



From Bedside to Bench: Comroe and Dripps Revisited

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PREFACE

The Health Economics Research Group (HERG) at Brunel University is involved in a long-term programme analysing the benefits from health research, with an emphasis on the payback from health services research. This programme is being expanded, in collaboration with colleagues working on these issues elsewhere, to include exploration of methodologies for assessing the impact from basic or early clinical biomedical research. A central collaborator is Jonathan Grant, formerly Head of Policy at the Wellcome Trust, and now at RAND Europe. In simultaneously publishing two reports as part of the HERG Research Report series we bring together several elements of this research, and draw on them to make proposals for further work.

In HERG Research Report 30, *From Bedside to Bench: Comroe and Dripps Revisited*, Grant *et al* examine whether it is possible to replicate, and validate, the pioneering work of Comroe and Dripps in the 1970s. The latter traced back from then current clinical practice to the knowledge behind the advances. They claimed that more than half of the articles identified as making a key contribution to the clinical advances resulted from basic research. The attempted replication proved difficult, but Grant *et al* describe how they developed and applied an alternative methodology.

In HERG Research Report 31, *From Bench to Bedside: Tracing the Payback Forwards from Basic or Early Clinical Research--a Preliminary Exercise and Proposals for a Future Study*, Hanney *et al* describe a joint HERG/Wellcome Trust project that in part builds on the emerging findings from Grant *et al*'s study of the Comroe and Dripps methodology. Recognising the difficulties in tracing *backwards* from clinical practice, the project described here attempts instead to work *forwards* by tracing the impact from research conducted 20 years ago. Having described how the methods were applied in a preliminary study, the report goes on to outline how the work could be developed in a larger study.

The research undertaken for both reports was primarily funded by the R&D Directorate of the NHS Executive London, whose Director of R&D, Sally Davies, has been a stalwart supporter of such research and of its aim to provide an evidence-base for health research funding policies.

Martin Buxton

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CONTRIBUTORS, ACKNOWLEDGEMENTS AND CONTACTS

Contributors: Jonathan Grant conceived and oversaw the study and wrote the final report. Liz Green and Barbara Mason developed the protocol, managed the project and undertook data analysis.

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The views expressed in this report are those of the authors and do not necessarily reflect the views of any of the bodies mentioned.

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EXECUTIVE SUMMARY

Twenty-five years ago a paper published in *Science* by Julius Comroe and Robert Dripps purported to demonstrate that 41 per cent of all articles judged to be essential for later clinical advances were not clinically oriented at the time of the study and 62 per cent of key articles were the result of basic research.

Since that analysis, support for basic research has increased in the G7 countries. In the UK, Research Council expenditure on basic research has increased from a low of £444 million (or 42 per cent of total civil R&D) in 1991/92 to £769 million (or 61 per cent of total civil R&D) in 1998/99. Although it would be difficult to argue that Comroe and Dripps were directly responsible for a strategic shift (or drift) in the type of science supported by research funders, their arguments are often cited (albeit at times implicitly) in support of the increased funding for basic biomedical research.

In 1987 Richard Smith wrote a critical paper reassessing Comroe and Dripps. His main argument was that the original study was in itself 'unscientific' and that it should be "followed by bigger and better studies". This study is, in part, an answer to that challenge.

Given the increased support for basic research, and the apparent importance based on the work of Comroe and Dripps, we felt it was important to investigate Smith's comments by replicating Comroe and Dripps's study and at the same time try to improve upon the methodology. The current project had two objectives:

1. To see if the original Comroe and Dripps's methodology was 'replicable'.
2. To validate the key findings of Comroe and Dripps.

By looking at neonatal intensive care (NIC), we concluded that Comroe and Dripps' study – as reported – is not repeatable, reliable or valid, and thus is an insufficient evidence base for increased expenditure on basic biomedical research. We did, however, develop an alternative methodology which used bibliographic databases and bibliometric techniques to describe the research underpinning five of the most important clinical advances in NIC, as identified through a Delphi survey.

Using the revised bibliometric protocol, we demonstrated that after a time-lag of about 17 years, between 2 and 21 per cent of research underpinning the clinical advances could be described as basic. This observation is at odds with Comroe and Dripps's finding that 62 per cent of key research articles judged to be essential for latter clinical advance were the result

of basic research.

In reaching this conclusion we are acutely aware of the significant limitations to the revised methodology and, therefore, we caution against the over-interpretation of our results. However, we would argue that there needs to be a greater understanding of how basic research supports healthcare and hope this report will inform part of this wider debate.

CHAPTER 1: INTRODUCTION

Twenty-five years ago a paper was published in *Science* which, arguably, would not meet today's standards of peer-review. All the same, the paper, by Julius Comroe and Robert Dripps, was a seminal piece of research.¹ By examining the top ten key advances in the field of cardiovascular and pulmonary medicine and surgery they demonstrated that 41 per cent of all articles judged to be essential for later clinical advance were not clinically oriented at the time of the study and 62 per cent of key articles were the result of basic research.

Yet, as with much of science policy, it would be wrong to see these results in isolation from the political debate at the time. The Comroe and Dripps study was inspired by a 1966 US Department of Defense study, *Project Hindsight*, that examined the effectiveness of basic research in the development of military weapons.² This report concluded that: (a) contributions of university research were minimal; (b) mission-oriented research proved to be most effective; and (c) the time-lag between discovery and application was shortest when funding was focused. Consequently, in the USA, contract- and commission-initiated research became vogue. For example, in 1966 President Lyndon Johnson said that "Presidents...need to show more interest in what the specific results of research are – in their lifetime, and in their administration. A great deal of basic research has been done...but I think the time has come to zero in on the targets".^{3, a}

Comroe and Dripps were concerned that applying lessons from military R&D policy to medical R&D policy was, in itself, invalid. So, they set out to design a study that provided a more objective basis for developing long-term policies to support biomedical research. Comroe and Dripps did this by identifying the ten most important clinical advances in cardiovascular and pulmonary medicine and then reviewing, with the help of experts, the medical literature relevant to the clinical advance. They selected a set of key articles and, again with the help of experts, determined among other things, whether the key research was basic or clinically oriented at the time of the study.

In addition to Comroe and Dripps's response to *Project Hindsight*, the US National Science Foundation initiated the 'Technology in Retrospect and Critical Events in Science' study (TRACES). TRACES methodology involves using historiographical tracings of key advances in a field in order to identify major technological innovations. For example, in 1968 the US National Cancer Institute (NCI) published a study that evaluated the impact of research by research setting and funding mechanisms.⁴ Thirteen key advances in cancer research were traced back to papers which had a significant impact on their development and, where

a This quote is taken from the Introduction to the Comroe and Dripps's study report.

relevant, to the NCI mechanism which supported the underlying research. The study concluded that research setting (e.g. large *versus* small institutes, universities *versus* medical schools etc.) did not have a major impact on the occurrence of advances. It also concluded that all NCI support mechanisms contributed significantly to the advances, with research project grant and an intramural programme being among the most effective.

A decade later Richard Smith (formerly assistant editor, and now editor of the *BMJ*) wrote a critical paper reassessing Comroe and Dripps.⁵ His main argument was that the original study was in itself 'unscientific'. Notwithstanding this, Smith concluded that "the real lesson from Comroe and Dripps – and I am sure that they understood this themselves – is that we need to research research so that we can allot funds in a more intelligent and less empirical and (to use their favourite word) anecdotal way". He goes on to state that "sadly, Comroe and Dripps's paper has not been followed by bigger and better studies" and that "the lessons from Comroe and Dripps have not been learnt to any great extent by those funding medical research".

The rise of basic research

Despite Smith's analysis, it seems that Comroe and Dripps's conclusions entered the 'psyche' of policy makers in both Europe and North America, as support for basic research has been on the increase over the past decade. A comparison of gross expenditure on basic R&D in five countries is given in Figure 1.1. It should be noted that these data are for *all* research areas by all funding sectors and include military R&D expenditure, the majority of which is classified as applied research. UK and Canadian data are unavailable for this OECD data series. Figure 1.1 shows a general increase for support of basic research across the five countries, although it is interesting to note how the European countries are supporting more basic research than USA and Japan. That said, in the USA a recent report concluded that "in the late 1990s [research funding] agencies were tending to protect basic and university research relative to applied research and other performers".⁶

A similar trend is also apparent in the UK. This is illustrated in Figure 1.2 for civil UK Research Council expenditure on R&D by the Frascati categories.^b These figures are not directly

^b The Organisation for Economic Co-operation and Development (OECD) provides the most reliable and consistent international analysis of R&D expenditures. In the Frascati Manual,^b the OECD subdivides R&D into three related activities: basic research is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view; applied research is also original investigations undertaken in order to acquire new knowledge. It is, however, directed primarily towards a particular aim or objective; experimental development is systematic work drawing on existing knowledge gained from research and practical experience that is directed to producing new materials, products or devices; to installing new processes, systems or services, or to improving substantially those already produced or installed.

comparable with those presented in Figure 1.1 as they exclude non-Research Council expenditure (such as industry, medical charities, HEFCs etc.). Expenditure on basic research has increased from a low of £444 million (or 42 per cent of total civil R&D) in 1991/92 to £769 million (or 61 per cent of total civil R&D) in 1998/99, while applied research has declined from a high of £683 million (or 58 per cent of total civil R&D) in 1992/93 to £486 million (or 38 per cent of total civil R&D) in 1998/99.

Within the biomedical sciences, the major funders of biomedical science, such as the UK's Medical Research Council (MRC) and the USA's National Institutes of Health (NIH), all support a substantial amount of basic research. For example, the NIH has increased the budget of its General Medical Science (GMS) arm to a high of US\$1.4 billion for Fiscal Year 2001. The National Institute of GMS primarily supports basic biomedical research that is not targeted to specific diseases or disorders.⁷

This trend is also noticeable in bibliometric data. For example, the proportion of basic biomedical research publications acknowledging the Wellcome Trust has increased by ten percentage points (from 47 per cent in 1989 to 58 per cent in 1998), while the trend for MRC-acknowledged papers has stayed more constant from 48 per cent in 1988 to 50 per cent in 1998 (Figure 1.3).⁸ At the same time, relative support for clinical research has declined: the proportion of Wellcome Trust-acknowledged papers that have a clinical address (i.e. at least one of the collaborators records an address with the strings 'NHS', 'HOSP' or 'INFIRM' in the address field) has fallen from 38 per cent in 1988 to 29 per cent in 1998 (Figure 1.4).

While not wanting to give the impression that Comroe and Dripps were responsible for a strategic shift (or drift) in the type of science supported by research funders, their arguments are often cited (albeit at times implicitly) in support of the increased funding for basic biomedical research evidenced in Figures 1.1–1.4.

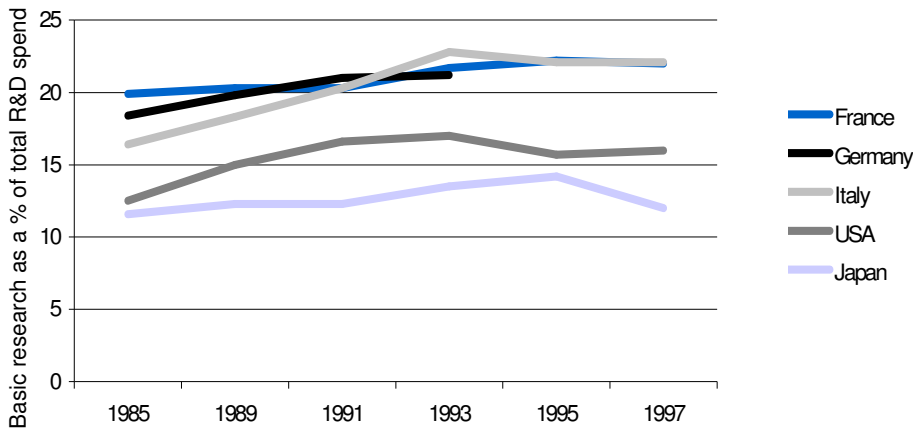
Study objectives

Given the increased support for basic research, and the apparent importance based on the work of Comroe and Dripps, we felt it was important to take up Smith's challenge by replicating their study, but at the same time addressing Smith's concerns by trying to improve upon the methodology. The current project had two objectives:

1. To see if the original Comroe and Dripps's methodology was 'replicable'.
2. To validate the key finding of Comroe and Dripps, that is to see if two-thirds of all research judged to be essential for later clinical advance could be described as basic.

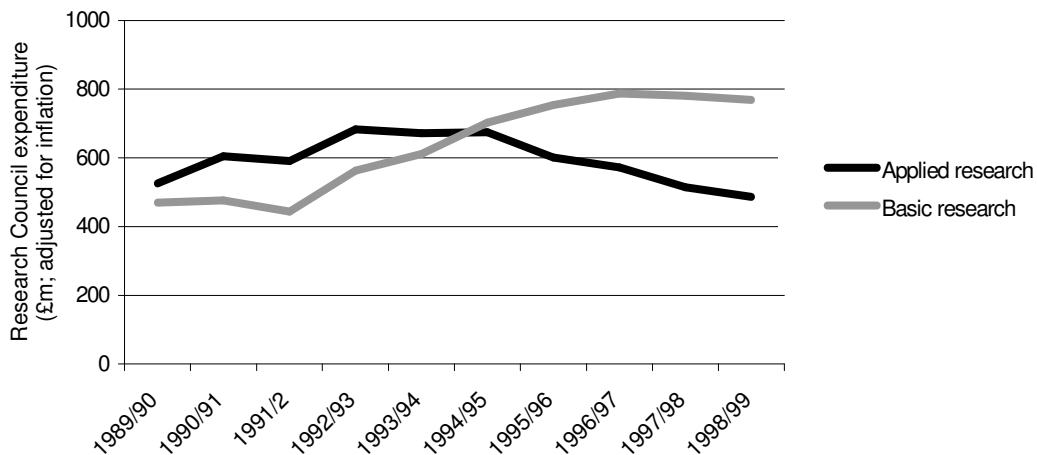
Chapter 2 describes our attempt to repeat Comroe and Dripps, and concludes that their assumed protocol was not workable. Chapter 3 therefore describes an alternative, bibliometric, approach which we developed to build on the work we undertook in Chapter 2. The final chapter pulls together our findings, discusses a number of substantial methodological problems that are identified in the report and offers some policy interpretations.

Figure 1.1: Basic research as a percentage of the total of R&D spend for five countries



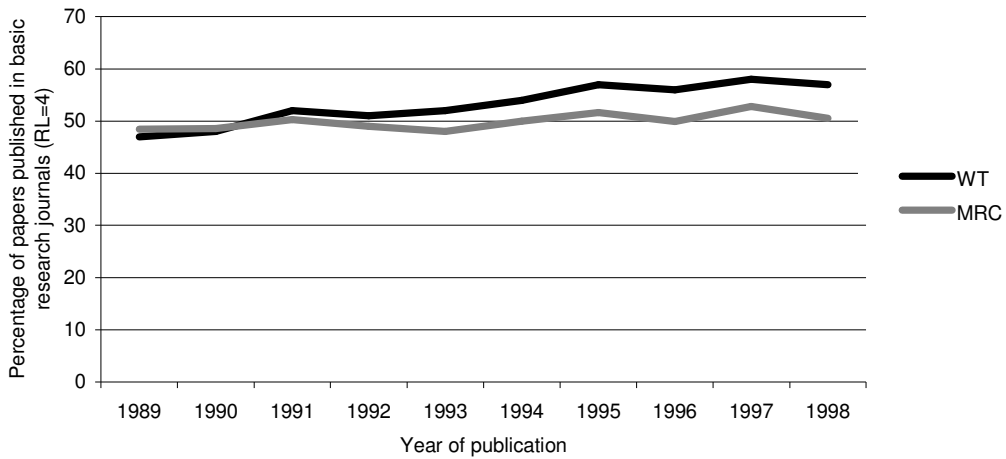
Source: Office of Science and Technology (2000). *Science and Engineering and Technology Statistics, 2000*. HMSO, Norwich

Figure 1.2: Analysis of UK Research Council expenditure by Frascati type of research activity



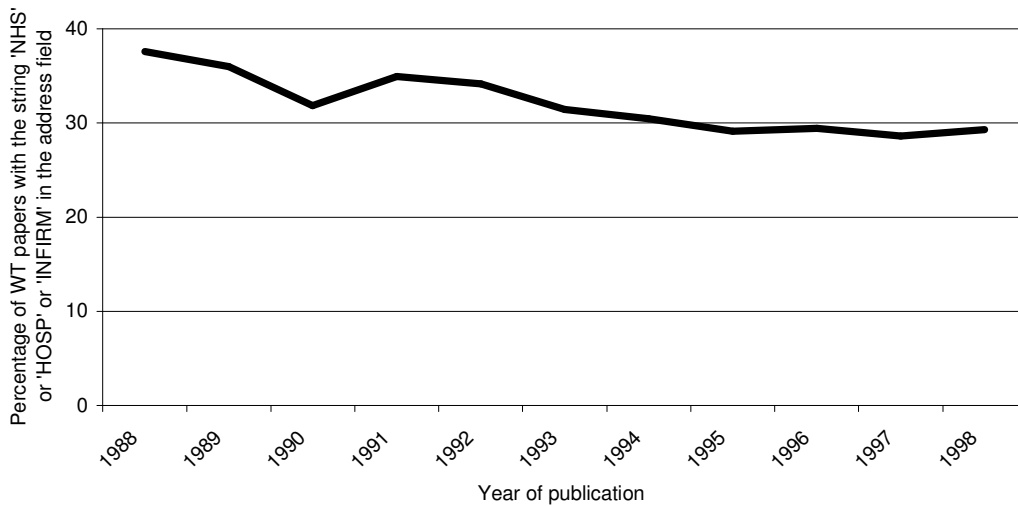
Source: Office of Science and Technology (2000). *Science and Engineering and Technology Statistics, 2000*. HMSO, Norwich

Figure 1.3: Proportion of papers published in basic biomedical research journals acknowledging Wellcome Trust (WT) and Medical Research Council (MRC) funding



Source: Research Outputs Database

Figure 1.4: Proportion of papers acknowledging Wellcome Trust funding undertaken in a clinical setting



Source: Research Outputs Database

CHAPTER 2: COMROE AND DRIPPS REVISITED^c

The Comroe and Dripps study can be divided into three stages: the identification of clinical advances; the identification of key research articles which describe, in the language of Comroe and Dripps, the ‘essential bodies of knowledge’ that led to the clinical advance; and the analysis of these research articles in order to identify factors that lead to research success.

Table 2.1 compares the methodology used by Comroe and Dripps with that developed in the current study. The first difference is in the choice of field for investigation. Comroe and Dripps investigated cardiovascular and pulmonary medicine; we examined neonatal intensive care. We chose this field for several reasons: first, it has had a short but active history,⁹ with neonatal mortality rates declining in the UK from 59 infant deaths per 1000 live births in 1940 to 7 in 1990;¹⁰ second, it has traditionally been an area of interest to the Wellcome Trust; third, the Trust held a Witness Seminar in Neonatology in April 1999, the participants of which provided an essential resource of expertise in developing the study.^{d, 11}

Table 2.1: Comparison of the Comroe and Dripps, and the current study

Comroe and Dripps	Current study
Selected cardiovascular as field of study.	Selected neonatal intensive care as field of study.
Stage 1: Identified ten most important clinical advances via consultation with physicians. Identified ‘bodies of essential knowledge’ within these advances with the help of consultants (physicians, medical scientists, medical historians, etc.).	Stage 1: Identified ten most important clinical advances via modified Delphi survey. Three rounds carried out. Sample included physicians, nurses, midwives, medical technologists and specialists. Identified ‘bodies of essential knowledge’ via internet search, advisory panel, sample of physicians.
Stage 2: Reviewed medical literature for relevant journal articles. Identified ‘key article’ subset of 663 ‘important’ papers. Key article defined by Comroe and Dripps as having an important effect on the direction of subsequent research, or report new data, drugs or techniques.	Stage 2: Searched Science Citation Index 1995–99 for relevant articles. The articles collected became generation 1. All the articles cited by the papers of generation 1 were collected, and ranked by the number of times they were cited. The top 5 per cent of the articles cited became generation 2. This process was repeated until four generations of articles had been collected.
Stage 3: Analysed key articles as to the percentage that could be classified as basic research, clinically oriented research, funding source etc.	Stage 3: Analysed the four generations of articles using bibliometric techniques. Articles were classified as describing either basic or clinical research.

^c This critique draws heavily on the work of Smith (1987) (reference 5).

^d A witness seminar is a vehicle used by the Wellcome Trust Centre for the History of Medicine at UCL’s History of Twentieth-century Medicine Group to bring academics and clinicians together to discuss the history of a particular therapeutic area or treatment. The transcripts of these seminars are published as an oral history (see www.ucl.ac.uk/histmed).

Stage 1 – Identification of clinical advances

In stage 1, Comroe and Dripps identified the essential bodies of knowledge around cardiovascular clinical advances. Forty physicians were asked to list what they considered to be important advances in their field. Comroe and Dripps compiled their responses into lists that were submitted to a further sample of '40 to 50 specialists' in cardiovascular and pulmonary medicine, who were asked to vote for the most important advance. However, as Smith points out, we do not know how they chose the initial 40 physicians^e and the 40–50 specialists; what were the respective response rates (did they ask more than 40 physicians, and only 40 replied or did they ask 40 and fewer replied?); and what method of voting was used and how were the votes tallied? Nevertheless, the responses were tabulated and the 'top ten' list of advances was developed, as illustrated in Table 2.2.

Table 2.2: The top ten clinical advances in cardiovascular and pulmonary medicine and surgery in the last 30 years

Advance	Comprising
Cardiac surgery	Including open-heart repair of congenital defects and replacement of diseased valves
Vascular surgery	Including repair or bypass of obstructions or other lesions in aorta, coronary, cerebral, renal and limb arteries
Drug treatment of hypertension	
Medical treatment of coronary insufficiency	Myocardial ischaemia
Cardiac resuscitations	Including defibrillation, cardioversion and pacing in patients with cardiac arrest, slow hearts, or serious arrhythmias
Oral diuretics	In treatment of patients with congestive heart failure or hypertension
Intensive cardiovascular and respiratory care units	Including those for postoperative care, coronary care, respiratory failure, and disorders of the newborn
Chemotherapy and antibiotics	Including prevention of acute rheumatic fever and treatment of tuberculosis, pneumonias and cardiovascular syphilis
New diagnostic methods	For earlier and more accurate diagnosis of disease of cardiovascular and pulmonary-respiratory systems
Prevention of poliomyelitis	Especially of respiratory paralysis due to polio

We tailored this methodology by employing three rounds of a modified Delphi survey to identify the leading advances in neonatal intensive care. In the first round, participants and attendees ($n = 41$) of the Wellcome Trust Witness Seminar in Neonatology were asked to

^e In the report (reference 3), Comroe and Dripps have a footnote saying that the physicians are listed in the August 1975 Preliminary Report to the National Heart and Lung Institute, but we have been unable to trace this publication.

propose major advances in neonatal intensive care and to suggest a definition of NIC.¹⁰ The 21 responses (response rate = 58 per cent) were compiled into a pilot questionnaire that was sent to a sample of 19 individuals who were invited, but did not participate, in the Witness Seminar and 50 randomly selected practising neonatal/paediatric healthcare providers identified in *The Neonatal Nurses Association Yearbook*.^{f, 12} The 69 survey participants were requested to vote for their top ten advances, and to add any they felt had been omitted. The 31 responses (response rate = 45 per cent) were then used to develop the final questionnaire (see Appendix A), which was sent to the balance ($n = 1758$) of neonatal/paediatric healthcare providers within the UK.⁹ A response rate of 45 per cent was achieved in the final, third round of the Delphi survey. A simple counting of votes prioritized the list of advances (Figure 2.1 and Table 2.3).

We were conscious that the professional background of the respondents and their experience in the field may have had some effect on the ranks. However, as illustrated in Tables 2.3, with some minor exceptions, this proves not to be the case and therefore we restricted our analysis to the global list.

There were, however, a number of complications with the Delphi survey which were pointed out by final round participants. First, there were a few choices that could be considered to be closely overlapping. For example it was mentioned that the choices of 'incubator' and 'temperature control' were to all intents and purposes the same, as were 'light therapy' and 'control of jaundice'. Second, due to an office error, antenatal steroids appeared twice in the final questionnaire (and thus could be one of the reasons why it was voted number three on the list). Third, the inclusion of antenatal steroids seemed to be inappropriate as their purpose was to prevent NIC. Finally, there was some concern that the definition we used for neonatal intensive care was too broad.

Although these criticisms of the Delphi survey may be just, we would argue that they do not undermine the study, as its primary purpose was to understand how basic research fed into clinical advances that had impacted on healthcare. The Delphi survey provided us with a method of identifying a shortlist of high-impact clinical advances. We therefore decided to take the top three advances (mechanical ventilation, replacement surfactant and antenatal steroids) and, following discussions with our sponsors,^h parenteral nutrition and ultrasound

f The healthcare professionals were randomly selected from a list of all neonatal and paediatric intensive care units in the UK published in *The Neonatal Nurses Association Yearbook* (reference 12).

g In order to assure that the actual rank of the advances in the questionnaire did not influence the respondents' answers, five sets of questionnaires were developed each with a different ordering of the list.

h The R&D Directorate of the London regional office of the NHS.

(see Box A for a description of these advances) for further study.

Figure 2.1: Leading advances in neonatal intensive care

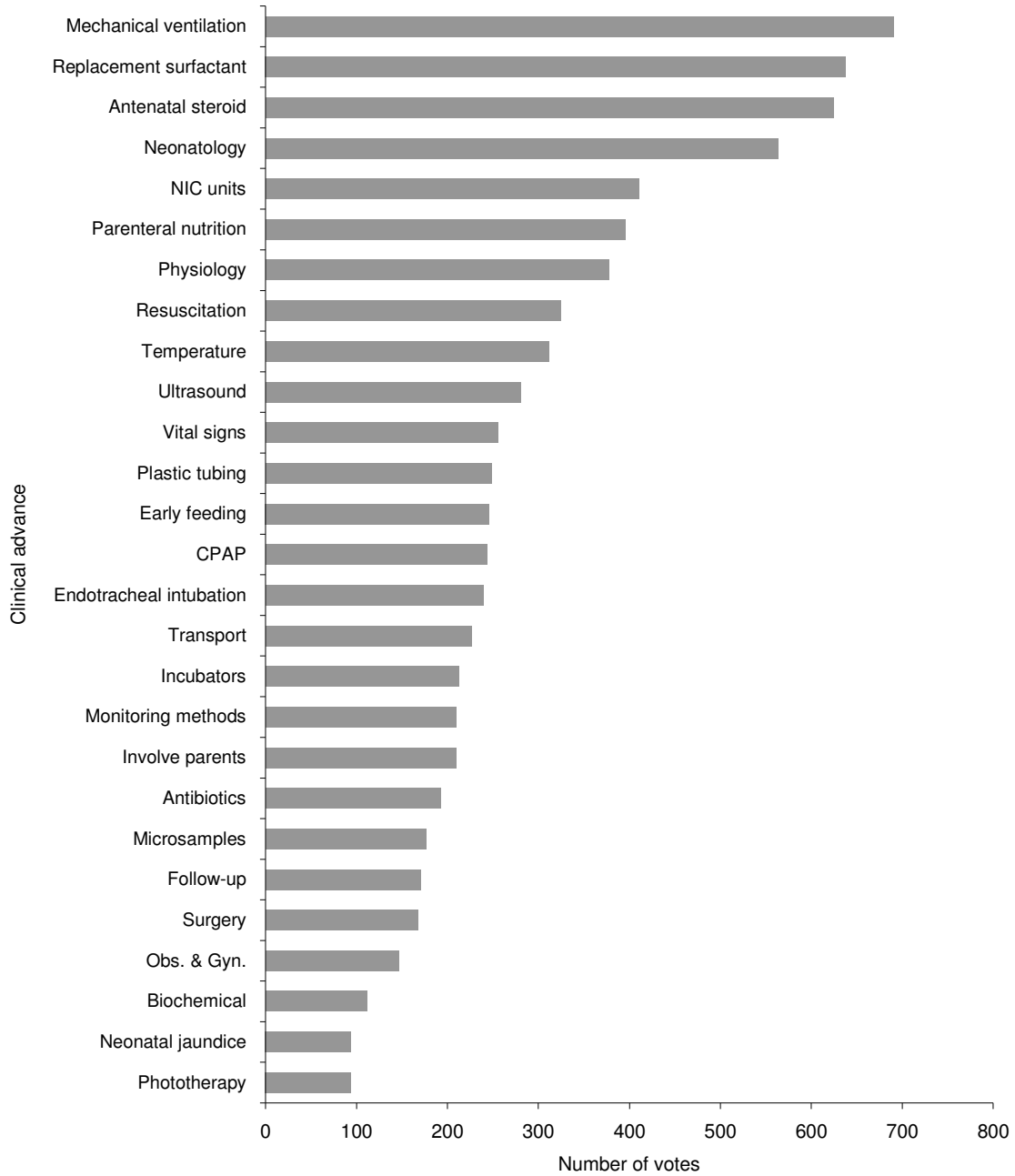


Table 2.3: Top ten advances in neonatal intensive care – overall ranking, by profession and by years of experience

Advance	Total votes	Rank	Clinical	Nursing	Managers	1–10 years' experience	11–20 years' experience	20+ years' experience
Mechanical ventilation	643	1	1	4	1	1	1	1
Replacement surfactant	589	2	2	1	3	2	2	2
Antenatal steroids	577	3	3	2	2	3	3	3
Neonatology as subspecialty	517	4	4	3	4	4	4	4
Neonatal intensive care units	384	5	6	7	5	5	6	5
Parenteral nutrition	371	6	5	8	6	7	5	6
Physiology of neonate	351	7	7	6	7	6	7	7
Resuscitation techniques	300	8		5	8	8	8	10
Temperature control	286	9	9		9		10	
Ultrasound imaging	264	10					9	8

Box A: Glossary of selected clinical advances

Mechanical ventilation	If a neonate is unable to breath normally, a mechanical ventilator can be used to maintain a flow of air into and out of the patient's lungs.
Development of replacement surfactant	Surfactant is a wetting agent consisting of a complex mixture of compounds that prevent the air sacs of the lungs from collapsing by reducing surface tension. Its absence, such as in immature lungs of premature babies, leads to atelectasis (the failure of the lung to expand) and respiratory distress syndrome (RDS). Replacement surfactant can help treat these conditions.
Use of antenatal steroids	This is the practice of giving a single course of corticosteroids to pregnant women between 24 and 34 weeks' gestation who are at risk for preterm delivery. The drugs, administered intramuscularly, accelerate the maturation of fetal lungs and other organs, and reduce the risk of respiratory distress syndrome (RDS), brain haemorrhage, and mortality in preterm infants.
Total parenteral nutrition (TPN)	This is providing the body's nutritional needs by a balanced mixture of basic constituents supplied by intravenous infusion.
Ultrasound imaging	A diagnostic procedure that projects high-frequency sound waves into the body and changes the echoes into pictures (sonograms) shown on a monitor. Different types of tissue reflect sound waves differently. This allows detailed anatomical images to be built up that can assist with diagnosis in the fetus and neonate.

NB. The descriptions used in this glossary are the same as those identified and used in the Delphi survey (Appendix A), although in the text of the report short descriptions are used.

Stage 2 – Review of literature supporting clinical advances

Once Comroe and Dripps had identified the top ten advances, they worked with external consultants to identify the “essential bodies of knowledge that we believe had to be developed before each of the 10 clinical advances could reach its present stage of achievement”. It appears that 144 consultantsⁱ were involved in this process; however, the depth or format of consultation was not explained, although they indicate that 46^j of the consultants were interviewed (suggesting that the other 98 were surveyed).

From their consultations, Comroe and Dripps identified 137 ‘essential bodies of knowledge’ that were needed for the advance to occur. (As an example, Table 2.4 illustrates the essential bodies of knowledge required for open heart surgery.) They ‘examined’ 4000^k articles on cardiovascular/pulmonary medicine, ‘identified’ 2500^l of them for special consideration. How the initial review was carried out, or how articles were identified as relevant, is not explained. Comroe and Dripps then arranged the “specific scientific reports that were particularly important for the development of one or more of the 137 essential bodies of knowledge” into chronological tables.

Comroe and Dripps went on to select 529 ‘key articles’.^m Key articles were those articles which Comroe and Dripps, with the help of consultants, considered to be essential for one or more of the top ten clinical advances because:

- “It had an important effect on the direction of subsequent research and development, which, in turn proved to be important for clinical advance in one or more of the ten clinical advances under study.”
- “It reported new data, new ways of looking at old data, a new concept or hypothesis, a new method, a new drug, or a new technique that either was essential for full development of one or more of the clinical advances (or necessary bodies of knowledge)...”
- “A study is not a key study if it has not yet served directly or indirectly as a step towards solving one of the ten clinical advances.”
- “An article is a key article if it described the final step in the clinical advance.”

i The reporting of a number of figures vary between the paper (reference 1) and the report (reference 3). For example, the paper refers to 144 consultants while the report puts this number at 166. In this analysis we use the figures cited in the paper, but footnote those in the report. We *assume* these differences are because the report was published in 1977 and the paper 1976, hence allowing further analysis and updates of late responses etc.

j 49 in report (see footnote i).

k 6000 in report (see footnote i).

l 3400 in report (see footnote i).

m 663 in report (see footnote i).

Table 2.4: Essential bodies of knowledge required for successful open-heart surgery

<p>Preoperative diagnosis of cardiac defects</p>	<p>Anatomic and clinical Physiologic: electrocardiography, other noninvasive tests Physiologic: cardiac catheterization Radiologic: selective angiocardiography</p>
<p>Preoperative care and preparation</p>	<p>Blood groups and typing: blood preservation; blood banks Nutrition Assessment of cardiac, pulmonary, renal, hepatic and brain function Management of heart failure</p>
<p>Intraoperative management</p>	<p>Asepsis Monitoring ECG, blood pressure, heart rate, ECG and blood O₂ and pH Anaesthesia and neuromuscular blocking agents Hypothermia and survival of ischemic organs Ventilation of open thorax Anticoagulants Pump-oxygenator Elective cardiac arrest; defibrillation Transfusions; fluid and electrolytes; acid–base balance Surgical instruments and materials Surgical techniques and operations</p>
<p>Postoperative care</p>	<p>Relief of pain General principals of intensive care; recording and warning systems Management of infection Diagnosis and management of circulatory failure Diagnosis and management of other postoperative complications Wound healing</p>

Comroe and Dripps took 42 (of the 137) chronological tables and, using the above description, identified the ‘key articles’. They also sent the same table to reviewers for their independent selection (with, one assumes, their definition of a key article). Again, we do not know why there were 42 tables and how they were selected. We do not know the make-up of the reviewers. Tellingly, in a footnote to a table analysing the reviewers and their classification of key articles, Comroe and Dripps note that “the total number of key articles selected by reviewers is higher than the number selected by us because (i) the reviewers on average selected 8.4 key articles per table and we selected on average only 6.7 for these 42 papers; and (ii) we sent some tables to more than one reviewer”. Unfortunately we do not know the inter-rater reliability of Comroe and Dripps and the independent reviewers. Nevertheless,

Comroe and Dripps went on to use the 529 key articles to form the basis of their analysis. We tried to refine Comroe and Dripps's approach by drawing up 'developmental maps' that identified both key events and key researchers in the development of a clinical advance.ⁿ These would be our equivalent of the chronological tables of key bodies of knowledge. We began to do this for the first three advances on our list – mechanical ventilation, artificial surfactant and antenatal steroids (see Figures 2.2–2.4 for our *draft* attempts). The maps were based on desk research (undertaken by Barbara Mason) using Internet, bibliographic databases, review papers etc. The development maps were then modified on the basis of discussions with three experts in the field.^o Finally, the modified maps were sent to a random sample of 15 participants (response rate 4/15, 27 per cent) from the final round of the Delphi survey for comments, which we planned to incorporate in the final road map, after consultation with the advisory panel.^p

It was at this stage that we had to address two seemingly insoluble problems which, given the preceding ambiguities, began to undermine the whole study. First, how does one define an 'essential body of knowledge'? Comroe and Dripps used a fairly flexible definition: "as knowledge that we believe had to be developed before each of the 10 clinical advances could reach its present state of achievement". The trouble with this definition is that if it is applied rigorously, it results in a generic path from a basic discovery, through animal trials to human trials to clinical practice (as illustrated in Figures 2.2–2.4). If a less stringent interpretation is used, it is difficult to contain the path that would extend from biomedical science to statistics, engineering and research methods. For example, in studying the development of antenatal steroids it became apparent that the knowledge had existed within the clinical community for some time, but was only comprehensively implemented – and thus became an advance – when a meta-analysis systematically¹³ combined a number of previous trials (Figure 2.3). In this case, therefore, the statistical methodology developed by Peto and colleagues^{14, 15} for combining trial data was an essential body of knowledge.

Our second major concern was how can the scientific publications associated with an essential body of knowledge be *systematically* identified? That is, how can we identify a set of scientific publications which, using an identical research protocol, would also be selected by another independent investigator? Our initial approach was to use searchable bibliographic databases to locate articles around the essential bodies of knowledge for each advance. However, we soon discovered that this approach was not workable in a systematic way, as

n This work draws on the historiographical TRACES study (reference 4).

o See Acknowledgements for names.

p If we had continued with this approach, we would have circulated the draft maps to a wider sample, but at this stage we were simply piloting the methodology.

the sample would 'snowball' in an unpredictable – and thus potentially unrepeatably – manner. Furthermore, we were at a loss to know how to determine, again in a systematic, repeatable way, which researchers and papers were more 'essential' or 'key' than others.

Given Smith's original comments, it is perhaps not surprising that we found ourselves questioning whether the study was feasible. Indeed, it could be argued that we should not have tried to repeat Comroe and Dripps's methodology in the first place. By trying to repeat it we had hoped to be able to work our way through some of the issues Smith had highlighted but, as described, found this not to be possible. We therefore concluded that we could not repeat the Comroe and Dripps study, as set out in their reports, but were in a position to take forward a revised methodology which built on the results of the Delphi survey and utilized today's bibliographic resources in identifying the scientific basis of clinical advances.

Stage 3 – Analysis of 'key articles'

For the sake of completing the story, Comroe and Dripps analysed the 529 'key articles' by assessing whether the goal of the research was clinically oriented or not (Table 2.5). Research was clinically oriented "if the author, anywhere in his paper (excluding speculation at the end of his article), mentions, even briefly, an interest in diagnosis, treatment or prevention of a clinical disorder or in explaining the basic mechanisms of a sign or symptom of the disease itself...even if this research was performed entirely on animals, tissues, cells or subcellular particles". Research was not clinically oriented "if the authors...never state or suggest any direct or indirect bearing that their research might have on a clinical disorder of man".

They also assessed whether the key articles described basic research, and defined this as to mean research "when the investigator, in addition to observing, describing and measuring, attempts to determine the mechanism responsible for the observed effects". Having settled on this definition, Comroe and Dripps used six categories to analyse the key articles and showed that the total number of studies in basic research, either unrelated or related to a clinical problem, was 62 per cent of the total number of entries (Table 2.6).

The study does not explain what steps were taken to ensure the validity of the categorization process. Was each article rated by each of them, and consensus reached? If not, inter-rater variability must be expected. Comroe and Dripps themselves admitted that many articles did not fit neatly into one category or the other, and that the expectations of the analyst would colour the results of the process.

Summary

We concluded that the Comroe and Dripps methodology cannot be repeated without making fundamental changes to the study design; these are changes of such a magnitude that a comparison between our results, and those obtained by Comroe and Dripps would be of dubious value. However, at this stage of the research study, we had identified the leading clinical advances in neonatal intensive care, developed draft 'maps' for three of these advances and begun to identify papers underpinning these developments. We decided that it would be a missed opportunity not to use these data as the basis for a revised study looking at the relationship between basic research and healthcare.

Figure 2.2: Draft 'map' illustrating the development of mechanical ventilation

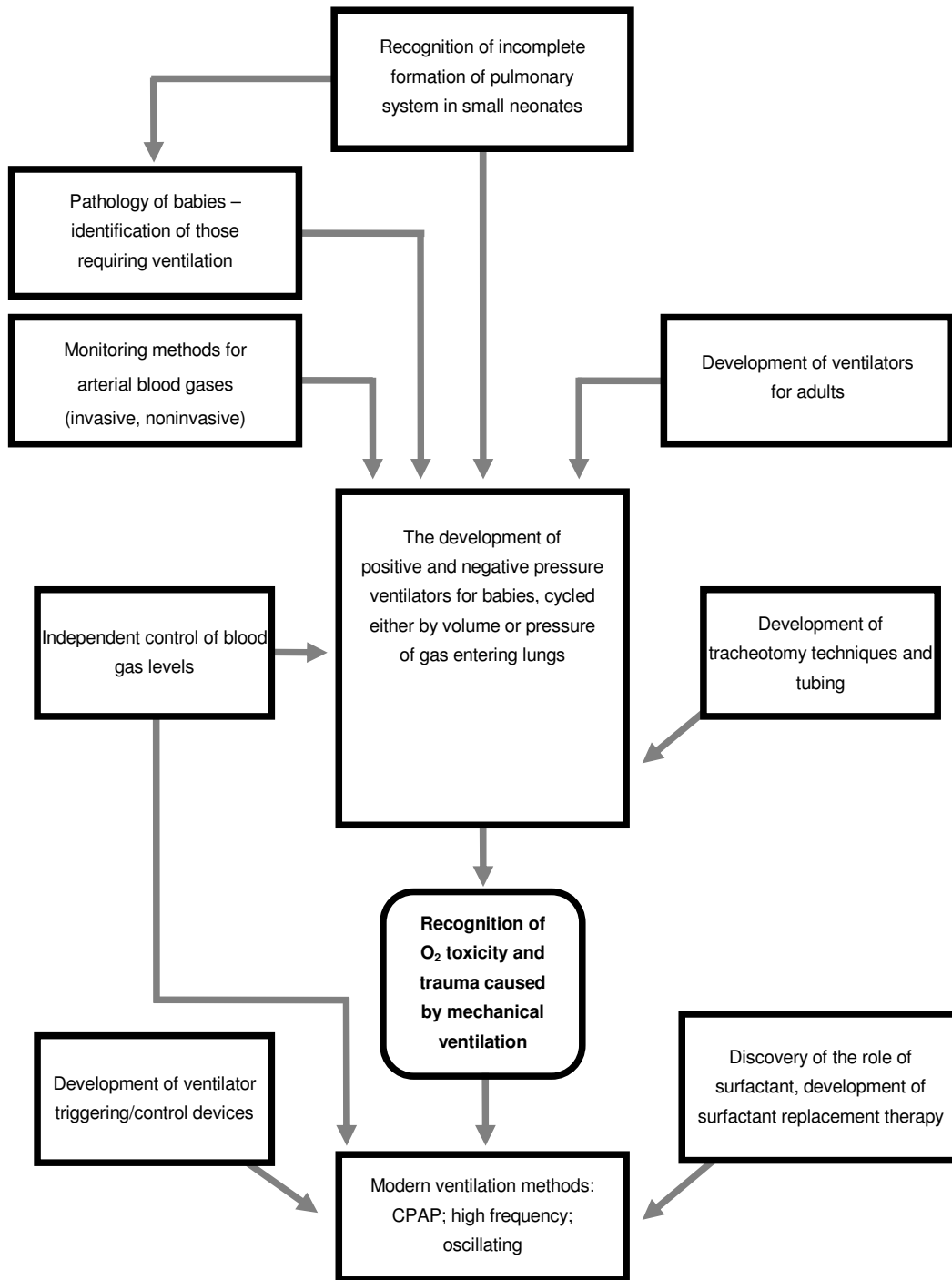


Figure 2.3: Draft 'map' illustrating the development of artificial surfactant

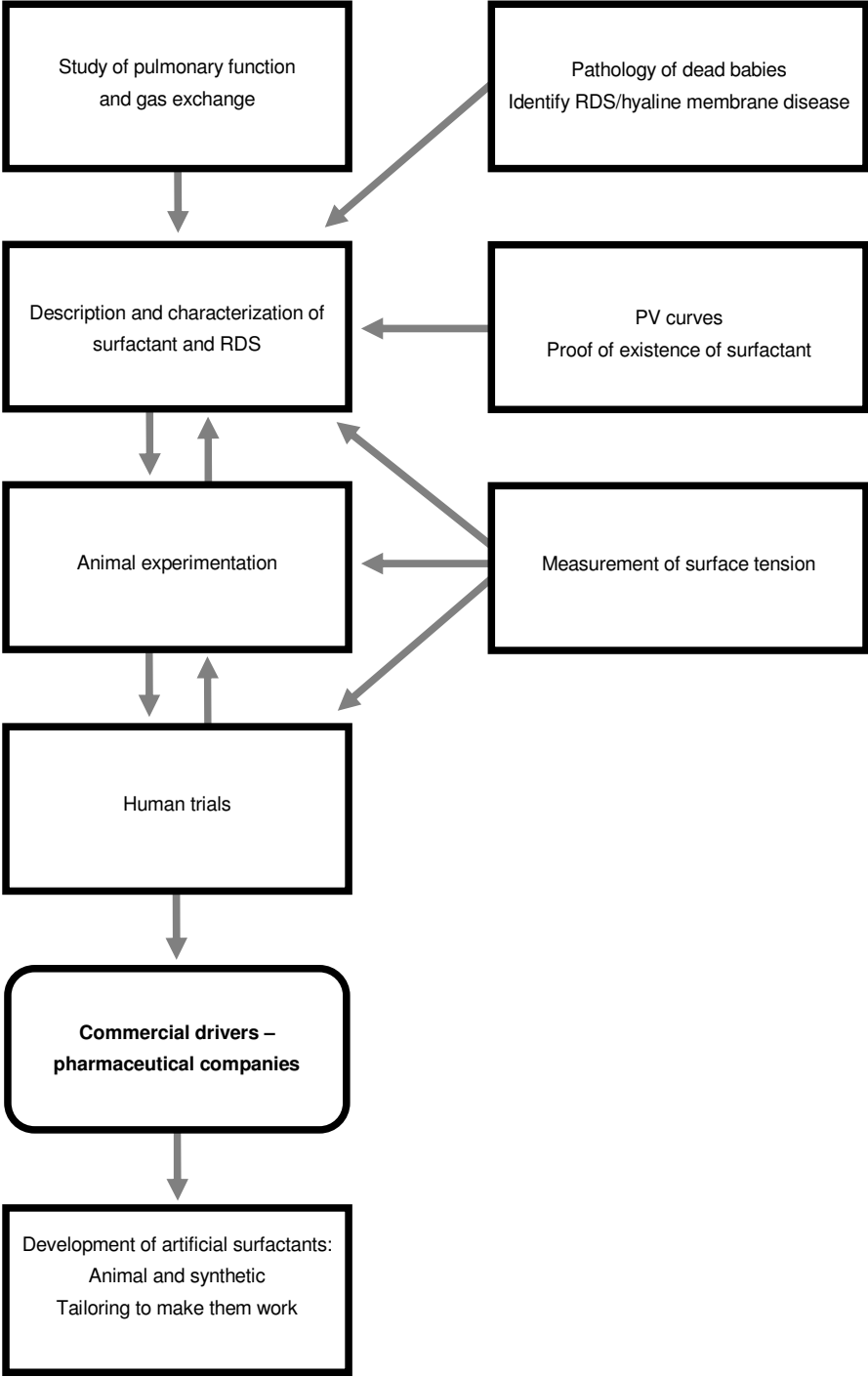


Figure 2.4: Draft 'map' illustrating the development of antenatal steroids

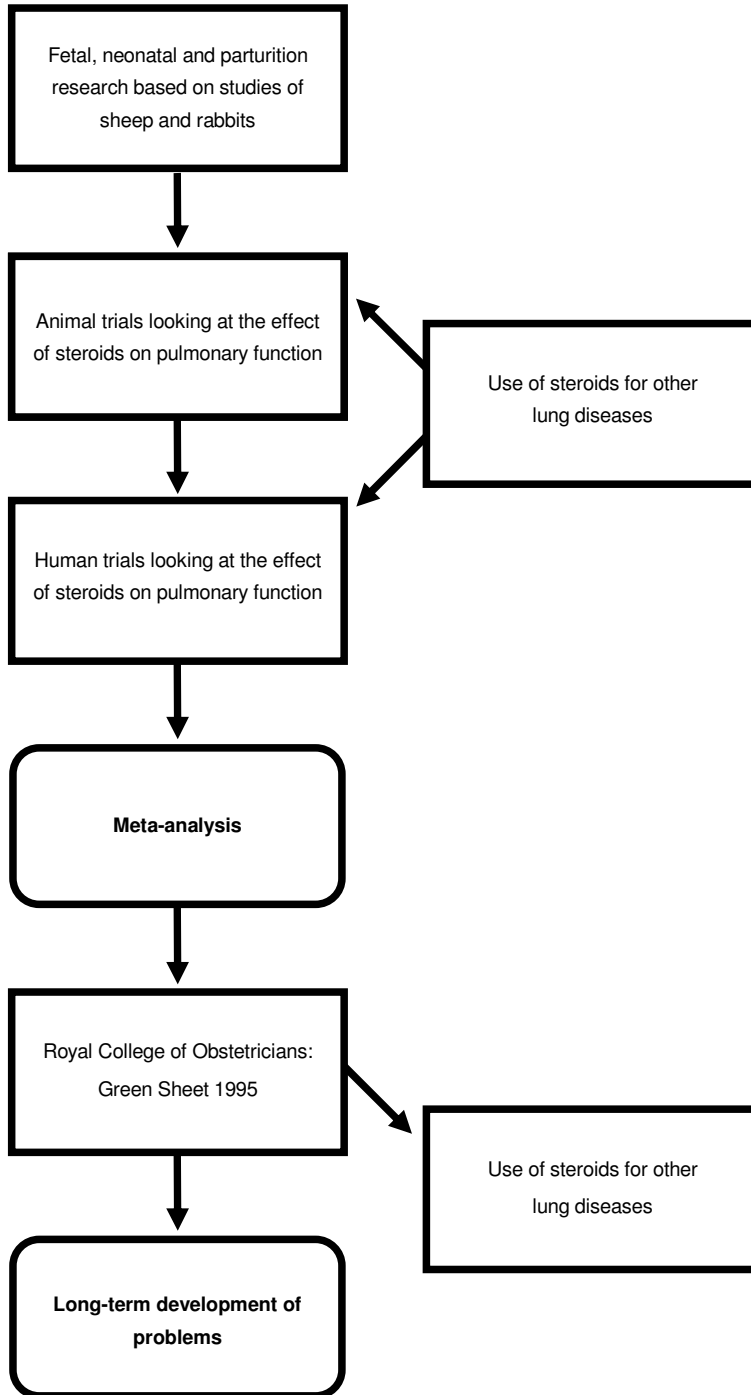


Table 2.5: Goal of authors of 529 key articles that later were judged to be essential for a clinical advance (taken from Comroe and Dripps, 1976)

Clinical advance	Clinically oriented	Not clinically oriented	Total	% of total of non-clinically oriented
Cardiac surgery	53	35	88	39.8
Vascular surgery	40	8	48	16.7
Hypertension	35	44	79	55.7
Coronary insufficiency	44	21	65	32.3
Cardiac resuscitation	24	16	40	40.0
Oral diuretics	19	24	43	55.8
Antibiotics	40	13	54	24.5
New diagnostic methods	41	53	94	56.4
Poliomyelitis	16	3	19	15.8
Total	312	217	529	41.0

Table 2.6: Type of research reported in 529 key articles (taken from Comroe and Dripps, 1976)

Clinical advance	Basic research not clinically oriented	Basic research clinically oriented	Other clinically oriented studies	Review of synthesis	Development or engineering for research use	Development or engineering for clinical use	Total
Cardiac surgery	34	23	19	0	3	11	90
Vascular surgery	9	7	14	3	0	21	54
Hypertension	42	16	21	2	0	0	81
Coronary insufficiency	21	20	22	1	1	3	68
Cardiac resuscitation	16	11	9	0	0	6	42
Oral diuretics	23	13	6	1	0	3	43
Antibiotics	12	18	21	1	0	2	54
New diagnostic methods	49	21	5	2	17	22	116
Poliomyelitis	3	12	3	0	1	0	19
Total	209	141	120	10	22	65	567
% of total	37	25	21	2	4	11	

NB. The total (567) exceeds the number of papers reviewed as some papers can fit into more than one category.

CHAPTER 3: HOW DOES BASIC SCIENCE SUPPORT CLINICAL RESEARCH?

Our main motive for trying to repeat Comroe and Dripps's study was to improve our understanding of how basic biomedical research feeds into and supports the development of clinical practice. Therefore, once we had reached the conclusion that, given the information provided in Comroe and Dripps's paper and report, we could not repeat their analysis, we re-appraised our approach and came up with a different methodology. In short, we felt that, using bibliographic databases and bibliometric techniques, we could evaluate how much basic research is underpinning the clinical advances that we identified in the Delphi survey. It must be remembered that Comroe and Dripps did not have access to the databases and techniques that we describe and utilize in this new analysis.

In this chapter we describe the revised methodology and the results of the analysis. In the final chapter we draw out a number of conclusions from this and the previous chapter and assess the policy implications of our analysis.

Bibliometric data and methodology

We decided to use the same methodology that we had developed for assessing the scientific basis of clinical practice guidelines.^{16, 17} Just as it is possible to build up a family tree by identifying a child's parents, grandparents and so on, it is possible to create a 'genealogy' for a clinical practice guideline or, in the current case, for a clinical advance, using citation analysis as illustrated in Figure 3.1. Once the 'genealogy' has been mapped, it is then possible to undertake bibliometric analysis on the cited papers at the different 'generations'.

For five clinical advances – mechanical ventilation, replacement surfactant, antenatal steroids, parenteral nutrition and ultrasound – we searched the Science Citation Index (SCI) for the years 1995–99 inclusive. This timescale was selected in order to collect a contemporary set of papers for each advance with a time span that would generate a sufficient number of papers to analyse. The search was made using the filter for neonatology developed in-house (see Annex B1), amended to limit the articles identified to the subject of interest by inserting key words, such as 'mechanical ventilation', 'mechanical respiration', 'replacement surfactant', 'artificial surfactant', 'antenatal steroids' and 'corticosteroid' (as illustrated in Annex B3). In the case of antenatal steroids, we combined the neonatology filter with the obstetrics/gynaecology filter (Annex B2) as antenatal steroids are provided to the expectant mother.

The articles identified via this search were labelled generation 1. The references contained in each of the generation 1 articles were collected and arranged in descending order, based on

the number of times each had been referenced. The top 5 per cent of these papers formed generation 2.^q By selecting the most cited papers we assumed that they were high impact and of importance to the development of the clinical advance. This methodology was repeated twice more, resulting in four 'generations' of articles per advance. Thus generation 1 contains the most recent papers (dating from 1995–99) while generation 4 contains the oldest papers, some dating from decades ago.

All the papers (i.e. generation 1, 2, 3 and 4 papers) were either looked up on the SCI or in libraries. Detailed bibliographic information was imported or entered into a bespoke database. In addition, all the papers were looked up in libraries to determine their funding sources by using standard methodology developed by the Wellcome Trust's Policy Unit.⁸ Extramural funding was taken from the formal acknowledgements section, (e.g. "We thank the Wellcome Trust for funding this study"), and intramural funding from the addresses (e.g. the MRC's National Institute for Medical Research in London). Funding bodies were classified into three main sectors: government (GOV), private-non-profit (PNP), and industry (IND). If the paper was not indexed on the SCI, then the extra or missing information (such as addresses, titles etc.) were also noted.

Analysis was based on either paper or journal details, and included examination of: (a) the knowledge cycle time, i.e. the time between a paper's publication and its citation by another paper in the 'parent' generation; (b) the country of authorship, based on analysis of the address fields; (c) the type of cited research, that is the extent to which the papers describe basic (or clinical) research; (d) the research setting, that is whether in a university or hospital or both, based on analysis of the address fields; and (e) source of funding, as measured by acknowledgements on papers.

The third analysis (i.e. c above) used a journal classification system developed and updated by CHI Inc., which is based on expert opinion and journal-to-journal citations, and has become a standard tool in bibliometric analyses.¹⁸ Journals are allocated into four hierarchical levels in which each level is more likely to cite papers in journals at the same level or the level below it and vice versa. Hence, only 4 per cent of papers in level 1 'clinical observation' journals (e.g. *British Medical Journal*) will cite papers in level 4 'basic' journals (e.g. *Nature*), compared to 8 per cent for level 2 'clinical mix' journals (e.g. *New England Journal of Medicine*), and 21 per cent for level 3 'clinical investigation' journals (e.g. *Immunology*). By looking at the journals in which papers cited on clinical advances are published, it is possible to characterize the

q In selecting the top 5 per cent, all papers that had been referenced an equal number of times to those in the mathematical top 5 per cent were also included. Therefore most generations of articles contain slightly more than 5 per cent of the article population.

research and estimate how long it takes for basic research to feed into clinical practice.

We adopted this approach as it eliminated the threat of rater bias, and allowed us to use a transparent, systematic and generally accepted method of identifying basic research. It also removes the hurdle of building our own definition of basic research. There are, however, two caveats. First, we made the assumption that the research levels of the journals have remained constant over time. Second, this type of analysis remains rather crude as it allocates all papers within a journal to one level, despite a strong likelihood that there is variation in the type of research published in any given journal.

Results from the bibliometric analysis

The number of articles identified and analysed, by advance and generation, is given in Table 3.1. The first row in this table ('Papers identified using SCI search, 1995–99') gives the first generation of papers. These were identified using the neonatology filter (and in the case of antenatal steroids, also the obstetrics and gynaecology filter), along with the advance-specific key words listed in Table 3.2. The second set of data refers to generation 2 papers, the third set to generation 3 papers and the fourth set to generation 4 papers. Duplicate papers were removed since a number of the generation 2 papers, for example, would have been cited more than once by different generation 1 papers. The number of times a paper was cited was recorded and those 5 per cent of papers that were referenced the most were then selected and used for the analysis. By selecting the most cited papers we assumed that they were high impact and of importance to the development of the clinical advance. In the case of replacement surfactant this means that the 321 generation 1 papers referenced 12 747 generation 2 papers, of which 5402 were unique (i.e. there were $12\,747 - 5402 = 7345$ duplicate references). If these 5402 papers were listed in descending order of the number of times they were cited, then the top 270 papers would fall within the fifth percentile. However, as the fifth percentile dissected papers which had been cited seven times, the citation boundary was extended to include all such papers (i.e. 306 in the case of replacement surfactant).

Table 3.1 also shows that the number of papers identified in generation 1 ranged from 321 (for replacement surfactant) to 58 (for total parenteral nutrition). As can be seen in Figure 3.2, the replacement surfactant advance actually grew (in terms of publication output) over the four generations of analysis, while the total parenteral nutrition stayed stable. In contrast, outputs in antenatal steroids and ultrasound decline over the four generations of analysis.

Table 3.1: The number of papers, references and duplicate papers per generation by the five clinical advances

	Mechanical ventilation	Replacement surfactant	Antenatal steroids	Parental nutrition	Ultrasound
Papers identified using SCI search for 1995–99	281	321	291	58	121
Total reference from generation 1 papers	7949	12 747	9063	1805	3147
Total unique references	5367	5402	6615	1432	2574
Top 5% of papers	281	306	392	77	352
Found papers	274	304	379	63	274
Citation boundary	4	7	3	3	2
Total reference from generation 2 papers	8157	10 295	15 040	1477	8711
Total unique references	4928	4660	10 345	1130	5460
Top 5% of papers	256	261	854	75	339
Found papers	250	250	800	61	279
Citation boundary	5	7	3	3	4
Total reference from generation 3 papers	6548	10 332	29 545	1293	7867
Total unique references	3574	4669	17 289	1025	4453
Top 5% of papers	183	226	926	58	244
Found papers	180	215	875	51	201
Citation boundary	6	7	5	3	5

Figure 3.1: Tracing the ‘research tree’

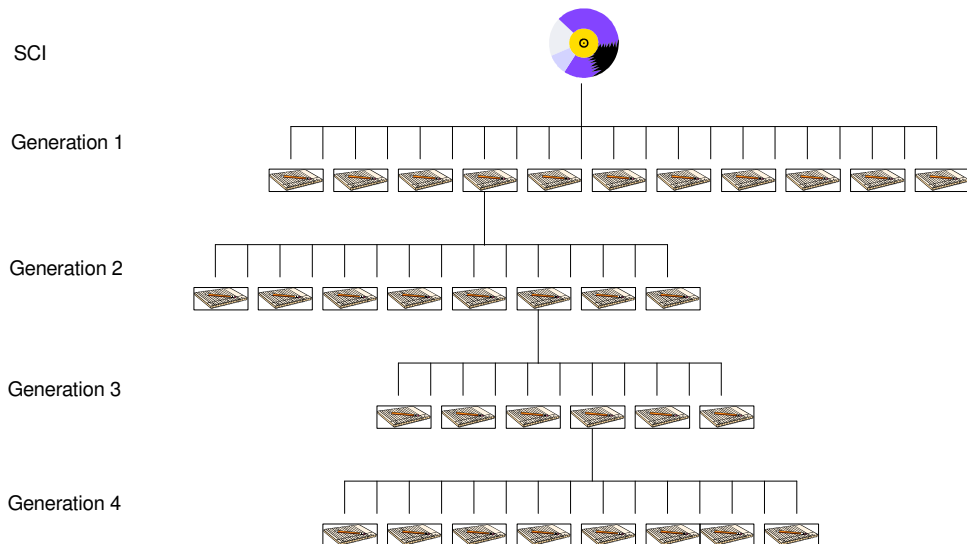
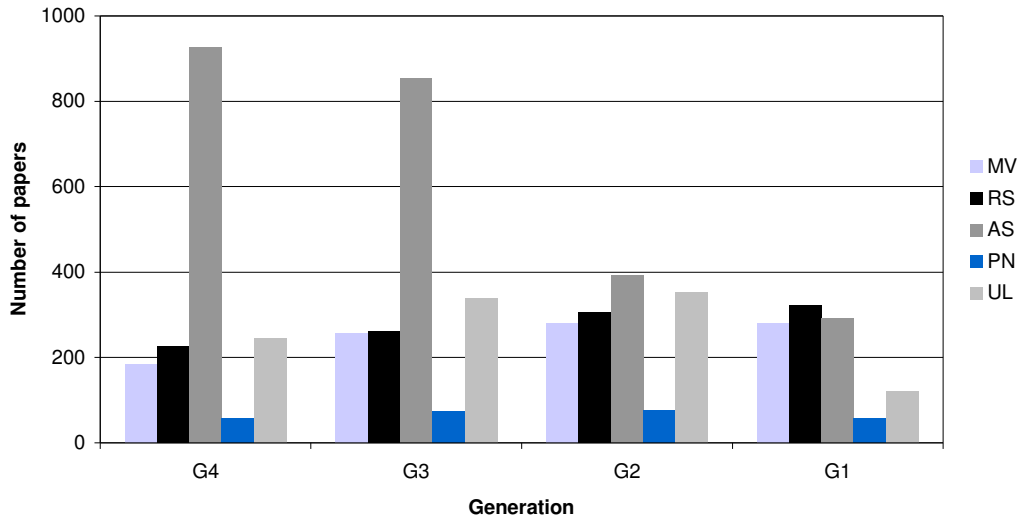


Figure 3.2: Number of papers per generation by advance

MV= mechanical ventilation; RS = replacement surfactant; AS = antenatal steroids; PN = parenteral nutrition; and UL = ultrasound



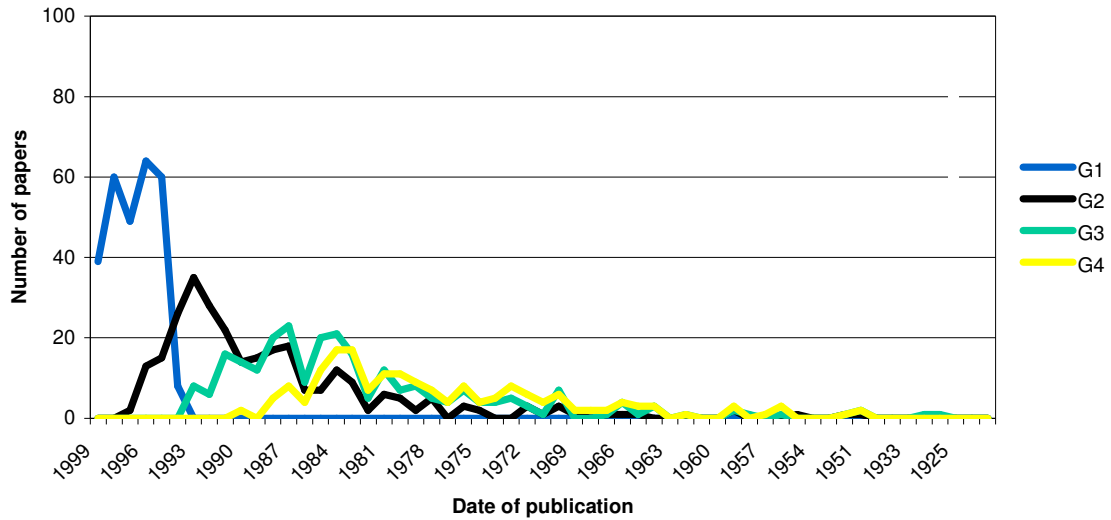
Knowledge cycle time

Previously we defined the knowledge cycle time as the median time between two generations of papers.^{15,16} This is illustrated in Figures 3.3a to 3.3e, which plot the number of papers published each year for each generation. For replacement surfactant (Figure 3.3b), the knowledge cycle time between generations 1 and 2 is five years (i.e. the difference between the median date of publication for the first generation, which is 1996, and the median date of publication for the second generation, which is 1991). It should be noted that the first generation papers are truncated, in the sense that we only looked at papers indexed on the SCI CD-ROMs for 1995–99, and that the second and subsequent generation represent those top 5 per cent of cited papers. Hence the point of real interest is the time between each generation of publication. This is summarized in Table 3.2, where the median publication date for each generation for the five clinical advances is tabulated. The overall time between generations 1 to 4 ranges from 13 years (for artificial surfactant) to 21 years (for parenteral nutrition). The other three advances took 17 years to develop through four generations of citations. It is worth remembering that we have only gone back four generations and therefore the knowledge cycle time is only for generations 1 to 4, and other generations (i.e. 5,6,7 etc.) would extend the time horizon.

Table 3.2: Median age of publication

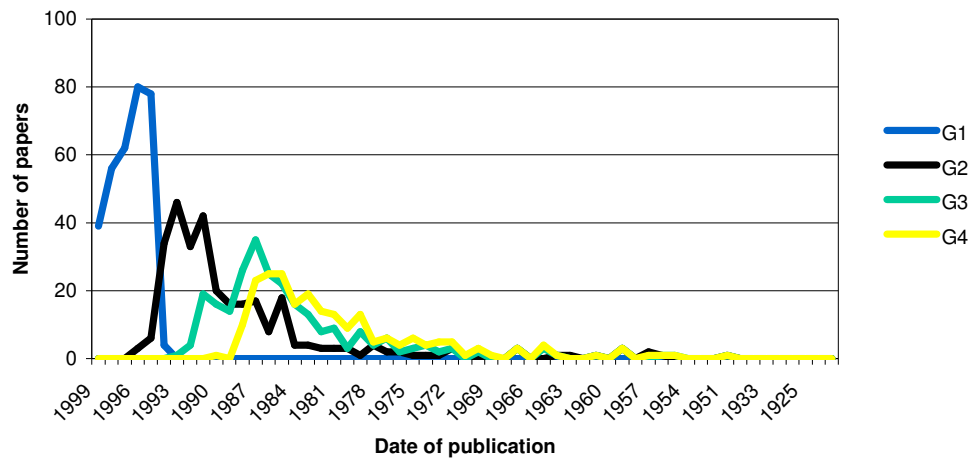
Generati on	Clinical advance				
	Mechanical ventilation	Replacemen t surfactant	Antenatal steroids	Parenteral nutrition	Ultrasound
G1	1997	1996	1997	1997	1997
G2	1990	1991	1991	1988	1998
G3	1985	1986	1985	1981	1984
G4	1980	1983	1980	1976	1980

Figure 3.3a: Number of papers per generation of mechanical ventilation by year of publication



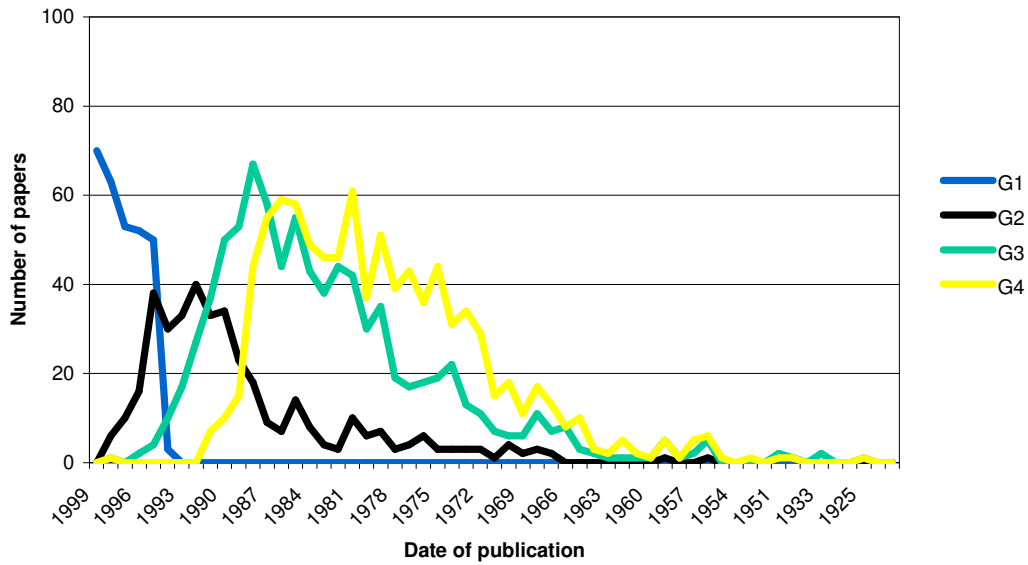
G1 refers to generation 1; G2 to generation 2 and so on.

Figure 3.3b: Number of papers per generation of replacement surfactant by year of publication



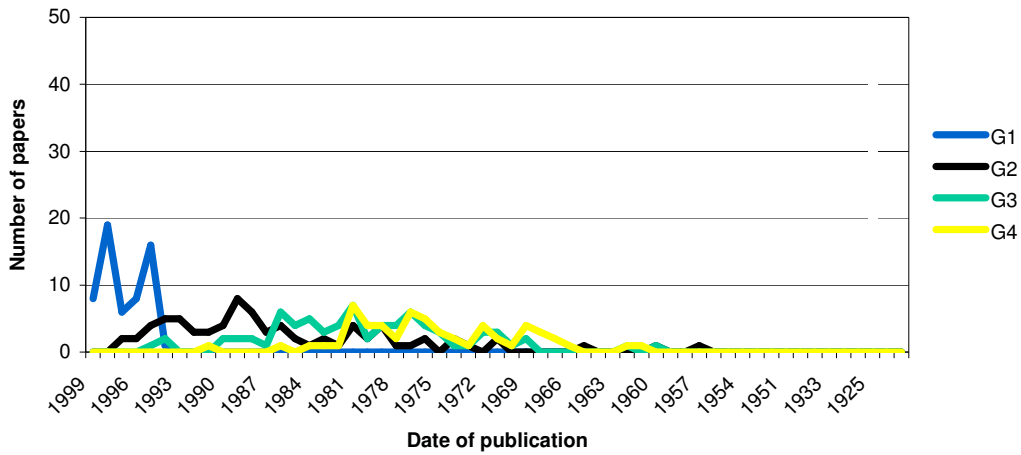
G1 refers to generation 1; G2 to generation 2 and so on.

Figure 3.3c: Number of papers per generation of antenatal steroids by year of publication



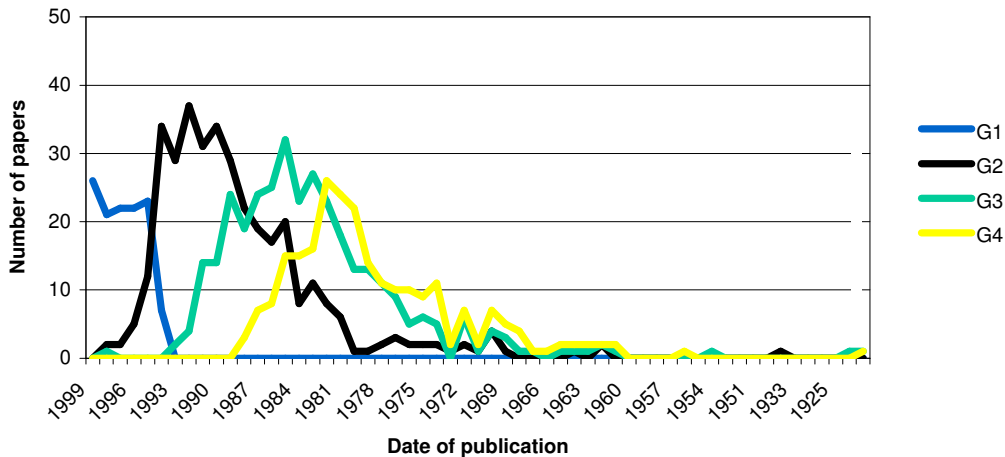
G1 refers to generation 1; G2 to generation 2 and so on.

Figure 3.3d: Number of papers per generation of parenteral nutrition by year of publication



G1 refers to generation 1; G2 to generation 2 and so on.

Figure 3.3e: Number of papers per generation of ultrasound by year of publication



G1 refers to generation 1; G2 to generation 2 and so on.

Country of authorship

Table 3.3 shows the distribution of papers by the country of the author and the generation of citation for the five clinical advances. The first row provides comparison data for 1998 taken from the SCI using a title keyword and specialist journal search strategy developed for biomedicine and described elsewhere.¹⁹ This shows that approximately four in ten biomedical research papers are authored by Americans, and one in ten papers by UK and Japanese scientists. By comparing the expected proportion of papers (i.e. outputs in 1998 by country)

with those first-generation papers, it is possible to identify those countries which have a comparative research advantage for a particular advance. For example, Canada and the UK are particularly strong in research supporting parenteral nutrition – Canada produces nearly five times more papers than expected (i.e. 23/5), and the UK more than twice as much as expected (i.e. 25/10). Conversely the USA and the other G7 countries are weak in this area. A second observation to be made from Table 3.3 is that the contribution from the USA declines from the oldest (generation 4) papers to the most recent (generation 1) papers by between 22 (mechanical ventilation) and 41 (parenteral nutrition) percentage points over the four generations analysed.

Type of research

The next analysis was based on the journals in which each generation of papers was published, and was used to determine the extent to which basic or clinical research underpinned the five clinical advances. The papers were split into four categories or levels: level 1 (clinical observation), level 2 (clinical mix), level 3 (clinical investigation) and level 4 (basic research). In addition, a proportion of journals did not have a research level. Table 3.4 illustrates the number of papers (*n*) and the proportion of papers (%) for each research level by generation for each of the five clinical advances. A number of observations can be made from this table. First, and as illustrated in Figure 3.4, the distribution of papers (across all generations) varies between each clinical advance and the portfolio of UK biomedical research published between 1988 and 1995. Second, it is notable that over a third of papers did not have a research level (and this is, in part, addressed in the following analysis on research setting). Finally, as illustrated in Figure 3.4, across all five advances, but especially so for replacement surfactant and antenatal steroids, there is a decrease in the proportion of papers published in basic journals, ranging from the oldest (generation 4) papers to the more recent (generation 1) papers (Figure 3.5). In other words, generation 4 papers are more likely to be describing basic research than generation 1 papers.

Setting of research

Given that over a third of papers did not have a research level (Table 3.4), we decided to try and develop a new method based on research setting. This we defined as being in a hospital (and thus included the string 'HOSP', 'NHS' and 'INFIRM' in the address field) or in a university (and included the string 'UNIV', 'COLL' and 'SCH' in the address field). The results of this analysis are presented in Table 3.5. Between 60 per cent (mechanical ventilation and antenatal steroids) and 75 per cent (parenteral nutrition) of research occurred in universities, while between 26 per cent (antenatal steroids) and 55 per cent (parenteral nutrition) of research occurred in hospitals (note that this figures can add up to more than a 100 per cent

as research can occur in both places). In developing this methodology, we hypothesized that university research may proxy basic research and that hospital research would be predominately clinical. It is therefore interesting to note how the proportion of hospital research increased from (the oldest) generation 4 papers (e.g. 20 per cent for replacement surfactant) to the (most recent) generation 1 papers (e.g. 48 per cent), and this increase is consistent over all five advances and ranges between six and 28 percentage points.

Table 3.3: Distribution of papers by country of publication and mean number of authors per paper, by generation and clinical advance

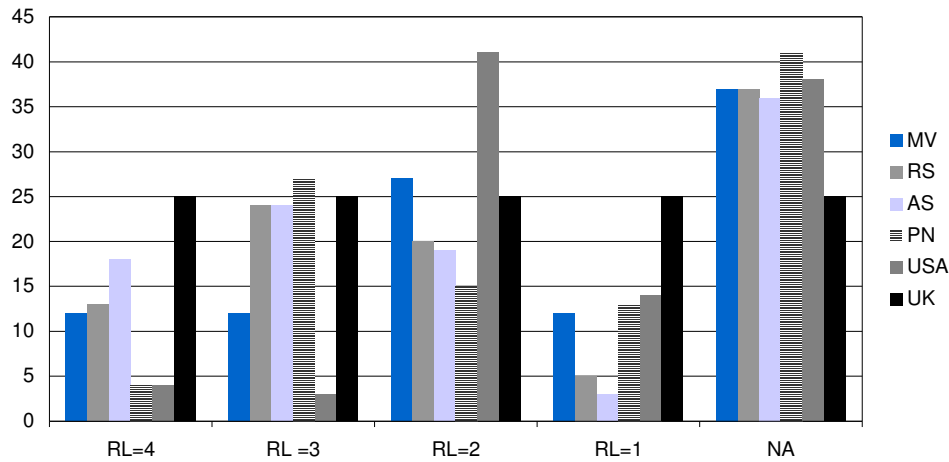
		Authors/ paper	Proportion (%) of papers with address from G7 country						
			USA	UK	Japan	France	Germany	Italy	Canada
Biomedicine (1998)		–	41	10	10	6	8	4	5
Mechanical ventilation	G1	4.42	48	10	2	4	12	1	5
	G2	2.32	61	13	2	4	3	1	14
	G3	2.36	68	14	2	2	2	1	11
	G4	5.38	70	12	2	1	2	0	12
	All	4.33	58	12	2	3	6	1	11
Replacement surfactant	G1	3.26	52	7	5	3	9	4	6
	G2	4.41	67	5	5	1	5	1	9
	G3	4.27	72	6	6	0	3	0	11
	G4	3.50	72	6	6	0	2	0	12
	All	3.75	64	6	5	1	6	2	8
Antenatal steroids	G1	3.31	46	11	5	2	4	3	9
	G2	2.89	64	12	2	1	3	1	8
	G3	3.15	73	8	1	3	3	1	9
	G4	3.08	73	6	2	4	3	0	8
	All	3.08	66	9	2	3	3	1	8
Parenteral nutrition	G1	2.59	32	25	0	2	2	0	23
	G2	2.90	40	17	2	5	5	2	24
	G3	1.72	56	20	0	3	3	0	15
	G4	2.20	73	12	0	0	0	0	16
	All	2.47	50	18	1	3	3	1	18
Ultrasound	G1	1.58	26	19	3	6	5	3	5
	G2	2.48	48	27	1	0	1	2	4
	G3	2.27	47	27	3	1	0	0	9
	G4	2.40	50	27	2	1	0	0	9
	All	2.19	46	23	2	2	1	2	7

Table 3.4: Research level of papers, by generation and clinical advance

		Research level									
		Basic (RL = 4)		Clinical investigation (RL=2)		Clinical mix (RL=3)		Clinical observation (RL = 1)		Not available	
Mechanical ventilation	G1	21	10%	31	14%	56	26%	44	20%	68	31%
	G2	26	9%	27	10%	73	27%	27	10%	121	44%
	G3	45	18%	26	10%	68	27%	18	7%	93	37%
	G4	33	18%	28	15%	46	26%	9	5%	65	36%
	All	86	12%	80	12%	188	27%	81	12%	254	37%
Replacement surfactant	G1	21	8%	95	35%	68	25%	25	9%	60	22%
	G2	43	14%	54	18%	73	24%	11	4%	123	40%
	G3	39	16%	39	16%	49	20%	4	2%	119	48%
	G4	45	21%	39	18%	30	14%	2	1%	99	46%
	All	102	13%	187	24%	159	20%	43	5%	292	37%
Antenatal steroids	G1	27	11%	68	28%	81	33%	15	6%	52	21%
	G2	59	16%	83	22%	88	23%	12	3%	137	36%
	G3	140	18%	178	22%	147	18%	19	2%	317	40%
	G4	198	23%	192	22%	136	16%	11	1%	339	39%
	All	309	18%	408	24%	323	19%	53	3%	602	36%
Parenteral nutrition	G1	1	2%	14	32%	6	14%	11	25%	12	27%
	G2	3	5%	20	32%	11	17%	6	10%	23	37%
	G3	3	5%	14	23%	10	16%	5	8%	29	48%
	G4	2	4%	9	18%	9	18%	3	6%	28	55%
	All	7	4%	47	27%	27	15%	22	13%	72	41%
Ultrasound	G1	3	3%	3	3%	30	34%	21	24%	31	35%
	G2	16	6%	6	2%	107	39%	35	13%	110	40%
	G3	12	4%	9	3%	110	39%	31	11%	117	42%
	G4	4	2%	10	5%	90	45%	19	9%	78	34%
	All	22	4%	20	3%	251	41%	85	14%	235	38%

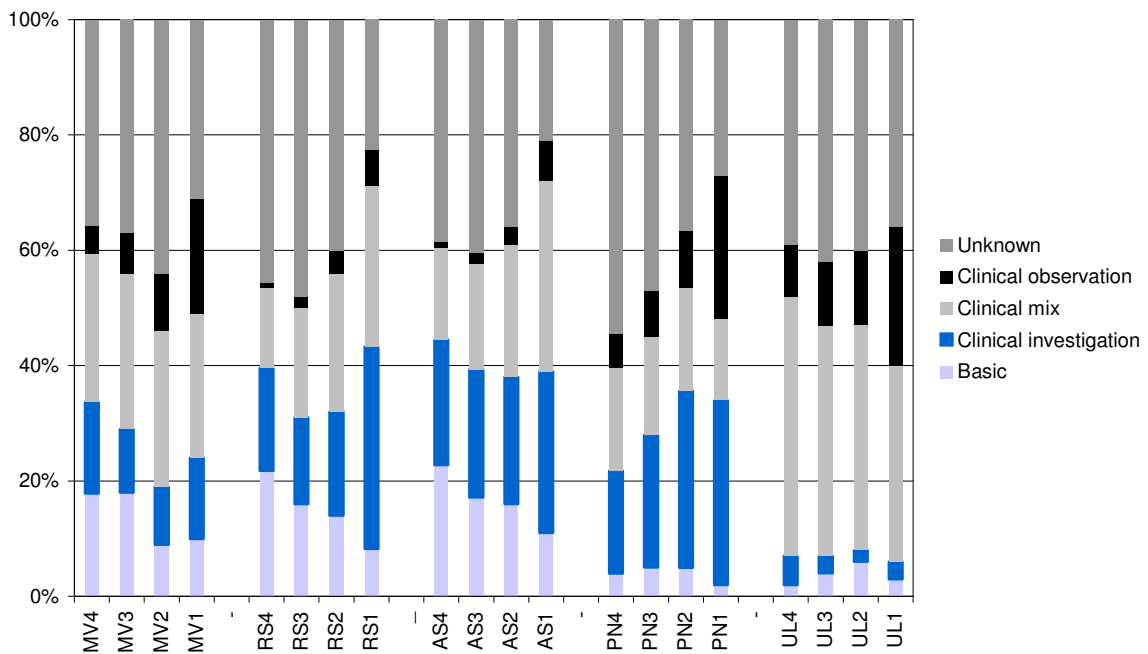
NB. The sum of the four generations of papers is greater than all the papers, as some papers can occur in multiple generations.

Figure 3.4: Proportion of papers by research level for five clinical advances and for UK & USA biomedical outputs



MV= mechanical ventilation; RS = replacement surfactant; AS = antenatal steroids; PN = parenteral nutrition; and UL = ultrasound. (USA and UK data are provided as comparators.)

Figure 3.5: Proportion of papers by research level for five clinical advances



MV= mechanical ventilation; RS = replacement surfactant; AS = antenatal steroids; PN = parenteral nutrition; and UL = ultrasound. The numbers refer to generations 1 to 4. For example, RS2 refers to replacement surfactant generation 2.

Table 3.5: Research setting of papers, by generation and clinical advance

		Research setting							
		University		Hospital university and		Hospital		Other	
Mechanical Ventilation	G1	149	68%	56	26%	96	44%	30	14%
	G2	141	51%	46	17%	113	41%	65	24%
	G3	154	62%	47	19%	103	41%	39	14%
	G4	116	64%	36	20%	66	37%	33	19%
	All	414	60%	141	20%	289	42%	127	19%
Replacement surfactant	G1	195	72%	88	33%	130	48%	31	12%
	G2	182	60%	70	23%	109	36%	82	17%
	G3	154	62%	39	16%	70	28%	65	16%
	G4	130	60%	25	12%	44	20%	66	31%
	All	494	63%	175	22%	281	36%	177	23%
Antenatal steroids	G1	181	74%	59	24%	89	37%	31	13%
	G2	217	57%	61	16%	120	32%	101	27%
	G3	484	61%	120	15%	206	26%	228	29%
	G4	506	58%	119	14%	186	21%	300	35%
	All	1011	60%	262	15%	437	26%	503	30%
Parenteral nutrition	G1	32	73%	19	43%	26	59%	5	11%
	G2	49	78%	26	41%	34	54%	6	10%
	G3	47	77%	22	36%	29	48%	6	11%
	G4	39	76%	21	41%	27	53%	6	12%
	All	131	75%	74	42%	97	55%	20	12%
Ultrasound	G1	51	58%	29	33%	54	61%	11	14%
	G2	190	69%	80	29%	137	50%	25	10%
	G3	186	67%	73	26%	132	47%	33	12%
	G4	131	65%	45	22%	89	44%	24	13%
	All	413	67%	169	28%	299	44%	65	11%

NB. The sum of the four generations of papers is greater than all the papers, as some papers can occur in multiple generations.

Support for research

The distribution of funding body acknowledgements by sector is shown in Table 3.6. For all the cited papers which were found, between 24 per cent (ultrasound) and 38 per cent (replacement surfactant) acknowledged the private not-for-profit sector (PNP), between 3 per cent (ultrasound) and 22 per cent (parenteral nutrition) industry and between 34 per cent (ultrasound) and 66 per cent (antenatal steroids) government. A further 24 per cent (replacement surfactant) and 51 per cent (ultrasound) of papers did not have a funding body acknowledgement. In the UK these papers are typically published from either NHS hospitals or universities, and therefore they may represent public-sector support. Hence the final column of data in ('public') is the combined output of government and unacknowledged (that it, 'none').

Table 3.6: Acknowledged funding sector by generation and clinical advance

		Funding acknowledgement									
		PNP		Industry		Government		No acknowledgment		Public	
Mechanical Ventilation	G1	59	27%	38	17%	86	39%	96	44%	168	83
	G2	77	28%	55	20%	151	55%	77	28%	205	83
	G3	71	28%	43	17%	156	62%	56	22%	187	84
	G4	49	27%	31	17%	128	71%	33	18%	136	88
	All	194	28%	115	17%	368	53%	215	31%	649	84
Replacement surfactant	G1	86	32%	60	22%	116	43%	105	39%	221	83
	G2	117	38%	55	18%	202	66%	57	19%	259	85
	G3	43	45%	30	12%	199	80%	32	13%	131	93
	G4	89	41%	20	9%	168	78%	35	16%	203	94
	All	248	38%	134	17%	491	63%	188	24%	679	87
Antenatal steroids	G1	79	33%	25	10%	113	47%	87	36%	200	83
	G2	126	33%	35	9%	220	58%	113	30%	333	88
	G3	275	34%	68	9%	549	69%	195	24%	744	93
	G4	333	38%	72	8%	646	74%	179	20%	825	94
	All	610	36%	145	9%	1112	66%	425	25%	1547	91
Parenteral nutrition	G1	10	23%	11	25%	22	50%	21	48%	43	98
	G2	19	30%	19	30%	34	54%	18	29%	52	83
	G3	8	13%	5	8%	25	41%	31	51%	56	92
	G4	11	22%	10	20%	28	55%	19	37%	47	92
	All	43	25%	39	22%	91	52%	65	37%	156	89
Ultrasound	G1	14	16%	3	3%	19	22%	64	77%	83	99
	G2	70	26%	9	3%	99	36%	130	47%	229	83
	G3	69	25%	10	4%	108	39%	124	46%	237	85
	G4	61	30%	6	3%	83	41%	78	39%	261	80
	All	148	24%	20	3%	207	34%	315	51%	522	85

NB. The sum of the four generations of papers is greater than all the papers, as some papers can occur in multiple generations.

These numbers fall in the range of UK biomedical outputs in 1995, where 32 per cent of papers acknowledged the PNP, 17 per cent industry and 34 per cent government (33 per cent of papers have no funding acknowledgment).^r In addition to the variation in funding profile for each of the clinical advances, it is notable that acknowledged government funding actually decreased over the four generations.

^r Note that the percentages add up to more than 100 per cent as papers can acknowledge more than one funding sector.

Summary

In this chapter we have developed and applied a new bibliometric protocol to assess the scientific basis of neonatal intensive care. By looking at five clinical advances deemed by experts to be the most important over the past 30 years, we have analysed how basic research has fed into clinical practice and have profiled research outputs at different generations. In the next chapter we attempt to interpret these findings and highlight some of the limitations associated with this revised methodology.

DISCUSSION AND IMPLICATIONS

We began this project two years ago in naive trepidation. As strong advocates for developing an evidence base for research policy by researching research, we were fully aware of the limitations of Comroe and Dripps's study. We also knew that the original study took ten years to complete and that, sadly, Julius Comroe died during this time.

Therefore in concluding this report, it is perhaps worth noting how Comroe and Dripps themselves summed up their original study:

“The conclusions of our study are diametrically opposite to those of Project Hindsight, a 1966 study by the Department of Defense (DOD) on research and development of military hardware. Because no extensive study of this type had been done in the field of biomedical research and development and because such research is both time consuming and difficult, many policy makers were satisfied to extrapolate the conclusions of the DOD study on military hardware to the entirely different field of biomedical research. Without questioning the validity of the DOD study, we can now state with confidence that it was incorrect of Presidents, Congress and the Office of Management to make this extrapolation.”

We find it striking how we have reached a similar conclusion. Our current study – if not ‘diametrically opposed’ to the Comroe and Dripps’s work – at least questions the validity of their results. We therefore have major concerns that Comroe and Dripps’s findings have, seemingly, been ‘extrapolated’ to biomedical science policy as demonstrated by the increased support for basic research shown in Figures 1.1–1.4.

At the same time, we are conscious that we have not necessarily met the challenge of improving on Comroe and Dripps. We have, in our opinion, indisputably demonstrated that their study – as reported – is not repeatable, reliable or valid. However, we would also be the first to accept that there are significant limitations to the revised methodology and conclusions that we present in this report. That said, we do believe that there are some legitimate policy issues that arise from this study and therefore, in this chapter, we highlight the methodological challenges and draw out some policy conclusions.

Methodological caveats

We would highlight three issues that need consideration in interpreting the results of this study. The first is the sensitivity of our bibliometric search filters; the second is the

measurement of basic and clinical research; the third is the legitimacy of making 'inter-advance' comparisons given that each clinical advance is likely to have a unique development cycle, starting at different points in history.

The sensitivity of bibliometric search filters

As explained in the previous chapter, we adopted a bibliometric approach in defining the essential bodies of knowledge of each clinical advance. This permitted us to claim that our sample was systematic and transparent in the sense that any other independent researcher could use the filters present in Appendix B and the appropriate version of the SCI and repeat this study. The disadvantage of this method was that the bibliometric search filters were an expert's opinion of what a particular field (neonatology or obstetrics and gynaecology) looked like. Also, as with any keyword search methodology, we are likely to have included some papers that were not related to the clinical advance and excluded others that were associated with the clinical advance.

Obviously it is not possible to measure those unknown papers, but we could review those papers that were identified by the search filter and see which ones were not associated with an advance. We therefore looked at antenatal steroids and asked a member of our expert advisory group to review the sensitivity of our search filter. We chose antenatal steroids as we felt that this would provide a 'worst-case' example given that it is based in the intersection of two filters with added keywords. Using MEDLINE, we looked up and printed the abstracts of all the generation 1 papers. Of the 291 generation 1 papers, 280 were identified on MEDLINE.

These papers were then classified into three groups:

- antenatal use of steroids (i.e. relevant to development of the lungs in human or animal);
- postnatal use of steroids (i.e. looking at the effects on lungs, other organs and follow-up);
- irrelevant, or too distant, from the effects of antenatal steroids on lungs.

This analysis resulted in 56 of the 280 papers (i.e. 20 per cent) being classified as 'irrelevant', although it is difficult to say whether this is satisfactory and what impact it has on the subsequent analyses.

Defining basic and clinical research

One of the key purposes of this study was to understand the relationship between basic and clinical research. Therefore, by necessity, we had to define what we meant by basic and clinical research. We used two indicators – research levels and research setting. As explained

in Chapter 3, research levels are a crude indicator as they are based on analysis of the journal of publication, despite the likelihood that there is variation in the type of research that is published in any given journal. Therefore we developed a research setting indicator, which was based on the hypothesis that research undertaken in a university was basic, and that research undertaken in a hospital setting was clinical. This was an assumption underlying the analysis and if wrong, would undermine our conclusions.

The legitimacy of inter-advance comparisons

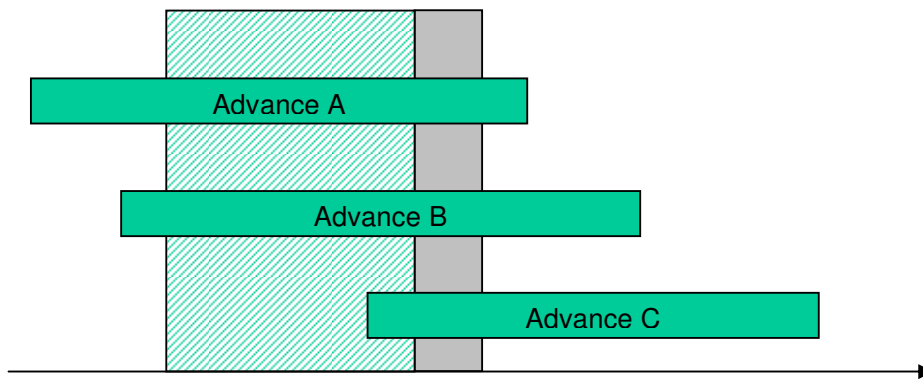
One further consideration in interpreting this analysis is that we have compared advances cross-sectionally. This is perhaps best illustrated in Figure 4.1, where we have depicted three advances as horizontal lines. The first advance (A) has a long history while the third advance (C) is a relatively new discovery. The shaded horizontal box is the time period we used to define our generation 1 papers, that is publications between 1995 and 1999, while the unshaded box illustrates those generation 2–4 papers picked up through the citation tracing analysis.

From Figure 4.1 it is apparent that the three advances are at different stages in their development cycle at the point of exposure to the bibliometric analysis. Therefore it is likely that advance A will be dominated by more clinical papers than advance C. One way to calibrate the development process would be to compare the time when an advance was first evaluated, using a human population (i.e. through a randomized controlled trial). For example, in Figures 2.3 and 2.4 there are boxes relating to human trials. The one for replacement surfactant refers to a paper published in 1980,²⁰ while the one for antenatal steroids refers to a study published in 1972.²¹ This would suggest that the development of antenatal steroids would be more clinically advanced than replacement surfactant. However, a comparison of the data describing research type (Table 3.4 and Figure 3.5) and research setting (Table 3.5) reveals that the reverse is true: there are proportionately more, albeit marginally, generation 1 basic research papers describing antenatal steroids (11 versus 8 per cent; Table 3.4) and proportionately fewer generation 1 papers being published from a hospital setting (37 versus 48 per cent; Table 3.5).

Such an observation is difficult to interpret. It may be because the point of calibration is inappropriate. For example, we do know that there was considerable time between the 1972 trial and the uptake of antenatal steroids in clinical practice and a more appropriate – but harder to define – calibration point may be when an advance was first used in a routine non-evaluative setting. An alternative method (and study) would be to start with more basic or early clinical science and try to follow the development, using citation tracing, through to

clinical advance. Rather than working back from the desired outcome to the science base, this approach would look forward (with hindsight), thus ensuring that all advances are starting at the same point in time. Indeed, in collaboration with the Health Economics Research Group at Brunel University, we are in the process of piloting such a study that should further inform our understanding of the relationship between basic and clinical research.

Figure 4.1: Schema illustrating difficulties in comparing advances



Policy implications

Because of these methodological limitations, this study may raise more questions than it answers. That said, it does raise three important science policy issues that we address below.

Developing public accountability and support for science

In their concluding chapter Comroe and Dripps have a section entitled *Public Support of Science*. Given that this report was published in 1977, and considering the current debate surrounding public engagement in science,²² it is interesting to note Comroe and Dripps's visionary comments that: "Public support of science depends in part on public understanding that a major advance is actually the achievement of innumerable scientists... This will require some change in science education, from elementary schools through professional medical education; in science writing; in the scientist's presentation of his own work to other scientists and to the public." Indeed, we have argued in the past that we need to undertake research to develop our understanding of how research funding impacts on healthcare to enhance public perception and understanding of biomedical science and the scientific process.^{16, 17}

Given these comments, it was serendipitous that, in the process of the current study, we identified an exemplar of how basic research feeds into clinical research and healthcare. The work of Liggins (1969) was originally funded by the Wellcome Trust and examined how, when glucocorticoids triggered the onset of labour in pregnant sheep, the lambs born prematurely

had well aerated lungs, while many of the control animals died of respiratory distress syndrome (RDS).²³ It is possible to trace this original, basic scientific, observation from animal studies, through to randomized controlled trials on humans, (systematic) literature reviews, economic evaluations, policy recommendations, practice reviews and, more recently, analysis of research payback. Today, in the UK, the use of corticosteroids (described as ‘antenatal steroids’ by our Delphi survey participants), is the norm when preterm delivery is expected.²⁴ An NIH economic assessment claimed that, between 1976 and 1983, US\$7.4 million was spent on research evaluating the use of antenatal steroids and, in terms of reduced treatment costs, this produced a potential annual saving of between US\$16.5 million and US\$145.1 million. The complexity of some of the various stages of this advance were demonstrated in initial payback analysis,²⁵ but will be described in a forthcoming paper.²⁶ However, this example is particularly interesting for a number of reasons. First, the original research was sponsored by the Wellcome Trust and presents an excellent ‘good news story’ for promoting the work of the Trust. Second, if it were not for the use of animal models the clinical advance, and associated health benefit, is unlikely to have occurred, and therefore this case study illustrates the need for, and the use of, animals in research. Thirdly, there was a considerable time lag between the basic research (1969) to development and widespread clinical use (1999), illustrating the slow and incremental nature of much of scientific progress. Finally, the development and ultimate success (in terms of improving human and animal health) of the basic research described by Liggins (1969) could not have been predicted at the time of the study.

The time between discovery and application

As this study has shown, the process of following an initial discovery through to clinical advance is highly complex. One of the most striking features of our analysis was how similar the knowledge cycle time was across the five clinical advances (Table 3.2 and Figures 3.3a–e). The overall median time of publication between the (oldest) generation 4 papers and the (more recent) generation 1 papers was 13 years for artificial surfactant, 17 years for mechanical ventilation, antenatal steroids and ultrasound, and 21 years for parenteral nutrition. This is nearly identical to the findings of a methodologically similar, but independent, study that used clinical guidelines^{16, 17} and showed that it takes about 17 years for the fourth-generation research papers to feed into a clinical guideline. From a policy viewpoint, this begs the questions as to what is the optimum time for research to be fully evaluated and put into practice, and whether this process needs to and can be speeded up.

Role of basic science in supporting clinical advance

The relationship between basic research, and how it supports clinical research, is at the core of any biomedical research strategy. The unifying mission of all biomedical research funders is to improve healthcare. As we have seen in Chapter 1 (Figures 1.1–1.4), support for basic research is high and has been on the increase for the past decade.

Using the revised bibliometric protocol, we have shown in this study that after four generations of citation, between 2 per cent and 21 per cent of research was basic (Table 3.4). This corroborates the findings of the clinical guidelines study^{16, 17} that showed that after four generations of citation only 8 per cent of research was basic. These two observations are at odds with Comroe and Dripps's finding that 40 per cent of all research articles judged to be essential for latter clinical advance were not clinically oriented at the time of the study, thus undermining the evidence base that has, in the past, supported the increased funding of basic research.

We are not arguing that research funders should not be supporting basic research, but we are making the case that there needs to be a greater understanding of how basic research supports clinical advances and, in light of these conclusions, a critical reappraisal of current research funding priorities. Indeed, perhaps it is the advocacy of evidence-based policy that confirms Comroe and Dripps's work as truly seminal.

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APPENDIX A: QUESTIONNAIRE



The Wellcome Trust

Factors that lead to advances in neonatal intensive care

Instructions for participants

The purpose of this questionnaire is to identify the *most* important advances that have occurred in the development of neonatal intensive care since 1960. We wish to ensure that the resulting list of the most important advances reflects the considered opinion of experts within this speciality.

Please indicate the ten advances that you believe have been most important in the development of neonatal intensive care from 1960 onwards. Please do not prioritise your choices.

The definition of neonatal intensive care we are working to is,

‘The nursing and medical care required for a neonate where one or more organ systems require continuous support and monitoring’

Please return to The Wellcome Trust in the prepaid envelope, or by fax (0171 6118742) by Friday 15th October, or at your earliest convenience.

We look forward to receiving your responses.

If you have any queries regarding the completion of this questionnaire, please contact Elizabeth Green or Barbara Mason, Research Officers, on 0171 6117206.

Name

Job Title

Length of time in the field **(Years)**

Please tick the ten most important advances

Phototherapy

Total Parental Nutrition

Increased understanding of the physiology of the neonate

Recognition of the importance of early feeding

Temperature control

Development of neonatology as a subspeciality (training of clinicians and nurses devoted to this field)

Development of artificial Surfactant

Use of antenatal steroids

Development of neonatal intensive care 'units'

Communication and collaboration between obstetrician and paediatrician

Antibiotics for the newborn

Mechanical ventilation

Use of antenatal steroids

Improved resuscitation techniques

Endotracheal intubation

Continuous monitoring of vital signs

Involvement of parents in care and decision making

Ultrasound imaging

Surgical techniques specifically for neonates

Follow-up studies of very low birth weight and preterm babies

Monitoring methods specifically designed for babies

Introduction of plastic tubing, cannulas etc.

Measurement of biochemical variables of neonates

Use of incubators

Transport of mothers and babies at risk

CPAP

Management of neonatal jaundice

Use of microsamples for pathological analysis

Thank you for your assistance.

APPENDIX B: BIBLIOMETRIC SEARCH FILTERS

B1 Neonatology filter

1. Field:: Abbr journal
Statement:: BIOL-NEONATE OR CLIN-PERINATOL OR EARLY-HUM-DEV OR J-PERINATAL-MED
2. Field:: Abbr journal
Statement:: ACTA-PAEDIAT OR ARCH-DIS-CHILD OR ARCH-PEDIATR-ADOLESC-MED OR ARCHIVES-PEDIATRIE OR CHILD-NERV-SYST OR CLIN-PEDIAT OR DEVELOP-MED-CHILD-NEUROL OR EUR-J-PEDIAT
3. Field:: Abbr journal
Statement:: EUR-J-PEDIATR-SURG OR INT-J-PED-OTORHINOLARYNGOL OR J-CHILD-NEUROL OR J-DENT-CHILD OR J-PAEDIATR-CHILD-HEALTH OR J-PEDIAT OR J-PEDIAT-ENDOCRINOL OR J-PEDIAT-GASTROENTEROL-NUTR OR J-PEDIAT-HEMATOL-ONCOL OR J-PEDIAT-SURG
4. Field:: Abbr journal
Statement:: J-PEDIATR-ENDOCRINOL-METAB OR J-TROP-PEDIAT OR MED-PEDIAT-ONCOL OR NEUROPEDIATRICS OR PAEDIATR-PERINAT-EPIDEMIOL OR PEDIAT-CARDIOL OR PEDIAT-CLIN-N-AMER OR PEDIAT-INF-DIS-J OR PEDIAT-NEUROSURG OR PEDIAT-PULM
5. Field:: Abbr journal
Statement:: PEDIAT-RADIOL OR PEDIAT-RES OR PEDIATR-HEMATOL-ONCOL OR PEDIATR-PATHOL-LAB-MED OR PEDIATRICS OR J-DEVELOP-PHYSIOL
6. Field:: Title
Statement:: APNEA OR ASPHYXIA OR HYPOXIA OR IMMATUR* OR PREMATUR* OR RESPIRATORY DISTRESS SYNDROME OR RETINOPATH* OR SURFACTANT
7. Field:: Set
Statement:: 6 AND (2 THRU 5)
8. Field:: Title
Statement:: AFTER BIRTH OR BIRTH RELATED OR (BIRTH* AND WEIGH* AND (G OR LESS)) OR BRONCHOPULMONARY DYSPLASIA OR ECMO OR ELBW OR EXTRACORPOREAL MEMBRANE OXYGENATION OR (FIRST MONTH AND LIFE) OR FULL TERM
9. Field:: Title
Statement:: ((FETAL OR FETUS) AND (BREATHING OR CEREBRAL OR HYPOXIA OR LUNG OR NMDA OR OXYGEN* OR TERM)) OR HUMAN MILK OR HYPOXI* ISCHEMI* OR INFANT FORMULA OR (INFANT* AND TERM) OR INFANT* DELIVER*
10. Field:: Title
Statement:: ((INTRAVENTRICULAR OR PERIVENTRICULAR) AND (HEMORRHAGE OR LEU*OMALACIA)) OR LBW OR LOW BIRTH WEIGHT OR MECONIUM ASPIRATION OR MILK FORMULA* OR NEAR TERM OR NECROTIZING ENTEROCOLITIS OR NEONAT* OR NEWBORN*

-
11. Field:: Title
Statement:: PERINATAL OR POSTHEMORRHAGIC HYDROCEPHALUS OR POSTNATAL OR
PRE TERM OR (PREMATUR* AND (INFANT* OR RETINOPATHY)) OR (PRENATAL NOT
(DETECT* OR DETERMIN* OR DIAGNOS* OR SCREEN*)) OR PRETERM
 12. Field:: Title
Statement:: (PROGRAM* AND (METABOLISM OR NUTRITION* OR PROTEIN)) OR
PULMONARY HEMORRHAGE OR SGA OR SMALL FOR GESTATIONAL AGE OR VLBW
 13. Field:: Title
Statement:: CHICK* OR EMBRYO*
 14. Field:: Set
Statement:: (1 OR (7 THRU 12)) NOT 13
 15. Field:: Set
Language:: <No Limit>
Doctype:: Article
Update:: <No Limit>
Statement:: 14
 16. Field:: Set
Doctype:: Note
Statement:: 14
 17. Field:: Set
Doctype:: Review
Statement:: 14
 18. Field:: Set
Statement:: 15 THRU 17

B2 Obstetrics/Gynaecology filter

1. Field:: Abbr journal
Statement:: ACTA-OBSTET-GYNECOL-SCAND OR AMER-J-OBSTET-GYNECOL OR AMER-
J- REPROD-IMMUNOL OR ARCH-GYNECOL-OBSTET OR BAILLIERE-CLIN-OBSTET-GYN
OR BRIT-J-OBSTET-GYNAECOL OR CLIN-OBSTET-GYNECOL OR CLIN-PERINATOL OR
CONTRACEPTION
Field:: Abbr journal
2. Field:: Abbr journal
Statement:: EUR-J-OBSTET* OR FERT-STERIL OR GEBURTSFRAU* OR GYNECOL-
OBSTET-INVEST OR GYNECOL-ONCOL OR HUM-REPROD OR HYPERTENS-PREGNANCY
OR INT-J-FERTIL-MENOPAUSAL-STUD OR INT-J-GYNECOL- CANCER OR INT-J-
GYNECOL-OBSTET OR INT-J-GYNECOL-PATHOL
3. Field:: Abbr journal
Statement:: J-GYNECOL-SURG OR J-REPROD-IMMUNOL OR J-REPROD-MED OR J-SOC-
GYNECOL-INVESTIGATION OR MOL-REPROD-DEV OR OBSTET-GYNECOL OR OBSTET-
GYNECOL-CLIN-N-AMER OR PLACENTA OR PRENATAL-DIAG OR REPROD-FERT-

DEVELOP OR REPROD-TOXICOL

4. Field:: Title
Statement:: ABORTION* OR AMNIO* OR ANDROGEN OR ANTENATAL OR BARTHOLIN* OR (BIRTH NOT (CHILD* OR INFANT*)) OR (CERVICAL NOT (HEAD OR NECK OR SPIN* OR VERTEBRA*))
5. Field:: Title
Statement:: CERVIX OR CESAREAN OR CHORIONIC OR CLITOR* OR COLPO* OR CONTRACEPTI* OR DECIDUA* OR DYSTOCIA OR ECLAMPSIA OR ENDOMETRI* OR ESTRADIOL OR ESTROGEN OR FALLOPIAN OR FETAL OR FETUS* OR GESTATION* OR GONAD* OR GRANULOSA OR GYNECOLOG*
6. Field:: Title
Statement:: HYSTERECTOMY OR INSEMINAT* OR INTRAFALLOPIAN OR INTRAUTERINE OR INTRAVAGINAL OR LH OR LUTEAL OR LUTEINIZING OR MENOPAU* OR MENSTUA* OR MYOMETRI* OR OBSTETRIC* OR OVAR* OR OVULAT* OR OXYTOCIN OR PARTURITION OR PELLUCIDA OR PELVIC
7. Field:: Title
Statement:: PERINATAL OR PLACENTA* OR POSTHYSTERECTOMY OR POSTPARTUM OR PREECLAMP* OR PREGNANC* OR PREGNANT OR PREMENOPAUSAL OR PREMENSTRUAL OR PRENATAL OR PRETERM OR PROGEST* OR PROSTAGLANDIN*
8. Field:: Title
Statement:: TRANSPLACENTAL OR TRANSVAGINAL OR TRIMESTER OR TROPHOBLAST* OR TUBAL OR UMBILICAL OR UTERINE OR UTERO* OR UTERUS OR VAGINA* OR VULVA
9. Field:: Set
Statement:: 1 THRU 8
10. Field:: Set
Doctype:: Article
Statement:: 9
11. Field:: Set
Doctype:: NOTE
Statement:: 9
12. Field:: Set
Doctype:: Review
Statement:: 9
13. Field:: Set
Statement:: 10 THRU 12

B3 Key words used in SCI database search

Antenatal steroids	Betamethasone Dexamethasone Antenatal steroids Antenatal corticosteroids
Mechanical ventilation	Ventil* (use of wild card to capture all forms of ventilate/ventilation)
Replacement surfactant	Hyaline Surfactant Surface tension
Parenteral nutrition	Parenteral
Ultrasound	Ultrasound