection of his publications is possible. He was possibly the Henry Ford of anaesthesia in the United Kingdom at this time, although for a great period of this time Belfast was very troubled.

He ran the research like a factory and papers rolled off the production lines at about ten a year. Dundee himself was the first author on 50% of the publications and was a regular attendee at the Anaesthetic Research Society meetings. His first publication was on “Acquired sensitivity to thiopentone” in the British Medical Journal [1]. He was to publish another 36 involving thiopentone in some way [1-37].

In 1962 the ‘factory’ became organised and two sets of publications were begun. Papers with the phrase “Clinical studies of” [17-20, 22, 23, 25, 38-51],

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i Photograph courtesy of James Murray, Queen’s University, Belfast.  
publications); these were about anaesthesia induction agents and varied from standard agents like thiopentone to new agents with code numbers and ethanol. The second set began with the phrase “Studies of drugs given before anaesthesia” [52-73] and involved the assessment of premedicants and antiemetics in a variety of combinations.

**Clinical studies of...**

Five topics were ‘a comparison of nine barbiturates in electroconvulsive therapy’ [38], diazepam [42], ‘Ethanol’ and ‘Further investigations with ethanol’ [43, 45], the effect of premedicants and supplements on ketamine anaesthesia [48] and Althesin [25, 49].

Barbiturates in electroconvulsive therapy:
In this 1962 paper with Barron is seen the genesis of the ‘factory’ style. It is commented that for true comparisons “a fairly uniform patient population” is required and two such populations were those patients undergoing dilatation and curettage (D&C) and electroconvulsive therapy (ECT). One thousand administrations of a barbiturate were reported for ECT and, to make comparisons easier, ECT patients do have more than one session. It is interesting to note that, in 1962, there is no mention of ethical committee consideration, or patient consent.

The side effects studied were either excitatory (muscle tremor, twitching and other involuntary movements) or respiratory (coughing, hiccough and larygospasm). There were differences but it was stated that all drugs were satisfactory for routine use in the doses used in the study. Twenty two patients received seven of the barbiturates. Hexobarbitone and methohexitone had a high incidence of excitatory phenomena. They were able to tease out the fact that the thio barbiturates were the ones that either caused a very low incidence of problems or some respiratory upset whilst it was the ‘methyl’ barbiturates that caused the excitatory effects. A classification of barbiturates was proposed base on the incidence of side effects rather than on length of duration of effect.
Diazepam; Diazepam was released on the market in 1963 by Hoffmann-La Roche and in 1968 Dundee, together with Stuart Brown, wrote about the slowness of onset of the agent when given intravenously, about a minute. The variability of the patients’ responsiveness was also noted. The good side was that even with doses up to 0.8mg kg\(^{-1}\) (a huge dose) it was not possible to guarantee the induction of anaesthesia. They commented on the absence of side effects even with large doses...the amnesia it produced was the “outstanding feature”. Some patients (30%) did experience dizziness up to 24 hours after the injection and some receiving higher doses developed local venous thrombosis. At the time it was a major addition to the anaesthetist’s armamentarium.

The study of ethanol as a potential induction agent for anaesthesia is a little unexpected, even though ethanol has, by ‘legend’, been used for centuries to
relieve the pain of surgery without anaesthesia. The reading of this paper does not recommend its use. Forty patients with an atropine premedication were studied; they received up to 550 ml of 5 – 10% w/v ethanol over 5 – 8 minutes (39-55 g alcohol). Methohexitone was frequently used to complete the induction (respiratory depression only occurred when the ethanol was supplemented). There were no cardiovascular complications but emergence delirium was high!

The study was carried out on “fit female patients undergoing minor gynaecological procedures”, a phrase to be heard at many ARS meetings. In this paper (1969) patient consent was sought until “For a time it was used almost routinely in one gynaecological unit and patient permission was not then sought.”

Delirium on induction as well as on emergence and methohexitone was used to overcome this problem. The anaesthesia was maintained with 75% nitrous oxide with oxygen. All four patients classed as “drinkers” needed the methohexitone supplementation. All patients were cardiovascularly stable.

Some patients who required methohexitone had significantly prolonged recovery, emergence delirium occurring in about 50%, it did not seem to upset the study patient but it did upset other nearby patients. Amnesia, “surprisingly”, did not occur, but emesis and headache were – was this an iatrogenic hangover?

The second paper involving further observations on ethanol as an induction agent followed in 1970. Three hundred patients were studied; some were premedicated with chlordiazepoxide, some just with atropine. Surprisingly greater doses of alcohol were required with the chlordiazepoxide premedication than without. Cardiovascular stability was noted but all the adverse sequelae of the previous study were still a problem making ethanol an unsuitable agent for routine use.

Ketamine was introduced in 1962 by Parke-Davis and quickly found a role in anaesthesia. Bovill and Clarke et al investigated the role of premedicants in the suppression of those ketamine effects that were undesirable, primarily the hypertensive response and emergence sequelae. Sixteen different combinations of drugs were studied...contrary to (my) general understanding, “Tranquillizer and
hypnotic drugs and droperidol-containing mixtures were the least effective.” Even 30 mg diazepam was reported as being unsatisfactory in controlling the emergence phenomenon. Opiate and hyoscine mixtures were the most efficacious. Compared to other conventional intravenous induction agents it was not as easy to use.

Finally in this brief overview of “Clinical studies of…” we come to CT1341 (Glaxo Research Laboratories). In 1971 this was “a new steroid anaesthetic”. The first steroid anaesthetic was hydroxydione (1955). CT1341 had been shown to be rapidly acting, short duration and with few side effects. This paper was a dose finding study in 300 patients; the doses given ranging from 20µl/kg to 200µl/kg. Because CT1341 was a mixture of two agents its dosage was more conveniently expressed as a volume per unit weight. The same protocol was used for assessing induction and recovery as in other papers discussed previously.

Above 30µl/kg all patients became unconscious, excitatory effects increased with dose as did hypotension. It was determined that the 50 – 60 µl/kg doses were ideal. It had a low postoperative nausea rate and unpleasant dreams were rare (6%).

Four years later CT1341 was now Althesin. Carson et al. (including Dundee) studied 150 patients and compared Althesin with thiopentone and methohexitone. Althesin was found to be a very suitable agent for outpatient anaesthesia but the recovery rate was not as fast as methohexitone.

This overview indicates the sort of work carried out on ‘the factory floor” by Dundee and his team.

Studies of drugs given before…

This selection of papers starts at the same time, 1962, all published in the British Journal of Anaesthesia. The first was “A method of pre-operative assessment”[52]; a variety of studies followed involving a whole range of combinations of drugs, atropine and hyoscine (1964) for example and several

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morphine related papers (1965/66); benzodiazepines (1968-1977) and in 1968 there was a further evaluation of the method of study, a review of the experience with 10,000 patients.

The first paper obviously sets the scene for all the others...as the authors set out in the abstract “The need exists for a comprehensive study of the effects of drugs given before anaesthesia, including an assessment of their pre-operative effects, action on course of anaesthesia, and sequelae which may be attributed to their use. The subjects for such a study should be from the same sex and age group, from one hospital, and the operative procedure and anaesthetic technique should be constant.” The main point being made here is that for good comparisons there must be consistency in all aspects of the study and that the patients should also be as consistent as possible. Sedation, apprehension, excitement, local effects, dizziness, emetic and cardiovascular effects were all noted. The initial study was that of atropine vs. atropine and pethidine. The desired effects were given a positive score and the toxic effects a negative one, a net rating was then possible. The statistical analysis was not straightforward, it used RIDIT analysisiv. To quote the paper again, “In ridit analysis a specified series of patients is chosen as the control reference set (“identified distribution”) and all comparisons are made Relative to the Identified Distribution—hence origin of the word RIDIT. The individual scores in the identified distribution are replaced by ridits, which bear a relationship to the incidence of each score in the total series.”

The 1964 paper comparing atropine and hyoscine as premedicants is a good example of the 1962 initial benchmarking study. Ridit analysis is not specifically stated but reference to desired and toxic effects and net scores is made, and a reference to the 1962 paper. Atropine produced tachycardia without sedation and hyoscine produced sedation with a low incidence of tachycardia, it also reduced postoperative emesis.

Tacrine (tetrahydroaminacrine) is an anticholinesterase and had been promoted as a drug that a) prolonged the effect of suxamethonium and b) as an antagonist to the sedation and respiratory depressant effects of morphine. The combination of tacrine and morphine was studied, as usual, in “healthy women scheduled for minor gynaecological operations” and the results were that tacrine seemed to increase dizziness and nausea, and postoperative muscle pains were worse in the tacrine/morphine group when suxamethonium was used – contrary to previous work by Gordh et al and several others.

Papaveretum was a popular, commonly used opiate for premedication in the 60s and 70s, used commonly with hyoscine, scopolamine, (Omn and Scop). Papaveretum was/is a mixture of alkaloids of opium, about 50% morphine (see the detailed description in the paper) and codeine, narcotine and papaverine. There was a substantial body of evidence against the benefits of papaveretum over morphine and yet, as is pointed out in the introduction to the paper there seemed to be a “curious divergence between apparent logic and clinical experience”. It was this that stimulated the study. There were no “startling” differences between the drugs. One difference was the low incidence of hypotension during anaesthesia with the papaveretum-hyoscine mixture – there did seem to be some “basic difference in the spectrum of pharmacological actions”. The bottom line was that papaveretum was not significantly better than morphine but that it had shown that it might be worthwhile studying various mixtures of the opium alkaloids.

Benzodiazepines were coming on the market in the 1960s and gaining a place in anaesthetic practice as premedication [61, 62, 66, 71, 72]. Chlordiazepoxide was the first and it was studied in a comparison with diazepam...together with a placebo. The comparison also included data from previous studies on opiates and phenothiazines. The results indicated that, indeed, these drugs did alleviate pre-

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operative anxiety and that they were as good as most opiates and with fewer side
effects. It was suggested that they could be used as a “pre-preanaesthetic-
medication”, i.e. the day before! The cost of these agents was a factor at that
time...diazepam being thirteen times as expensive as morphine.

Ten years later lorazepam was put through the factory mill [72]... it was
low in onset and long lasting, the i.m. injection was painful. Oral premedication
resulted in reliable sedation and was thought to be a useful premedicant as long as a
quick recovery was not necessary. Anterograde amnesia was significant.

Morrison, Hill and Dundee reported an evaluation of the ‘method of study'
in 1968 [63], by this time 10,000 patients had been enrolled. They wanted to
investigate the potential sources of bias; a significant paper, it does show a
concerted effort to ‘get it right’. In brief the study showed that age, body weight and
the use of different observers did not influence the outcome; the frequency of
observers’ visits to the patient, the type of operation and the duration of the
operation did.

Several pieces of advice may still apply today...eliminating patients who
weigh more than 89kg reduces the variance and positive skew of the distribution of
patient weight. Fixed doses of drugs vs. weight related doses was also discussed, in
small studies it was suggested that weight related doses should be used but that in
big studies (100 patients) fixed doses were acceptable as the results were
comparable to drugs given on an individual weight basis. Logistically this was much
to be preferred for blinded studies. Frequency of visits by the observers was
important...it was thought that the visits themselves might have a placebo effect, in
fact drowsiness was enhanced by more frequent visits as was apprehension, so both
arms of a study should have equality in the frequency of assessments. As the
duration of anaesthesia increases so do the emetic sequelae... in many of these
studies the length of anaesthesia only ranged from 2 – 12 minutes, the incidence of
emesis increasing by 100% or more, so once again, each arm of a study should have
procedures of equal length. To quote their closing sentence “Only by rigid
adherence to detail can reproducible results be obtained”; so true in the biological sciences.

**Case studies**

Dundee, like many other medical writers, found opportunistic case studies...Addison’s disease and adrenocortical insufficiency [2, 74], myasthenia gravis [75], dystrophia myotonica [5], porphyria [76, 77] and tetanus [78, 79]. There were also several publications on atopy and anaesthesia [80-82] and, as was appropriate at the time, halothane [83-86] and related hepatitis [87].

The Addison’s disease report is interesting on several (could possibly be considered pedantic) points. The units used in this 1951 publication include ‘stones’ for weight (6.35 Kg) but does include a conversion, similarly with morphia gr. 1/6 (10mg), percent for the haemoglobin value, a blood pressure 96/60 without units, and other blood component measurements, sugar and urea, in percent. The abbreviation D.O.C.A. was also used without elaboration. The most interesting of statements is “Owing to a misunderstanding 0.4 g. thiopentone was administered.” This may not be the first description of a drug error but it is interesting...in the author’s own experience of thiopentone use in the 1970s this dose would appear large for a 70Kg patient, this patient weighed 57Kg. Hypotension and prolonged sedation occurred.

With regard to the myasthenia gravis publication, a small dose of gallamine was used for the diagnosis of the disease; it was compared with d-tubocurarine. Two patients found gallamine less unpleasant and this was attributed to the ‘respiratory sparing’ effect of gallamine.

Porphyria and thiopentone [76, 77] was a lethal cocktail as the article in Anesthesia and Analgesia shows...in one series 77% of patients with paralysis had received a barbiturate whilst only 35% of patients without paralysis had

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vii Goldberg A. Quart. J. Med. 28:110 and 183,1959
Atopy, in combination with allergy and previous anaesthetic experience was covered in three articles [80-82]; after interviewing 10,000 patients in the British Isles the overall incidence of atopy (eczema, asthma and hayfever) was 8.5%, atopic patients had an incidence of allergy of 36% compared with the non-atopic population – 11%. Some unusual figures came out of the audit, the obstetric population has a higher incidence compared with non-pregnant females (does pregnancy induce atopy?) and the ‘cardiothoracic’ subset of male patients had a higher incidence, does this mean that males with atopy have a greater risk of cardiothoracic disease? From these 10,000 patients the frequency of type of anaesthesia was collected, 67% had had a previous anaesthetic, and 20% of these in the previous four weeks. Over half of them had been given halothane [83]. And so, finally, the old topic of halothane and hepatitis [84-87]. The first paper studied liver function tests after repeat (two or more) administrations of halothane (63 patients) and enflurane (66 patients). Halothane produced the higher incidence of enzymatic changes.

**Hypothermia and acupuncture**

Two subjects on which multiple papers were written were induced hypothermia [88-92] and acupuncture [93-109].

**Hypothermia**

Between 1953 and 1964 there were eight papers on hypothermia, one of the first, whilst he was working in Liverpool, was on the production of hypothermia and was an animal study. They used deep anaesthesia, curarization and a ‘lytic cocktail’, chlorpromazine, pethidine and promethazine. Cardiac arrest occurred in three dogs at 23, 23.5 and 26.5 degrees centigrade. Three types of hypothermia all appeared effective but chlorpromazine appeared to be the active ingredient of the ‘lytic cocktail’. The publication in 1955 [90] describes the management by induced hypothermia (on multiple occasions) of a patient who had a cerebral aneurysm bleed...in the sub-title of the paper are the words “a clinical study of a hopeless
case” viii. Jumping forward to 1964 [92], there is an article on the “Pharmacology of hypothermia”. This is a comprehensive document, co-authored with RS Clarke, on drugs used to induce hypothermia, reduce the untoward effects of hypothermia and how hypothermia influences the actions of other drugs, a fitting final publication on the theme.

**Acupuncture**

In the 1970s, perhaps even a little earlier, reports were coming out of China of the use of acupuncture for major surgery…it became a ‘hot topic’. Of the many claims for its use its antiemetic effect proved a valuable area for research. Of the seventeen papers, from 1986 to 1991, Dundee was the lead author in sixteen; he was obviously very interested in the topic of the antiemetic effect of stimulation of the P6 point.

The 1986 paper [93] reported two consecutive studies including a randomised set of anaesthetics, one arm received nalbuphine and acupuncture, one dummy acupuncture with premedication and one with premedication alone. It was reported that acupuncture significantly reduced perioperative nausea and vomiting; the mechanism inexplicable. It was reported to reduce morning sickness [97] and was shown to be effective against chemotherapy induced nausea [100, 105].

A 1991 study where either saline or 1% lignocaine was infiltrated at the P6 point is fascinating. There were 37 patients in each group; when saline was used 30 patients had neither nausea nor vomiting, in the lignocaine group, over the study period of six hours an average of 21 patients were free from symptoms, a p value of 0.014.

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viii A totally irrelevant comment here is that what we take for granted now in the quality of graphics was so far in the future...the graphs are hand drawn and can be seen to be so.
Odds and ends

To complete this partial, annotated bibliography, there are several other, single, publications of interest... David Waldie [110], who was he? Anaesthesia related iatrogenic disease [111], mysterious deaths at Ann Arbor [112] and the death of a volunteer [113] are some. There were also overviews of many subjects but one of note is that of total intravenous anaesthesia (1978 and 1984) [114, 115], looking forward to research in the eighties [116] published in 1979 and an enigmatic title “The last of the fifty – a time of change” [117]

David Waldie was a Scotsman who qualified as a surgeon in 1831 but he was more interested in chemistry and gave up medicine around 1840. He was responsible for improving, if not perfecting, the extraction of chloroform from chloric ether; could come in useful for Trivial Pursuits.

The anaesthesia related iatrogenic disease was published in the Nova Scotia Medical Bulletin...its impact factor is unknown to the author.

“Death of a volunteer” is a letter to British Medical Journal (Clinical Research Edition) commenting on a death associated with pharmacological research, involving midazolam...the volunteer developed aplastic anaemia. Comments are made on the remuneration of researchers and their inability of to cover potential damages. Still of great importance in the light of more recent deaths in volunteersix.

In New Zealand clinical research is either indemnified by a the drug company, if they are sponsoring the study, or by ACC, the no blame accident covering ‘insurance’ (Accident Compensation Corporation).

“Research in the eighties” is a one page editorial in the British Journal of Anaesthesia, the final two sentences are “Let the clinicians document the failings of our available agents or machines and the companies will know wherein lies the most profitable field for research. Proper feed-back from clinicians to research workers and industry will make research relevant to all concerned.” He extols the

ix http://www.i-sis.org.uk/LDTC.php (last visited 2010)
virtues of past researchers and, in effect, states that the modern academic is less likely to make such an impact as Magill or Macintosh.

“The last of the fifty – a time of change” [117] is an oration in October 1985 at the Royal Victoria Hospital (Belfast). It is an historical overview of change in medicine, and in particular anaesthesia. It is particular to Belfast but it could be mirrored in any British city. The “last of the fifty” refers to the consultant ‘Staff’ of fifty (there were others) who were elected to a body that communicated with the Hospital Management Committee and University. Positions only became available on the death or retirement of members. JW Dundee was the last of the fifty to be elected as it was a time of change.

The list of references below may well be incomplete, John Dundee published articles in non-English journals, and chapters in books, for example “Monitoring for drug safety” edited by William HW Inmanx.

Dundee and his team of workers produced a large body of work that portrays the use of para-anaesthetic and anaesthetic drugs over a period when anaesthesia was undergoing, arguably, its greatest change.

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Many of the references listed below have not been read by the author.

References:


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