Research Policy

Comroe and Dripps revisited

RICHARD SMITH

Everybody interested in research has a stock of stories to illustrate their theories on how important developments arise. Usually the stories are selected (consciously or unconsciously) to reflect the importance of the sort of work that the storyteller does. More than 20 years ago Julius Comroe, a professor of physiology, and Robert Dripps, a professor of anaesthetics, became tired and irritated by this approach and set about introducing some "science" into the subject.¹ In the introduction to the study they eventually produced they condemn the anecdotal and "let me give you an example" approach as suitable only for dinner parties and governmental committees. Scientists need something better, and certainly those who must decide how to spend limited research funds need something better.

A unique study

Comroe and Dripps looked at the sources of "the top ten clinical advances in cardiovascular and pulmonary medicine and surgery in the last 30 years." Their conclusion was that 41% of over 500 key articles that led to these advances were written by scientists who had no interest in disease and that 62% were the result of basic research. The paper is thus often quoted to justify basic research not just as an end in itself but as the ultimate key to important advances. It can also be used to illustrate the importance of clinical research in that more than half of the papers were (by their rather eccentric and overinclusive definition) the result of such research.

Arguments continue on how to divide up the research cake between basic and applied research and clinical and non-clinical research, and the work of Comroe and Dripps did not succeed in producing some neat formula for deciding how to allocate funds. Their study is, however, worth looking at in detail because, although published over 10 years ago (after 10 years' gestation), it still seems to be the only "scientific" study of innovations in medicine. Their rich data deserve critical assessment so that the real value of their work can be seen and their work followed up.

The study has obvious defects but is in many ways superior to the studies I quoted last week (21 November, p 1335), which looked at the sources of innovations in weapon systems, selected major discoveries (including some biological ones), and various commercially successful inventions. It has probably not been repeated because of the extraordinary amount of work needed to complete the study and because of the lack of interest shown by medical researchers in studying research itself. And there is no reason why an expert on, say, cell division should turn his attention to studying

research (and many reasons why he shouldn't), but surely the authorities responsible for medical research should divert some of their substantial funds into this sort of research.

Comroe and Dripps were inspired to undertake their study by the results of Project Hindsight, a study undertaken by the United States Department of Defence, which purported to show that most innovations arose from mission oriented research undertaken in government laboratories.² The contribution of basic and university science was small. Although the results were hotly disputed by the

academic community and applied only to military research, they did lead to the National Institutes of Health shifting more towards commissioned research.

Attempting to avoid bias

Comroe and Dripps, university scientists, might thus be said to have a vested interest in producing different results from those of Project Hindsight, and they must have recognised this because they thought that the major defect of Project Hindsight was that government scientists had chosen the subjects to be studied. Comroe and Dripps got round this problem by asking 40 physicians to list the advances that they thought most important. They do not, however, say in their paper whether they asked 40 and fewer replied or whether they asked more and only 40 replied. Nor do they say how they selected these 40, and nor do they say in their methods why they chose only physicians, although they are defensive in their discussion about having done so.

From the replies Comroe and Dripps produced a list of the top cardiovascular and pulmonary advances and sent them to "40 to 50 specialists in each field" and asked them to vote on the list. "Their votes selected the top 10 advances." Again this is very imprecise for a paper published in *Science*. Exactly how many specialists were contacted? How many responded? How were they asked to vote? How were the votes put together?

I make criticisms for two reasons. Firstly, they illustrate how "unscientific" is the paper by Comroe and Dripps and show how sad it is that their plea for more research into research has not been taken up by those interested primarily in medical research. As a physiologist and an anaesthetist they were forging a new subject and using new techniques, and inevitably—as with any new discipline—they were learning as they went along. Secondly, their methods of selecting the top advances may have resulted in some important gaps. For instance, if I had been asked about the most important advances I would have mentioned the evidence that proved that smoking was the cause of much cardiovascular and pulmonary disease. Comroe and Dripps might have responded that this was not a clinical advance, but I would have said that warning patients about their smoking was just about the most important therapeutic manoeuvre for most doctors treating lung and heart diseases. So we would have gone on (and I might also have suggested double blind randomised controlled trials as an important advance), but the main point is that very different results might have been produced with another method of selecting the top 10 advances.

Essential bodies of knowledge

Once they had their top 10 advances (table I) Comroe and Dripps "with the help of 140 consultants, including 46 interviewed personally" identified 137 "essential bodies of knowledge" that were needed for these to be made. They avoided the major criticism

TABLE I—The top 10 clinical advances in cardiovascular and pulmonary medicine and surgery in the 30 years before 1966

● 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 resuscitation, 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 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)

of Project Hindsight—that the researchers had used too recent a cut off point (30 years)—by having no cut off point at all. Thus an important event in the development of electrocardiography was the ancients rubbing amber.

Comroe and Dripps could not read all the papers published by these scientists since the dawn of time, but they did examine about 4000, which they narrowed down to 2500 "specific scientific reports that were particularly important to the development of one or more of the 137 essential bodies of knowledge." They do not say how they identified either the 4000 or the 2500 papers, but from them "with the advice of consultants" they selected 500 essential or key articles. They define "key articles" and describe how they themselves first identified the key articles and then, without disclosing their selection, invited reviewers (they do not say how many) to nominate key articles for 42 of the 137 tables. The reviewers selected almost twice as many key articles as Comroe and Dripps, but the latter were not worried because, they argued, the proportions that were clinically oriented (which is their key question) were virtually the same in the two groups.

Referees of the paper (if there were any) could not have been entirely happy with this validation, particularly when Comroe and Dripps say themselves that "bias in selecting [key articles] could invalidate our study. . . ." Furthermore, some of the key articles were very old, including, for instance, a paper published by Franklin in 1752 and papers published by Galvani in 1786 and 1791 (leading to the discovery of electrocardiography).

How many articles were clinically oriented?

Comroe and Dripps next decided which of the key articles were clinically oriented: "We define research as clinically oriented, even if it was performed entirely upon animals, tissues, cells, or subcellular particles, if the author 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." This would not be most people's definition of clinical research—it is too wide.

TABLE II—Goal of authors of key articles as selected by reviewers and by Comroe and Dripps from the same 42 tables

Key articles selected by	No of articles	Goal was not clinically oriented	Goal was clinically oriented	% of total not clinically oriented
Reviewers	494	189	305	38.3
Comroe and Dripps	267	101	166	37.8

The results (table II) show that "41% of all work judged to be essential or crucial for later clinical advances was not clinically oriented at the time of the research; 41% of the investigators, when they did their work, expressed no interest in a clinical problem—their goal was knowledge for the sake of knowledge."

Comroe and Dripps hammer home their central conclusion, and they were clearly happy that this was the result. They also pointed out from table III, which shows the proportions of clinically oriented and non-clinically oriented research in different subjects, that by choosing the right clinical advance an informed advocate could argue either that more money should be given to clinically oriented research or to non-clinically oriented research. Such "anecdotal evidence" is their *bête noir*, and they refer with distaste to "the imperfect memories of a group of scientists at a cocktail party."

How much basic research?

After another tranche of preaching Comroe and Dripps went on in their paper to ask how much of the key research was basic. To do

this they adopted an eccentric definition of basic research: "We classify research as basic when the instigator, in addition to observing, describing, or measuring, attempts to determine the mechanisms responsible for the observed effects." I can see the logic behind this definition, but it is far removed from how science policy researchers (and the government) define basic research. The Organisation for Economic Cooperation and Development, for instance, has produced the "standard" definition: basic research is "original investigation [undertaken] with the primary aim of a more complete knowledge or understanding of the subject under study."³ "Pure research" is then "basic research carried out without working for long term economic or social benefits other than the advancement of knowledge and no positive efforts being made to apply the results to practical problems, or to transfer the results to sectors responsible to application."

TABLE III—Goal of authors of 529 key articles that later were judged to be essential for a clinical advance

Clinical advance	Clinically oriented	Not clinically oriented	Total	% Of total not 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	53	24.5
New diagnostic methods	41	53	94	56.4
Poliomyelitis	16	3	19	15.8
Total	312	217	529	41.0

Thus Comroe and Dripps's definition of basic research hinges around the search for mechanisms, whereas most definitions are centred on the research being curiosity driven and not having any clearly foreseeable usefulness. These differences should be borne in mind when Comroe and Dripps are quoted—as they often are.

Using their definition of basic research as a starting point, Comroe and Dripps produced six categories for their key papers: (1) basic research unrelated to the solution of a clinical problem; (2) basic research related to the solution of a clinical problem; (3) research not concerned with basic biological, chemical, or physical mechanisms; (4) review and critical analysis of published work and synthesis of new concepts (without new experimental data); (5) development work or engineering to create, improve, or perfect apparatus or a technique for research use; and (6) development work or engineering to create, improve, or perfect apparatus or a technique for use in diagnosis or care of patients.

These categories seem to provide further sources of possible bias: firstly, work that falls into categories 5 and 6 is probably less likely to be published than work in the categories 1 and 2—and even if it is published it may not be in one of the major journals likely to be read by Comroe and Dripps and their unknown number of assisting physicians; secondly, physicians may be more likely to be able to

appreciate the importance of work done in categories 1 and 2 than that of work done in categories 5 and 6. Alternatively, it might be argued that as work done in categories 5 and 6 must be more recent than work done in categories 1 and 2 the physicians are more likely to remember it.

But, whatever the biases, the results for the 529 key articles are shown in table III. Overall 350 (62%) of the key articles fell into the categories of basic research either related or unrelated to a clinical problem. "Basic research," Comroe and Dripps conclude, "therefore was responsible for almost three times as many key articles as other types of research and almost twice as many as non-basic research and development combined."

Applying the results

So what should those who have responsibility for distributing research resources make of these results? Firstly, they show that different sorts of research are needed to make clinical advances and so "the problem is not either-or, but a question of how much to support one type and how much to another." Comroe and Dripps then conclude "that a generous portion of the nation's biomedical research dollars should be used to identify and then to provide long term support for creative scientists whose main goal is to learn how living organisms function, without regard to the immediate relation of their research to specific human diseases."

They acknowledge that they cannot "translate 'generous support' into a percentage" of a funding organisation's budget because of many unknown factors: the denominators of the numbers of clinically oriented and non-clinically oriented or basic and applied scientists at the times when the key papers were produced; the relative costs of supporting different sorts of scientists; and whether results obtained from studying cardiovascular and pulmonary research are applicable to other topics—for instance, cancer research.

Their ignorance of denominators (and this is my term not theirs) does not, however, stop them from falsely concluding that "basic research, as we have defined it, pays off in terms of key discoveries almost twice as handsomely as other types of research and development combined."

The many flaws in Comroe and Dripps's paper make it difficult for bodies that fund research to act in any but the most general way in response to their conclusions when they decide how to spend their money. And, as Irvine and Martin write: "They did not . . . address the crucial question of whether one can identify in a general way the areas of basic research most likely to yield clinical advances."

The real conclusion

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. "These data strongly support," they write, "our contention that those concerned with preserving or changing national biomedical science policy should disregard 'anecdotal' evidence no matter how convincingly the case is presented." They later hint at an awareness of the deficiencies of their own study (and after all every scientist knows that they are there) when they write: "In the long run, data and conclusions from any single study should stand, fall, or be modified not by anecdotes or gut reactions, but by confirmation or refutation by better studies with improved design and more objective methods." Sadly, Comroe and Dripps's paper has not been followed by bigger and better studies despite their arguing: "We believe that a \$2 billion industry [this was the budget of the National Institutes of Health in 1976; in 1986 it was \$5 billion] might well put more of its annual budget into research on improving its main product, which in this case is discovery and its application."

The lessons from Comroe and Dripps have not been learnt to any great extent by those funding medical research—despite the fact

TABLE IV—Types of research reported in 529 key articles

Type	Basic: not clinically oriented	Basic: clinically oriented	Not basic	Review and synthesis	Development: research	Development: clinical	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	0	43
Intensive care	*	*	*	*	*	*	*
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	36.8	24.9	21.2	1.8	3.9	11.4	

that these scientists are often the first to dismiss the "anecdotal" when assessing a piece of medical research or a grant proposal.

Comroe and Dripps ended their paper with a ringing declaration:

We believe that much more research needs to be done on the nature of research and its application so that data from objective studies can be applied to all aspects of biomedical research. Because the very nature of research on research, particularly if it is prospective, requires long periods of time, we recommend that independent, highly competent groups be established with ample, long term support to conduct and support retrospective and prospective research on the nature of scientific discovery, to analyse the causes of long and short lags between discovery and clinical application and to suggest and test means of decreasing long lags, and to evaluate present

and proposed mechanisms for the support of biomedical research and development.

Amen.

The tables are reproduced with the permission of *Science*.

References

- 1 Comroe JH, Dripps RD. Scientific basis for the support of biomedical science. *Science* 1976;192:105-11.
- 2 Sherwin CW, Isenson RS. *First interim report on Project Hindsight (summary)*. Washington: Office of the Director of Defense Research and Engineering, 1966.
- 3 Organisation for Economic Cooperation and Development. *The measurement of scientific and technical activities. (Frascati manual)*. Paris: OECD, 1981.
- 4 Irvine J, Martin B. *Foresight in science: picking the winners*. London: Frances Pinter, 1984.

MATERIA NON MEDICA

A human menagerie

The Paris auction house Hotel Drouot—always at home with Lalique vases and Louis Quinze furniture—was dealing in *objets d'art* of an altogether different kind recently. While some viewers passing through the ground floor galleries showed intense interest others shuddered with unease and nervous laughter.

The *salles des ventes* were filled with an eclectic disarray of human artefacts. Cheek by jowl with monstrous births and Siamese twins, a panoply of human genitals advertised their venereal stigmata. A sequence of beautifully crafted waxworks showing the phases of fetal development, and a number of obstetric manoeuvres, overlooked a full size wax trepanation in progress, an Egyptian mummy, and the desiccated corpse of a man long dead of starvation. Gun shot wounds and cancerous tongues vied for attention beside wax victims of erysipelas and the equine bacillus glanders.

The models on view were two job lots of uncertain age and origin. Several of the waxes were signed by nineteenth and early twentieth century continental modellers. A few of them had been commissioned from the

maison Talrich of Paris, founded in the 1830s by Dr Jacques Talrich, creator of the wax head for Jeremy Bentham's autoicon. The collection had been brought together for fairground display and was still on tour in Europe as recently as 1958. The fairground nature of some exhibits was obvious; like the hanged woman with noose still in situ, and the sword swallower—partly dissected to show the material basis of her magic. Others were more didactic in purpose, like the broken leg shown before and after a splint of straight twigs had been applied or the tourniquet in place on a wounded thigh. A young woman with a lip lesion embodied the cautionary tale that you can catch syphilis from a single kiss. This was not simply a chamber of horrors but a cabinet of curiosities with an educative dimension. No doubt people came to be entertained as well as horrified, but at the same time they learnt something of the normal functions of the body and its pathology.

The fairground collectors had trawled for their stock in trade from diverse sources: some of the models were medical in origin, such as the series of cervixes displaying cancerous and syphilitic lesions. Many specimens were ministered to by disembodied hands palpating pulses, removing placentas, and amputating limbs and beckoned the onlooker to identify with the doctor's role. The genealogy of other items was less easy to discern, but even those models self evidently designed for the fairground showed their makers' considerable anatomical knowledge. Although none of the waxes for sale approached the standard of Joseph Towne's work at Guy's, several were of high quality and had been made by modellers also employed by medical schools.

The waxes have stood the double test of time and peripatetic exhibition far better than the preparations of real human tissue, now shrivelled and blackened or decomposing in alcohol. The auction at Hotel Drouot was their last appearance *ensemble*. The entire troupe is now dispersed to new owners, individuals and museums throughout the world, who paid up to 30 000 francs (£3000) apiece. Monsieur Alain Weill, the vendor's expert, is well pleased.—RUTH RICHARDSON, historian, BRIAN HURWITZ, general practitioner, London.

(Photo courtesy of M Alain Weill, Paris.)

(Photo courtesy of M Alain Weill, Paris.)

(Photo: Hurwitz/Richardson.)

(Photo courtesy of M Alain Weill, Paris.)